

## Uniform Medical Plan coverage limits

*Updates effective 10/1/2020*

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

- Uniform Medical Plan (UMP) Classic (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.**

## Surgery

These services or supplies have coverage limits	The rules or policies that define the coverage limits	Limit applies to these codes (chosen by your provider to bill for services)
Ablation of Primary and Metastatic Liver Tumors	<a href="#">Regence Medical Policy Sur204</a>	<ul style="list-style-type: none"> <li>47370, 47371, 47380, 47381, 47382, 47383</li> </ul>
Adipose-derived Stem Cell Enrichment in Autologous Fat Grafting to the Breast	<a href="#">Regence Medical Policy Sur182</a>	<ul style="list-style-type: none"> <li>15769, 15771, 15772, 19366</li> </ul> <p>Notes:</p> <ul style="list-style-type: none"> <li>Codes 11950, 11951, 11952, 11954, 15769, 15771, 15772 and 19366 require pre-authorization (see other sections of this pre-authorization list) except when used for autologous fat grafting and adipose-derived stem cell enrichment for augmentation or reconstruction of the breast, where it is considered, and will deny as, investigational</li> <li>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</li> </ul>
Balloon Ostial Dilation for Treatment of Sinusitis	<a href="#">Regence Medical Policy Sur153</a>	<ul style="list-style-type: none"> <li>31295, 31296, 31297, 31298</li> </ul>
Bariatric Surgery	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>43644, 43770, 43771, 43772, 43773, 43774, 43775, 43820, 43846, 43848, 43860, 43886, 43887, 43888</li> <li><a href="#">Bariatric surgery</a> and HTCC guidelines apply, in order to establish eligibility for surgery and medical necessity.</li> </ul>

Blepharoplasty and Brow Ptosis Repair	<a href="#">Regence Medical Policy Sur12.05</a>	<ul style="list-style-type: none"> <li>• 15820, 15821, 15822, 15823, 67900, 67901, 67902, 67903, 67904, 67906, 67908, 67909, 67950</li> <li>• <b>Effective October 1, 2020: Updating medical policy name to Blepharoplasty, Repair of Blepharoptosis and Brow Ptosis Repair</b></li> </ul>
Chemical Peels	<a href="#">Regence Medical Policy Sur12.50</a>	<ul style="list-style-type: none"> <li>• 15788, 15789, 15792, 15793, 17360</li> </ul>
Cardiac Stenting	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>• 92928, 92933, 92937, 92941, 92943</li> <li>• Pre-authorization is not required for members being treated for a condition other than stable angina</li> </ul>
Carotid Artery Stenting	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>• 37215, 37216, 37217, 37246, 37247</li> </ul>
Catheter Ablation Procedures for Supraventricular Tachyarrhythmias (SVTA)	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>• 93653, 93655, 93656, 93657</li> </ul>
Cochlear Implant	<p>For Bilateral Cochlear Implants, UMP is subject to <a href="#">HTCC decision</a></p> <p>For Unilateral Cochlear Implant, UMP follows <a href="#">Regence Medical Policy Sur08</a></p>	<ul style="list-style-type: none"> <li>• 69930, L8614, L8619, L8627, L8628</li> </ul>
Cosmetic and Reconstructive Surgery	<a href="#">Regence Medical Policy Sur12</a>	<ul style="list-style-type: none"> <li>• 11920, 11921, 11922, 11950, 11951, 11952, 11954, 15769, 15771, 15772, 15773, 15774, 19355, 21244, 21245, 21246, 21248, 21249, 21295, 21296, 41510, 49250, 54360, 67950, 69300, G0429, Q2026, Q2028</li> <li>• Pre-authorization is required EXCEPT when services are rendered in association with breast reconstruction and nipple/areola reconstruction following mastectomy for breast cancer.</li> </ul>

		<ul style="list-style-type: none"> <li>Codes 11950, 11951, 11952, 11954, 15769, 15771, 15772 and 19366 require pre-authorization (see other sections of this pre-authorization list) except when used for autologous fat grafting and adipose-derived stem cell enrichment for augmentation or reconstruction of the breast, where it is considered, and will deny as, investigational</li> <li>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</li> </ul>
Cryosurgical Ablation of Miscellaneous Solid Organ, Pulmonary, and Breast Tumors	<a href="#">Regence Medical Policy Sur132</a>	<ul style="list-style-type: none"> <li>31641, 32994, 50542</li> </ul>
Deep Brain Stimulation	<a href="#">Regence Medical Policy Sur84</a>	<ul style="list-style-type: none"> <li>61850, 61860, 61863, 61864, 61867, 61868, 61885, 61886, C1820, L8679, L8680, L8685, L8686, L8687, L8688, L8682, L8683</li> </ul> <p>Deep brain stimulation is not a covered benefit for treatment-resistant depression, per <a href="#">HTCC decision</a></p>
Endometrial Ablation	<a href="#">Regence Medical Policy Sur01</a>	<ul style="list-style-type: none"> <li>58353, 58356, 58563</li> </ul>
Gastric Electrical Stimulation	<a href="#">Regence Medical Policy Sur111</a>	<ul style="list-style-type: none"> <li>43647, 43881, 64590, E0765, C1767, L8679, L8680, L8685, L8686, L8687, L8688</li> </ul>
Gastroesophageal Reflux Surgery	<a href="#">Regence Medical Policy Sur186</a>	<ul style="list-style-type: none"> <li>43279, 43280, 43281, 43282, 43325, 43327, 43328, 43332, 43333, 43334, 43335, 43336, 43337</li> </ul>

Hypoglossal Nerve Stimulation	<a href="#">Regence Medical Policy Sur215</a>	<ul style="list-style-type: none"> <li>64568, 0466T</li> </ul>
Hysterectomy Surgery	<a href="#">Regence Medical Policy Sur218</a>	<ul style="list-style-type: none"> <li>58150, 58152, 58180, 58260, 58262, 58263, 58267, 58270, 58275, 58280, 58290, 58291, 58292, 58293, 58294, 58541, 58542, 58543, 58544, 58550, 58552, 58553, 58554, 58570, 58571, 58572, 58573</li> <li>Pre-authorization is only required for diagnoses related to abnormal uterine bleeding, pelvic pain (including pain related to endometriosis, Essure placement, prior endometrial ablation, and vaginal agenesis), chronic pelvic inflammatory disease, pelvic adhesive disease, pelvic venous congestion, adenomyosis, cervical intraepithelial neoplasia, and leiomyoma. Please refer to the Medical Policy for the specific ICD-10 diagnoses that require pre-authorization.</li> </ul> <p>Hysterectomy procedures for the indication of gender dysphoria are subject to the <a href="#">Gender Affirming Interventions for Gender Dysphoria Medical Policy</a></p>
Implantable Cardiac Defibrillators	<a href="#">Regence Medical Policy Sur17</a>	<ul style="list-style-type: none"> <li>33230, 33231, 33240, 33249, 33270, 33271, C1721, C1722, C1882</li> </ul> <p>Pre-authorization is required EXCEPT when the member is age 17 or younger.</p>
Implantable Peripheral Nerve Stimulation for Chronic Pain of Peripheral Nerve Origin	<a href="#">Regence Medical Policy Sur205</a>	<ul style="list-style-type: none"> <li>64555, 64575, 64590, L8680, L8683</li> </ul>
Laser Treatment for Port Wine Stains	<a href="#">Regence Medical Policy Sur12.34</a>	<ul style="list-style-type: none"> <li>17106, 17107, 17108</li> </ul>

Leadless Cardiac Pacemakers	<a href="#">Regence Medical Policy Sur217</a>	<ul style="list-style-type: none"> <li>• 33274</li> </ul>
Left-Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation	<a href="#">Regence Medical Policy Sur195</a>	<ul style="list-style-type: none"> <li>• 33340</li> </ul>
Magnetic Resonance (MR) Guided Focused Ultrasound (MRgFUS) and High Intensity Focused Ultrasound (HIFU) Ablation	<a href="#">Regence Medical Policy Sur139</a>	<ul style="list-style-type: none"> <li>• C9747, 0398T</li> </ul>
Microwave Tumor Ablation	<a href="#">Regence Medical Policy Sur189</a>	<ul style="list-style-type: none"> <li>• 32998, 50592</li> </ul>
Negative Pressure Wound Therapy for Home Use (NPWT)	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>• 97605, 97606, 97607, 97608, A6550, E2402</li> </ul> <p>View the HTCC Decision: <a href="#">Definition of "Complete Wound Therapy Program"</a></p>
Occipital Nerve Stimulation	<a href="#">Regence Medical Policy Sur174</a>	<ul style="list-style-type: none"> <li>• 61885, 61886, 64553, 64555, 64568, 64575, 64590, 0466T</li> <li>• C1820, L8679, L8680, L8682, L8683, L8685, L8686, L8687, L8688</li> </ul> <p>Occipital Nerve Stimulation is considered investigational for all indications, including but not limited to headaches.</p> <p>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.</p>
Orthognathic Surgery	<a href="#">Regence Medical Policy Sur137</a>	<ul style="list-style-type: none"> <li>• 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</li> <li>• Codes 21145, 21196, 21198 require pre-authorization EXCEPT when the procedure</li> </ul>

		is performed for oral cancer dx 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 and Autograft Transplantation (OAT)	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>• 27415, 27416, 29866, 29867, J7330, S2112</li> </ul>
Ovarian, Internal Iliac and Gonadal Vein Embolization, Ablation, and Sclerotherapy	<a href="#">Regence Medical Policy Sur147</a>	<ul style="list-style-type: none"> <li>• 37241</li> </ul>
Percutaneous Angioplasty and Stenting of Veins	<a href="#">Regence Medical Policy Sur109</a>	<ul style="list-style-type: none"> <li>• 37238, 37239, 37248, 37249</li> </ul>
Panniculectomy	<a href="#">Regence Medical Policy Sur12.01</a>	<ul style="list-style-type: none"> <li>• 15830</li> </ul>
Pectus Excavatum	<a href="#">Regence Medical Policy Sur12.02</a>	<ul style="list-style-type: none"> <li>• 21740, 21742, 21743</li> </ul>
Phrenic Nerve Stimulation for Central Sleep Apnea	<a href="#">Regence Medical Policy Sur212</a>	<ul style="list-style-type: none"> <li>• C1823</li> </ul>
Radiofrequency Ablation (RFA) of Tumors Other Than the Liver	<a href="#">Regence Medical Policy Sur92</a>	<ul style="list-style-type: none"> <li>• 20982, 31641, 32998, 50542, 50592</li> </ul>
Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants	<a href="#">Regence Medical Policy Sur40</a>	<ul style="list-style-type: none"> <li>• 11920, 11921, 11950, 11951, 11952, 11954, 15769, 15771, 15772, 19316, 19318, 19324, 19325, 19328, 19330, 19340, 19342, 19350, 19355, 19366, 19370, 19371, L8600</li> </ul> <p>Pre-authorization is required EXCEPT when services are rendered in association with breast reconstruction and nipple/areola reconstruction following mastectomy for breast cancer.</p> <p>Codes 11950, 11951, 11952, 11954, 15769, 15771, 15772 and 19366 require pre-authorization (see other sections of this pre-authorization list) except when used for autologous</p>

		fat grafting and adipose-derived stem cell enrichment for augmentation or reconstruction of the breast, where it is considered, and will deny as, investigational 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 Mammoplasty	<a href="#">Regence Medical Policy Sur60</a>	<ul style="list-style-type: none"> <li>19318</li> </ul>
Responsive Neurostimulation	<a href="#">Regence Medical Policy Sur216</a>	<ul style="list-style-type: none"> <li>61850, 61860, 61863, 61864, 61885, 61886, L8680, L8686, L8688</li> </ul>
Rhinoplasty	<a href="#">Regence Medical Policy Sur12.28</a>	<ul style="list-style-type: none"> <li>30120, 30400, 30410, 30420, 30430, 30435, 30450</li> </ul>
Sacral Nerve Neuromodulation/Stimulation for Pelvic Floor Dysfunction	<a href="#">Regence Medical Policy Sur134</a>	<ul style="list-style-type: none"> <li>64561, 64581, 64590, C1767, L8679, L8680, L8682, L8683, L8685, L8686, L8687, L8688</li> <li>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.</li> </ul>
Sacroiliac Joint Fusion	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>27280, 27279</li> </ul>
Spinal Cord and Dorsal Root Ganglion Stimulation	<a href="#">Regence Medical Policy Sur45</a>	<ul style="list-style-type: none"> <li>63650, 63655, 63685, C1767, C1820, C1822, L8679, L8680, L8685, L8686, L8687, L8688</li> </ul> <p>Note: Please submit your pre-authorization request for the temporary trial AND the permanent placement at the same time. Spinal cord stimulation for the treatment of chronic neuropathic pain is not a covered benefit, per</p>

		<p><a href="#">HTCC Decision</a> when associated diagnosis codes are included:  G60.9  G89.28-G89.29  M47.20-M47.28  M47.811-M47.819  M50.10-M50.13  M50.121-M50.123  M54.10-M54.13  M51.14-M51.17  M54.16-M54.17  M54.30-M54.32  M54.40-M54.42  M54.5  M79.2  G89.4  M96.1  If treatment is for other than this indication, Regence medical policy applies.</p>
Spinal Surgery - Artificial Disc Surgery	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>• 22856, 22858, 22861, 0095T, 0098T</li> <li>• <a href="#">FDA indications and contraindications</a></li> <li>• Lumbar artificial disc is not a covered benefit: 22862, 22865, 0163T, 0164T, 0165T</li> </ul>
Stereotactic Radiation Surgery and Stereotactic Body Radiation Therapy	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>• 32701, 61796, 61797, 61798, 61799, 61800, 63620, 63621, 77371, 77372, 77373, 77432, 77435, G0339, G0340</li> </ul>
Surgical Treatments for Hyperhidrosis	<a href="#">Regence Medical Policy Sur165</a>	<ul style="list-style-type: none"> <li>• 32664, 64818, 69676</li> <li>• Code 32664 only requires pre-authorization for hyperhidrosis diagnoses L74.510 L74.511, L74.512, L74.513, L74.519, L74.52, R61</li> </ul>

Sleep Apnea Diagnosis and Treatment	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>• 21121, 21122, 21141, 21145, 21196, 21198, 21199, 21685, 41120, 42140, 42145, 42160</li> <li>• Codes 21145, 21196, 21198, 41120, 42160 do not require pre-authorization when the procedure is performed for oral cancer dx 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</li> <li>• HTCC does not apply to those under age 18. See Regence medical policy <a href="#">Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome (PDF)</a></li> </ul>
Temporomandibular Joint (TMJ) Surgical Interventions	MCG  Visit MCG's website at <a href="http://careguidelines.com/products/">careguidelines.com/products/</a> for information on purchasing their criteria, or contact us and we will be happy to provide you with a copy of the specific guideline.	<ul style="list-style-type: none"> <li>• 21010 - MCG A-0522</li> <li>• 21050 - MCG A-0523</li> <li>• 29800, 29804 - MCG A-0492</li> <li>• 21240, 21242, 21243 - MCG A-0523</li> </ul>
Transcutaneous Bone Conduction and Bone-Anchored Hearing Aids	<a href="#">Regence Medical Policy Sur121</a>	<ul style="list-style-type: none"> <li>• 69714, 69710, 69715, 69717, 69718, L8690, L8691, L8692, L8694</li> </ul>
Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD)	<a href="#">Regence Medical Policy SUR110</a>	<ul style="list-style-type: none"> <li>• 43192, 43201, 43236</li> </ul> <p>Note: Codes 43201 and 43236 may also be used for the administration of Botox for indications unrelated to GERD. Botox requires pre-authorization by Pharmacy. For Botox injections, please see the Pharmacy policy</p>
Upper Endoscopy for Gastroesophageal Reflux Disease (GERD) and Gastrointestinal (GI) Symptoms	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>• Upper Endoscopy for GERD and GI Symptoms for UMP members are subject to <a href="#">HTCC decision</a></li> <li>• CPT 43200, 43202, 43235, 43237, 43238, 43239, 43242</li> </ul>

		<p>and 43259 do not require pre-authorization, but may be subject to <a href="#">HTCC decision</a> and require an Upper Endoscopy for GERD and GI Symptoms Attestation Form.</p> <p>Notes:</p> <ul style="list-style-type: none"> <li>• Attestation forms may be submitted with the claim, or attestation may be completed pre-service through the Availity Portal</li> <li>• Attestation form is required for claims processing</li> <li>• Attestation form is required for adults only (member 18 years and older)</li> </ul>
Vagus Nerve Stimulation	<a href="#">Regence Medical Policy Sur74</a>	<ul style="list-style-type: none"> <li>• UMP is subject to <a href="#">HTCC decision</a>: 61885, 61886, 64553, 64568, C1822, 0466T, L8679, L8680, L8682, L8683, L8685, L8686, L8687, L8688</li> <li>• The HTCC does not apply to members under age 12. Please use Regence Medical Policy for requests for members under age 12.</li> <li>• Note: Vagal Nerve Stimulation for the treatment of epilepsy and depression are subject to HTCC Decision. If treatment is for other than these indications, Regence medical policy applies.</li> </ul>
Varicose Vein Treatment	<a href="#">HTCC decision</a>	<ul style="list-style-type: none"> <li>• 0524T, 36465, 36466, 36470, 36471, 36475, 36476, 36478, 36479, 36482, 36483, 37700, 37718, 37722, 37735, 37760, 37761, 37765, 37766, 37780, 37785, S2202</li> </ul> <p>Notes:</p> <ul style="list-style-type: none"> <li>• All varicose vein requests should be reviewed using the HTCC criteria.</li> <li>• Requests for multiple treatment sessions should refer to <a href="#">Regence Medical Policy</a> for criteria addressing</li> </ul>

		<p>multiple treatment sessions only, <b>and</b> use the HTCC criteria for all other aspects of the request.</p> <ul style="list-style-type: none"> <li>• Code 37241 is not appropriate to use in the coding of varicose vein treatment</li> </ul>
Ventral Hernia Repair	<a href="#">Regence Medical Policy Sur12.03</a>	<ul style="list-style-type: none"> <li>• 15734, 49560, 49565, 49652, 49654, 49656</li> <li>• Pre-authorization for 15734 required only with diagnosis code K43.0, K43.1, K43.2 K43.6, K43.7 or K43.9 for component separation technique (CST)</li> <li>• Pre-authorization for 49652 required only with diagnosis code K43.9 for ventral hernia</li> </ul>

# HTCC Decision: Negative Pressure Wound Therapy

Implementation 1/1/18

## Definition of “Complete Wound Therapy Program”

A minimum of the following measures must be addressed and documented:

- a. Evaluation, care and wound measurements by a licensed medical professional, and
- b. Application of dressings to maintain a moist wound environment, and
- c. Debridement of necrotic tissue if present, and
- d. Evaluation of and provision for adequate nutritional status, and
- e. Standard forms of treatment specific to the type of wound.

## Artificial Cervical Discs

Device Name	Manufacturer	FDA Approval	
Advent®	Orthofix®	No	N/A
BRYAN® disc	Medtronic	Yes - single level	<a href="https://www.accessdata.fda.gov/cdrh_docs/pdf6/p060023b.pdf">https://www.accessdata.fda.gov/cdrh_docs/pdf6/p060023b.pdf</a>
Cadisc™ -C	Rainier® Technology	No	N/A
Cervicare (metal on metal-cobalt-chromium-molybdenum)	Stryker	No - IDE status revoked by FDA	N/A
Discover™ (polyethylene on titanium alloy)	DePuy Synthes – (formerly DePuy Spine, Inc.)	No - IDE only	N/A
Freedom® Cervical Disc	AxioMed®	No	N/A
Kineflex® -C (cobalt-chromium-molybdenum)	SpinalMotion	No - IDE only	N/A
M6®-C	Spinal Kinetics™	Yes - single level	<a href="https://www.accessdata.fda.gov/cdrh_docs/pdf17/p170036a.pdf">https://www.accessdata.fda.gov/cdrh_docs/pdf17/p170036a.pdf</a>
Mobi-C®	LDR Spine USA	Yes - 1 and 2 level	<a href="https://www.accessdata.fda.gov/cdrh_docs/pdf11/p110009b.pdf">https://www.accessdata.fda.gov/cdrh_docs/pdf11/p110009b.pdf</a>
NeoDisc®	NuVasive®	No - IDE only	<a href="https://www.accessdata.fda.gov/cdrh_docs/pdf10/p100012b.pdf">https://www.accessdata.fda.gov/cdrh_docs/pdf10/p100012b.pdf</a>
PCM® (Porous Coated Motion) Cervical Disc (polyethylene-on-metal)	Cervitech, now part of NuVasive®	Yes - single level	<a href="https://www.accessdata.fda.gov/cdrh_docs/pdf10/p100012b.pdf">https://www.accessdata.fda.gov/cdrh_docs/pdf10/p100012b.pdf</a>
Prestige® Cervical Disc System (includes Prestige ST (titanium and ceramic)	Medtronic	Yes - single level	<a href="https://www.accessdata.fda.gov/cdrh_docs/pdf6/p060018b.pdf">https://www.accessdata.fda.gov/cdrh_docs/pdf6/p060018b.pdf</a>
Prestige® LP Cervical Disc	Medtronic	Yes - single and 2-level	<a href="https://www.accessdata.fda.gov/cdrh_docs/pdf9/p090029b.pdf">https://www.accessdata.fda.gov/cdrh_docs/pdf9/p090029b.pdf</a>
ProDisc® - C	DePuy Synthes	Yes - single level	<a href="https://www.accessdata.fda.gov/cdrh_docs/pdf7/p070001b.pdf">https://www.accessdata.fda.gov/cdrh_docs/pdf7/p070001b.pdf</a>
SECURE® - C	Globus Medical	Yes - single level	<a href="https://www.accessdata.fda.gov/cdrh_docs/pdf10/p100003b.pdf">https://www.accessdata.fda.gov/cdrh_docs/pdf10/p100003b.pdf</a>

**NOTE: This policy has been revised. The revised policy will be effective January 1, 2021. To view the revised policy, [click here](#).**

Medical Policy Manual

Surgery, Policy No. 01

## ***Endometrial Ablation***

**Effective:** January 1, 2020

**Next Review:** February 2020

**Last Review:** November 2019

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Endometrial ablation involves ablation or destruction of the endometrium using a variety of techniques to treat menorrhagia in women who fail standard therapy.

### **MEDICAL POLICY CRITERIA**

- I. Endometrial ablation, with or without hysteroscopic guidance, may be considered **medically necessary** when the clinical records document all of the following criteria (I.A-D) are met:
  - A. There is a diagnosis of abnormally heavy uterine bleeding in a patient who is not post-menopausal; *and*
  - B. Hysteroscopy, sonohysterography (SIS), or pelvic ultrasound has been performed and report is provided; *and*
  - C. Clinical documentation confirms counseling regarding hormonal treatment options has been addressed (see Policy Guidelines); *and*
  - D. Endometrial sampling or dilation and curettage (D&C) has been performed or is planned according to any of the following:

1. 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*
  2. 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*
  3. Cervical stenosis precludes endometrial sampling, and D&C is planned concomitantly with ablation procedure.
- II. Repeat endometrial ablation may be considered **medically necessary** when all of the following (II.A-C) criteria are met:
- A. There is a recurrent diagnosis of abnormally heavy uterine bleeding in a patient who is not post-menopausal; *and*
  - B. The initial endometrial ablation procedure was performed at least six months prior; *and*
  - C. Endometrial sampling or D&C has been performed or is planned according to any of the following:
    1. Endometrial sampling or D&C has been performed to evaluate the current abnormal bleeding episode within the past year, and report is provided. The histopathology report is provided showing absence of endometrial hyperplasia or uterine cancer; *or*
    2. 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*
    3. Cervical stenosis precludes endometrial sampling, and D&C is planned concomitantly with ablation procedure.
- III. Endometrial ablation using *any* technique is considered **not medically necessary** for all other indications not meeting the criteria in I.A-D, or II.A-C.

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

## POLICY GUIDELINES

### HORMONAL THERAPY OPTIONS

Counseling regarding hormonal treatment options has occurred, or uterine intracavitary abnormality (i.e., endometrial polyps, submucosal fibroids) is found on hysteroscopy, sonohysterography, pelvic ultrasound, or endometrial biopsy/curettings and endometrial ablation is to be performed concomitantly with surgical treatment of the uterine intracavitary abnormality.

## LIST OF INFORMATION NEEDED FOR REVIEW

### SUBMISSION OF DOCUMENTATION

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

- Endometrial histopathological report
- Hysteroscopy, sonohysterography (SIS), or pelvic ultrasound report
- Clinical notes which specify counseling regarding hormonal therapy in the absence of a structural abnormality

## CROSS REFERENCES

1. [Gender Affirming Interventions for Gender Dysphoria](#), Medicine, Policy No. 153
2. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12
3. [Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants](#), Surgery, Policy No. 40
4. [Autologous Fat Grafting to the Breast and Adipose-derived Stem Cells](#), Surgery, Policy No. 182
5. [Hysterectomy](#), Surgery, Policy No. 218

## BACKGROUND

Ablation or destruction of the endometrium is used to treat abnormal uterine bleeding in premenopausal women who fail standard medical therapy. Standard medical management typically includes a trial of nonhormonal therapy with adequate doses of nonsteroidal anti-inflammatory medication and oral tranexamic acid. If this fails, management with hormonal treatment to thin the endometrium may be tried. Hormonal treatment may include oral contraceptive pills, patch, vaginal ring, or progestin-only hormonal therapy (oral, IUD, implant, or injection). Ablation is considered a less invasive alternative to hysterectomy; however, as with hysterectomy, the procedure is not recommended for women who wish to preserve their fertility.

Techniques for endometrial ablation are generally divided into two categories:

### HYSTEROSCOPIC TECHNIQUES

Hysteroscopic techniques require skilled surgeons and, due to the requirement for cervical dilation, use of general or regional anesthesia. In addition, the need for the instillation of hypotonic distension media creates a risk of pulmonary edema and hyponatremia such that very accurate monitoring of fluids is required.

The initial hysteroscopic technique involved photovaporization of the endometrium using an Nd-YAG laser. This was followed by electrosurgical ablation using an electrical rollerball or electrical wire loop. The latter technique is also known as transcervical resection of the endometrium, or TCRE. Hydrothermal ablation is another technique involving hysteroscopy.

### NON-HYSTEROSCOPIC TECHNIQUES

Non-hysteroscopic techniques can be performed without general anesthesia and do not involve use of a fluid distention medium. Techniques include thermal fluid-filled balloon, cryosurgical endometrial ablation, instillation of heated saline, and radio frequency (RF) ablation.

### REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) indicated that endometrial devices are for use in premenopausal women with menorrhagia due to benign causes for whom childbearing is

complete. FDA-approved devices for endometrial ablation include, but may not be limited to, laser therapy, electrical wire loop, rollerball using electric current, and thermal ablation using a liquid-filled balloon, microwave, electrode array, or a cryosurgical device. Examples of devices for endometrial ablation are listed below. FDA product code: MNB.

- The Genesys HTA™ system (Boston Scientific), This system involves the instillation and circulation of heated saline into the uterus using hysteroscopic guidance and includes features such as a smaller console and simplified set-up requirements, was approved by the FDA in May 2010.
- The Microwave Endometrial Ablation (MEA) system (Microsulis Medical): This delivers fixed-frequency microwave energy and may be performed in a physician's office but does require use of the hysteroscope.
- The ThermaChoice® device (J&J Ethicon Gynecare): This device ablates endometrial tissue by thermal energy heating of sterile injectable fluid within a silicone balloon. Endometrial ablation will only work when there is direct contact between the endometrial wall and the fluid-filled balloon. Therefore, patients with uteri of abnormal shape, resulting from tumors such as myomas or polyps, or large size, due to fibroids, are generally not considered candidates for this procedure.
- The NovaSure™ impedance-controlled endometrial ablation system (Cytoc Corp): The system delivers RF energy to the endometrial surface. The device consists of an electrode array on a stretchable porous fabric that conforms to the endometrial surface.
- Her Option™ Uterine Cryoablation Therapy™ system (American Medical Systems): The system consists of, in part, a cryoprobe that is inserted through the cervix into the endometrial cavity. When cooled, an ice ball forms around the probe, which permanently destroys the endometrial tissue. Cryoablation is typically monitored by abdominal ultrasound.

## EVIDENCE SUMMARY

### SYSTEMATIC REVIEWS

Several published systematic reviews have evaluated the accumulated evidence for endometrial ablation. These reviews address both first- generation techniques (laser ablation, electrical wire loop, rollerball, or vaporizing electrode procedure) and second-generation techniques (newer techniques that generally do not require hysteroscopy such as balloon ablation, microwave ablation, and electrode ablation).

In 2018, an updated Cochrane systematic review and meta-analysis compared the efficacy and safety of different endometrial ablation techniques.<sup>[1-3]</sup> The review included RCTs that compared ablation techniques and assessed amenorrhea and patient satisfaction.

A total of 28 studies with 4,287 premenopausal women were eligible for the review. Five of the trials compared two “first generation” ablation methods (laser ablation, electrical wire loop, rollerball, or vaporizing electrode procedure) to one another and five trials compared “second generation” techniques to one another. Fifteen trials compared first- to second-generation procedures. Eighteen trials had adequate randomization methods, but in most trials blinding was not performed or was not reported. Of the studies that compared among second generation techniques, three described triple blinding and two described double blinding.

The investigators also conducted a meta-analysis that combined studies comparing first- and second-generation techniques. A pooled analysis of 12 studies (total n=2,085) did not find a

significant difference in the rate of amenorrhea at one year (OR: 0.94; 95% CI: 0.74–1.20). Eleven studies (total n=1,690) reported satisfaction rates at one year, and there was not a significant difference between first- and second-generation techniques (OR: 1.00; 95% CI, 0.97-1.02). Pooled analysis of adverse effects did not find any significant differences in the rate of perforation (eight studies), endometritis (four studies), or hemorrhage (four studies) using first- versus second-generation ablation techniques. Rates of fluid overload (three studies) and cervical lacerations (seven studies) and hematometra (five studies) were significantly higher with first-generation techniques than with second-generation techniques.

The authors of the Cochrane review concluded that, overall, the existing evidence suggests that success rates and complications profiles of second-generation techniques compare favorably with the first generation hysteroscopic techniques.

In 2011, the Health Technology Assessment (HTA) program in the U.K. conducted a meta-analysis of individual patient data from RCTs evaluating second-line treatments for menorrhagia.<sup>[4]</sup> They identified data on 2,448 women from 14 trials comparing first- and second-generation endometrial ablation devices and data on 1,127 women from seven trials comparing first-generation devices to hysterectomy. A limitation of the review is that individual patient data were not available for approximately 35% of women randomized in the trials. The most frequently measured outcome in the studies was patient satisfaction/dissatisfaction and this was used as the primary outcome of the meta-analysis. After 12 months of follow-up, 7.3% (57/454) of women treated with first-generation endometrial ablation devices and 5.3% (23/432) of women who had a hysterectomy were dissatisfied with their treatment outcome. This difference was statistically significant, favoring hysterectomy (OR: 2.46, 95% CI: 1.54 to 3.93, p=0.0002). Rates of dissatisfaction were similar among women treated with first-generation endometrial ablation devices (123/1,006 [12.2%]) and second-generation devices (110/1,034 [10.6%], p=0.20). The authors noted that rates of dissatisfaction were low for all treatments.

The HTA also conducted meta-analyses on several clinical outcomes. For example, when first- and second-generation endometrial ablation devices were compared, there was not a significant difference between groups in the rate of amenorrhea after 12 months. When findings from 13 studies were pooled, rates of amenorrhea were 326/899 (36%) with first-generation devices and 464/1,261 (37%) with second-generation devices (OR: 1.12; 95% CI: 0.93 to 1.35). There were insufficient data to conduct meta-analyses of longer-term amenorrhea rates. Similarly, the rates of menorrhagia after 12 months did not differ between groups. In a pooled analysis of 12 studies, rates were 111/899 (12.3%) with first-generation devices and 151/1,281 (11.8%) after second-generation devices (pooled OR: 0.97, 95% CI: 0.74 to 1.28). In addition, a pooled analysis of 6 studies did not find a significant difference in repeat endometrial ablations over 12 months after initial treatment with first-generation devices (4/589, 0.7%) or second-generation devices (4/880, 0.5%) (OR: 0.71, 95% CI: 0.17 to 2.94). The proportion of women requiring hysterectomy within 12 months after endometrial ablation did not differ significantly when first-generation devices (39/933 [4.2%]) or second-generation devices (35/1,343 [2.6%]) were used (OR: 0.77; 95% CI: 0.47 to 1.24 [11 studies]).

In addition to the meta-analyses of data from published studies, the HTA included an analysis of individual patient data from national databases in Scotland to evaluate long-term outcomes after hysterectomy or endometrial ablation. The investigators identified a total of 37,120 women who underwent hysterectomy and 11,299 women who underwent endometrial ablation for dysfunctional uterine bleeding between 1989 and 2006. Women who received endometrial

ablation were significantly older (mean of 42.5 years) compared to those receiving hysterectomy (mean of 41.0 years). The type of endometrial ablation device could not be determined. The median duration of follow-up was 6.2 years in the endometrial ablation group and 11.6 years in the hysterectomy group. During follow-up, 962 (8.5%) women who received endometrial ablation had additional gynecologic surgery compared to 1,446 (3.9%) women who had hysterectomy; this difference was statistically significant (adjusted hazard ratio [HR]: 3.56, 95% CI: 3.26-3.89). The most common types of additional surgery after endometrial ablation were intrauterine procedures (n=577, 5.1%) and repeat endometrial ablation (n=278, 2.5%). However, women who had initial endometrial ablation procedures were significantly less likely than those with initial hysterectomies to have surgery for pelvic floor repair (0.9% vs. 2.2%, respectively, adjusted HR: 0.50 to 0.77). Women were also less likely to have tension-free vaginal tape surgery for stress urinary incontinence after endometrial ablation than after hysterectomy (0.5% vs. 1.1%, respectively, adjusted HR: 0.55, 95% CI: 0.41 to 0.74).

In 2012, Daniels compared first- and second-generation methods using 14 trials previously addressed in the HTA assessment.<sup>[5]</sup> A pooled analysis of these studies yielded conclusions that were similar to the HTA group, in that no significant difference in amenorrhea rates was observed with the two types of techniques (OR: 0.72, 95% CI: 0.52 to 1.101). In addition, three studies compared the second-generation techniques, thermal balloon ablation and bipolar radiofrequency (RF) (total n=264). A pooled analysis showed a higher rate of amenorrhea with bipolar RF (OR: 4.56; 95% CI: 2.24 to 9.26).

In 2013, Kroft also reported no difference in amenorrhea rates when comparing first- and second-generation methods as a treatment for menorrhagia in premenopausal women (11 randomized controlled trials<sup>[6]</sup> were included in the review). However, authors did note a decrease in complication rates (seven studies with 1272 patients, rate ratio 0.52, 95% CI 0.35 to 0.76; p<0.001), operating time (16.6 minutes three studies with 486 patients, 95% CI 12.1 to 21.2 minutes; p<0.001) and improved compatibility with anaesthesia (three studies with 558 patients, rate ratio 1.87, 95% CI 1.04 to 3.37; p=0.04) in second-generation devices compared to first-generation methods. In addition, authors reported higher rates of amenorrhea in patients treated with Novasure compared to other second-generation devices (four studies with 407 patients, rate ratio 2.60, 95% CI 1.63 to 4.14; p<0.001).

Several medium and large nonrandomized studies have reported time to surgical reoperation rates, including repeat endometrial ablation, in women who fail initial procedure.<sup>[7-9]</sup> The majority of surgical reoperations occurred at least one year after the initial procedure.

## Section Summary

Evidence from these large systematic reviews do not demonstrate that one ablation technique is superior to another. Overall, these studies continue to report similar amenorrhea rates in first-generation and second-generation techniques.

## SAFETY

In 2012, Brown published an analysis of adverse events associated with endometrial ablation procedures that were reported in the U.S. Food and Drug Administration (FDA's) Manufacturer and User Facility Device Experience (MAUDE) database.<sup>[10]</sup> There were a total of 829 reported adverse events between 2005 and 2011. Nearly two-thirds of the adverse events (540 of 829, 65%) were genital tract or skin burns and 529 of these events (98%) were associated with hydrothermal endometrial ablation. The next two most frequent types of adverse events were

thermal bowel injury (93 of 820, 11%) and transmural uterine thermal activity (89 of 820, 11%). Of the 182 thermal injuries, 140 (77%) were associated with radiofrequency endometrial ablation. In addition, 47 instances of sepsis or bacteremia were reported, and 43 of these cases (91%) were associated with radiofrequency endometrial ablation. There were four reported deaths, two associated with radiofrequency ablation and one each associated with thermal balloon ablation and cryoablation. Sixty-six of the 829 events (8%) occurred when endometrial ablation was performed outside of the labeled instructions for use of the procedure. The authors did not report the total number of endometrial ablations performed during this time period, therefore the proportion of procedures with adverse events cannot be determined from these data.

A 2014 study by Dood examined whether women who undergo endometrial ablation are at increased risk of endometrial cancer compared with those with abnormal uterine bleeding that is managed with medication.<sup>[11]</sup> The data were collected from a population-based cohort in the U.S. and included a total of 234,721 women with abnormal bleeding, 4776 of whom underwent endometrial ablation. During a median follow-up period of 4.1 years, three women with a history of endometrial ablation and 601 women who were treated medically developed endometrial cancer. There was not a statistically significant difference in endometrial cancer rates between groups (age-adjusted HR=0.61, 95% CI, 0.20 to 1.89, p=0.17). Moreover, the median time to endometrial cancer diagnosis, 237 days after ablation and 299 days with medical management, did not differ significantly between groups.

## Section Summary

Adverse events have been associated with endometrial ablation procedures. Certain types of adverse events are more likely to occur with specific approaches to endometrial ablation. Due to lack of information about the total number of procedures and the number of each type of endometrial ablation procedure performed, conclusions cannot be drawn from these data about the relative safety of different types of endometrial ablation procedures.

## PRACTICE GUIDELINE SUMMARY

### PRACTICE COMMITTEE OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

In 2008, the American Society for Reproductive Medicine (ASRM) reviewed their 2006 Practice Committee report and reissued their statement on indications and options for endometrial ablation.<sup>[12]</sup> Conclusions were:

- “Endometrial ablation is an effective therapeutic option for the management of menorrhagia.
- Hysteroscopic and nonhysteroscopic techniques for endometrial ablation offer similar rates of symptom relief and patient satisfaction.
- Later definitive surgery may be required in 6% to 20% of women after endometrial ablation.
- Women who undergo hysterectomy after a failed endometrial ablation report significantly more satisfaction after 2 years of follow-up.
- Endometrial ablation generally is more effective when the endometrium is relatively thin.
- Ideally, hysteroscopic methods for endometrial ablation should be performed using a fluid monitoring system to reduce the risks and complications relating to fluid overload and electrolyte imbalance.

- Nonhysteroscopic methods for endometrial ablation require less skill and operating time.”

A 2015 patient fact sheet from the ASRM states that women who meet the following criteria should not have endometrial ablation:

“Women who are pregnant, who would like to have children in the future, or have gone through menopause should not have this procedure.”<sup>[13]</sup>

## **AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS**

The American Congress of Obstetricians and Gynecologists (ACOG) published a practice bulletin on endometrial ablation in 2007, which was later reaffirmed in 2013, 2015, and 2018.<sup>[14]</sup> ACOG made the following recommendations, as being based on good and consistent evidence:

“For women with normal endometrial cavities, resectoscopic endometrial ablation and nonresectoscopic endometrial ablation systems appear to be equivalent with respect to successful reduction in menstrual flow and patient satisfaction at 1 year following index surgery.”

“Resectoscopic endometrial ablation is associated with a high degree of patient satisfaction but not as high as hysterectomy.”

In addition, the ACOG practice bulletin regarding endometrial ablation included the following statement regarding preoperative evaluation:

“The structure and histology of the endometrial cavity should be thoroughly evaluated, both to assess for malignancy or endometrial hyperplasia and to ensure that the length and configuration is suitable for endometrial ablation. These parameters will vary depending on the technique or system used. Endometrial sampling, typically with an outpatient technique, can be used to evaluate all women for hyperplasia or malignancy, and results should be reviewed before ablation is scheduled. Women with endometrial hyperplasia or uterine cancer should not undergo endometrial ablation.”

In 2013, ACOG published guidelines (reaffirmed in 2017) regarding the management of acute abnormal uterine bleeding (AUB) in nonpregnant reproductive-aged women.<sup>[15]</sup> Recommendations regarding laboratory testing and imaging of these patients are as follows:

“Endometrial tissue sampling should be performed in patients with AUB who are older than 45 years as a first-line test. Endometrial sampling also should be performed in patients younger than 45 years with a history of unopposed estrogen exposure (such as seen in patients with obesity or polycystic ovary syndrome), failed medical management, and persistent AUB.”

Recommendations regarding surgical management of women who do not respond to medical management of symptoms are as follows:

“Surgical options include dilation and curettage (D&C), endometrial ablation, uterine artery embolization, and hysterectomy.”

“Endometrial ablation, although readily available in most centers, should be considered only if other treatments have been ineffective or are contraindicated, and it should be

performed only when a woman does not have plans for future childbearing and when the possibility of endometrial or uterine cancer has been reliably ruled out as the cause of the acute AUB.”

The 2013, ACOG practice bulletin regarding the management of abnormal uterine bleeding associated with ovulatory dysfunction (AUB-O) was reaffirmed in 2018.<sup>[16]</sup> The following recommendation is made primarily based upon consensus and expert opinion:

“Endometrial ablation is not recommended as a first-line therapy for AUB-O. Physicians must provide thorough informed consent and adequate counseling to women with AUB-O who desire endometrial ablation.”

Furthermore, the practice bulletin recommends combined hormonal contraceptive therapy or progestin therapy, and other medical management depending upon age group and menopause status. The bulletin stresses that contraindications to combined hormonal contraceptive therapy should be excluded.

## **SOCIETY FOR GYNECOLOGIC SURGEONS**

In 2012, the Society for Gynecologic Surgeons (SGS) published a clinical practice guideline on treatment of abnormal uterine bleeding.<sup>[17]</sup> The guideline recommends that, in women with bleeding caused mainly by ovulatory disorders or endometrial hemostatic disorders, any of the following treatments may be chosen depending on patient values and preferences: hysterectomy, endometrial ablation, systemic medical therapies or levonorgestrel-releasing intrauterine systems. In choosing between endometrial ablation and hysterectomy, if the patient’s preference is for amenorrhea, less pain or avoiding additional therapy, hysterectomy is suggested. If the patient’s preference is for lower operative and postoperative procedural risk, and a shorter hospital stay, endometrial ablation is recommended.

## **SUMMARY**

There is enough research to show that endometrial ablation improves overall health outcomes in women who have failed prior treatment for abnormal uterine bleeding and are otherwise considering hysterectomy. Clinical guidelines recommend endometrial ablation for clinical scenarios that generally align with the policy criteria. Therefore, endometrial ablation may be considered medically necessary when criteria are met.

Evidence and guidelines do not support the use of endometrial ablation when policy criteria are not met. Therefore, endometrial ablation for indications or using techniques other than those specified in policy criteria are considered not medically necessary.

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## CODES

Codes	Number	Description
CPT	58353	Endometrial ablation, without hysteroscopic guidance
	58356	Endometrial cryoablation with ultrasonic guidance, including endometrial curettage, when performed
	58563	Hysteroscopy, surgical, with endometrial ablation (e.g., endometrial resection, electrosurgical ablation, thermoablation)
HCPCS	None	

**Date of Origin:** September 2011

## ***Cochlear Implant***

**Effective:** July 1, 2020

**Next Review:** March 2021

**Last Review:** May 2020

### **IMPORTANT REMINDER**

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

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

## **DESCRIPTION**

A cochlear implant is a device for treatment of severe-to-profound hearing loss in individuals who only receive limited benefit from amplification with hearing aids.

## **MEDICAL POLICY CRITERIA**

### **Notes:**

- This policy does not apply to surgically anchored bone-conduction hearing aids or externally worn air-conduction hearing aids. Cochlear implants are not hearing aids. While hearing aids function by amplifying sound, cochlear implants replace the functions of an absent or nonfunctioning cochlea.
- This policy does not address the use of the Nucleus® 24 Auditory Brain Stem Implant, which is designed to restore hearing in patients with neurofibromatosis who are deaf secondary to removal of bilateral acoustic neuromas.
- Hybrid cochlear implant/hearing aid systems are devices that include a hearing aid integrated into the external sound processor of the cochlear implant. If hearing aid components of such systems are billed separately, there may be specific member benefit language addressing coverage of hearing aids that would be applicable. Contract language takes precedence over medical policy.

- Repeat hearing tests or trials of hearing aids are not necessary for patients who have previously met Criteria I. and II. as it is unlikely that natural hearing or the benefit from hearing aids will improve significantly over time.

I. **Unilateral or bilateral implantation of cochlear implants, other than cochlear implant/hearing aid hybrid devices, and associated aural rehabilitation may be considered **medically necessary** when all of the following criteria (A. – D.) are met:**

A. Meets one of the following age requirements:

1. Age 9 months or older for the Nucleus 24 cochlear implant system (with any of the Cochlear® sound processors); or
2. Age 12 months or older.

B. Meets one or more of the following:

1. Patients diagnosed with enlarged vestibular aqueduct (EVA) (greater than 1mm at the midpoint), as evidenced by MRI or CT imaging; or
2. Patients with both of the following (a and b):
  - a. Bilateral severe to profound pre- or postlingual (sensorineural) hearing loss, defined as a pure-tone average of 70 decibels (dB) hearing threshold or greater at 500 Hz (hertz), 1000 Hz and 2000 Hz; and
  - b. Limited or no benefit from hearing aids (defined below) unless hearing aids are unreasonable.
    - i. Adults: Scores less than or equal to 50 percent correct on tape recorded sets of open-set sentence recognition in the ear to be implanted.
    - ii. Children: Failure to develop basic auditory skills, and in older children, less than or equal to 30 percent correct on open-set tests.

C. Implanted device is FDA approved (PMA or 510k only).

D. Patients do not have any of the following contraindications:

1. Deafness due to lesions of the acoustic nerve (eighth cranial nerve), central auditory pathways, or brain stem in the implanted ear.
2. Active or chronic infections of the external or middle ear and mastoid cavity in the implanted ear, including but not limited to otitis media.
3. Tympanic membrane perforation.
4. Radiographic evidence of absent cochlear development in the implanted ear.
5. Inability or lack of willingness to participate in post-implantation aural rehabilitation.

II. **Unilateral implantation of hybrid cochlear implant/hearing aid systems that include the hearing aid integrated into the external sound processor of the cochlear implant may be considered **medically necessary** when all of the following criteria are met (A. – F.):**

- A. Age 18 years or older.
  - B. Bilateral severe to profound pre- or postlingual (sensorineural) hearing loss, defined as a pure-tone average of 70 decibels (dB) hearing threshold or greater at 500 Hz (hertz), 1000 Hz and 2000 Hz.
  - C. Limited or no benefit from hearing aids unless hearing aids are unreasonable, defined as scores less than 50 percent correct on tape recorded sets of open-set sentence recognition in the ear selected for implantation.
  - D. Meets all of the following (1. and 2.):
    - 1. All of the following in the ear selected for implantation (a. – c.):
      - a. Low frequency hearing thresholds no poorer than 60 dB hearing level up to and including 500 Hz (averaged over 125, 250, and 500 Hz; i.e., threshold average of 125, 250, and 500 Hz less than or equal to 60 dB hearing level); and
      - b. Severe to profound mid-to-high frequency hearing loss (threshold average of 2000, 3000, and 4000 Hz greater than or equal to 75 dB hearing level); and
      - c. Aided consonant-nucleus-consonant word recognition score from 10 percent to 60 percent in the preoperative aided condition.
    - 2. All of the following for the contralateral ear (a and b):
      - a. Moderately severe to profound mid-to-high frequency hearing loss (threshold average of 2000, 3000, and 4000 Hz greater than or equal to 60 dB hearing level); and
      - b. Aided consonant-nucleus-consonant word recognition score equal to or better than that of the ear selected for implantation but not more than 80 percent correct.
  - E. Implanted device is FDA approved (PMA or 510k only).
  - F. Does not have any of the following contraindications:
    - 1. Deafness due to lesions of the acoustic nerve (eighth cranial nerve), central auditory pathways, or brain stem in the implanted ear
    - 2. Active or chronic infections of the external or middle ear and mastoid cavity in the implanted ear, including but not limited to otitis media
    - 3. Tympanic membrane perforation
    - 4. Radiographic evidence of absent cochlear development in the implanted ear
    - 5. Inability or lack of willingness to participate in post-implantation aural rehabilitation
    - 6. A duration of severe to profound hearing loss of 30 years or greater.
- III. Implantation of cochlear implants is considered **not medically necessary** when Criterion I. or II. above is not met.
- IV. **Implant replacement**, including **replacement parts or upgrades** to existing cochlear implants and/or components, may be considered **medically necessary** when

components are no longer functional, or for functional devices only in the small subset of patients whose response to existing components is inadequate to the point of interfering with activities of daily living, which would include school and work.

- V. **Implant replacement, including replacement parts or upgrades** to existing cochlear implants and/or components, are considered **not medically necessary** when Criterion IV. is not met, including but not limited to upgrades of existing, functioning external systems to achieve aesthetic improvement, such as smaller profile components, or a switch from a body-worn external sound processor to a behind-the-ear (BTE) model.

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

## POLICY GUIDELINES

A Pure Tone Average (PTA) is determined by averaging the hearing threshold levels at a set of specified frequencies: for example, 500, 1000, and 2000 Hz ( $PTA = 500 \text{ Hz (T)} + 1000 \text{ Hz (T)} + 2000 \text{ Hz (T)} \div 3$ ).

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION:

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

- History and Physical/Chart Notes
- Manufacturer and Model Name of Cochlear Implant being requested
- Audiology test results

## CROSS REFERENCES

1. [Transcutaneous Bone-Conduction and Bone-Anchored Hearing Aids](#), Surgery, Policy No. 121

## BACKGROUND

A cochlear implant provides direct electrical stimulation to the auditory nerve, bypassing the usual transducer cells that are absent or nonfunctional in deaf cochlea. The basic components of a cochlear implant include both external and internal components. The external components include a microphone, an external sound processor, and an external transmitter. The internal components are implanted surgically and include an internal receiver implanted within the temporal bone, and an electrode array that extends from the receiver into the cochlea through a surgically created opening in the round window of the middle ear.

Sounds that are picked up by the microphone are carried to the external signal processor, which transforms sound into coded signals that are then transmitted transcutaneously to the implanted internal receiver. The receiver converts the incoming signals to electrical impulses that are then conveyed to the electrode array, ultimately resulting in stimulation of the auditory nerve.

Hearing loss is rated on a scale based on the threshold of hearing. Severe hearing loss is defined as a bilateral hearing threshold of 70-90 decibels (dB) and profound hearing loss is defined as a hearing threshold of 90 dB and above.

A post-cochlear implant rehabilitation program is necessary to achieve benefit from the cochlear implant. The rehabilitation program includes development of skills in understanding running speech, recognition of consonants and vowels, and tests of speech perception ability.

## REGULATORY STATUS

Note: Full FDA approval includes only Premarket Approval (PMA) and 510k approval. Devices with Investigational Device Exemption (IDE) or Humanitarian Device Exemption (HDE) are not considered fully FDA approved.

Several cochlear implants are commercially available in the United States. The FDA-labeled indications for currently marketed electrode arrays are summarized in the table below. Over the years, subsequent generations of the various components of the devices have been FDA approved, focusing on improved electrode design and speech-processing capabilities. Furthermore, smaller devices and the accumulating experience in children have resulted in broadening of the selection criteria to include children as young as 9 months.

Manufacturer and FDA approved Cochlear Implants	Indications for Adults or Children
<b>CONVENTIONAL COCHLEAR IMPLANTS</b>	
<p><b>Advanced Bionics®</b></p> <ul style="list-style-type: none"> <li>HiRes™ Ultra implant</li> <li>HiResolution Bionic Ear System (HiRes 90K*)</li> </ul> <p>Sound Processors:</p> <ul style="list-style-type: none"> <li>ClearVoice</li> <li>HiRes Fidelity 120</li> <li>HiRes Optima</li> </ul> <p>Predecessors:</p> <ul style="list-style-type: none"> <li>Clarion Multi-Strategy</li> <li>HiFocus CII Bionic Ear</li> </ul>	<p><u>Adults:</u></p> <ul style="list-style-type: none"> <li>≥ 18 years of age</li> <li>Post-lingual onset of severe to profound bilateral sensorineural hearing loss [≥70 decibels (dBs)]</li> <li>Limited benefit from appropriately fitted hearing aids, defined as scoring ≤ 50% on a test of open-set Hearing in Noise Test (HINT) sentence recognition</li> </ul> <p><u>Children:</u></p> <ul style="list-style-type: none"> <li>12 months to 17 years of age</li> <li>Profound bilateral sensorineural deafness (&gt;90dB)</li> <li>Use of appropriately fitted hearing aids for at least 6 months in children 2 to 17 years of age or at least 3 months in children 12 to 23 months of age.</li> <li>Lack of benefit in children &lt;4 years of age is defined as a failure to reach developmentally-appropriate auditory milestones (e.g., spontaneous response to name in quiet or to environmental sounds) measured using the Infant-Toddler Meaningful Auditory Integration Scale or Meaningful Auditory Integration Scale or &lt; 20% correct on a simple open-set word recognition test (Multisyllabic Lexical Neighborhood Test) administered using monitored live voice [70 dB SPL (sound pressure level)]</li> <li>Lack of hearing aid benefit in children &gt;4 years of age is defined as scoring &lt; 12% on a difficult open-set word recognition test (Phonetically Balanced-Kindergarten Test) or &lt; 30% on an open-set sentence test (HINT for Children)</li> </ul>

Manufacturer and FDA approved Cochlear Implants	Indications for Adults or Children
	administered using recorded materials in the soundfield (70 dB SPL)
<p><b>Cochlear®</b></p> <ul style="list-style-type: none"> <li>Nucleus 24 Implant</li> </ul> <p>Sound Processors:</p> <ul style="list-style-type: none"> <li>Kanso™</li> <li>Nucleus® 7</li> <li>Nucleus® 6</li> <li>Nucleus® 5*</li> <li>Nucleus Freedom</li> </ul> <p>Predecessors:</p> <ul style="list-style-type: none"> <li>Nucleus 22, 24</li> </ul>	<p style="text-align: center;"><u>Adults:</u></p> <ul style="list-style-type: none"> <li>≥ 18 years old</li> <li>Pre- or post-lingual onset of moderate to profound bilateral sensorineural hearing loss</li> <li>≤50% sentence recognition in the ear to be implanted</li> <li>≤60% sentence recognition in the opposite ear or binaurally</li> </ul> <p style="text-align: center;"><u>Children 9 months to 24 months:</u></p> <ul style="list-style-type: none"> <li>Profound sensorineural hearing loss bilaterally</li> <li>Limited benefit from appropriate binaural hearing aids</li> <li>Lack of progress in the development of auditory skills</li> </ul> <p style="text-align: center;"><u>Children 25 months to 17 years 11 months:</u></p> <ul style="list-style-type: none"> <li>Severe to profound bilateral sensorineural hearing loss</li> <li>Multi-syllabic Lexical Neighborhood Test (MLNT) scores of ≤30% in best-aided condition in children 25 months to 4 years 11 months</li> <li>Lexical Neighborhood Test (LNT) scores of ≤30% in best-aided condition in children 5 years to 17 years and 11 months</li> <li>Lack of progress in the development of auditory skills</li> </ul>
<p><b>Med EI®</b></p> <ul style="list-style-type: none"> <li>Maestro system</li> <li>Synchrony Implant</li> <li>Synchrony 2 Implant</li> <li>Concerto Implant</li> </ul> <p>Sound Processors:</p> <ul style="list-style-type: none"> <li>Sonnet</li> <li>Sonnet 2</li> <li>Concerto implant</li> <li>Opus</li> <li>Opus 2</li> <li>Rondo 2</li> </ul> <p>Predecessors:</p> <ul style="list-style-type: none"> <li>Combi 40+</li> <li>Sonata</li> <li>Pulsar</li> </ul>	<p style="text-align: center;"><u>Bilateral Hearing Loss</u></p> <p style="text-align: center;"><u>Adults:</u></p> <ul style="list-style-type: none"> <li>≥ 18 years old</li> <li>Severe to profound bilateral sensorineural hearing loss (≥70dB)</li> <li>≤40% correct Hearing in Noise test (HINT) sentences with best-sided listening condition</li> </ul> <p style="text-align: center;"><u>Children:</u></p> <ul style="list-style-type: none"> <li>12 months to 18 years with profound sensorineural hearing loss (≥90dB)</li> <li>In younger children, little or no benefit is defined by lack of progress in the development of simple auditory skills with hearing aids over a 3-6 month period</li> <li>In older children, lack of aided benefit is defined as &lt;20% correct on the MLNT or LNT depending upon the child's cognitive ability and linguistic skills</li> <li>A 3-6 month trial with hearing aids is required if not previously experienced</li> </ul> <p style="text-align: center;"><u>Single-Sided Deafness and Asymmetric Hearing Loss</u></p> <ul style="list-style-type: none"> <li>≥ 5 years old</li> <li>Single-sided deafness (SSD) or asymmetric hearing loss (AHL), where: <ul style="list-style-type: none"> <li>SSD is defined as profound sensorineural hearing loss in one ear and normal hearing or mild sensorineural hearing loss in the other ear.</li> </ul> </li> </ul>

Manufacturer and FDA approved Cochlear Implants	Indications for Adults or Children
	<ul style="list-style-type: none"> <li>○ AHL is defined as a profound sensorineural hearing loss in one ear and mild to moderately severe sensorineural hearing loss in the other ear, with a difference of at least 15 dB in pure tone averages (PTAs) between ears.</li> <li>• Limited benefit from an appropriately fitted unilateral hearing aid in the ear to be implanted.</li> <li>• For ages 18 years-old and above, limited benefit from unilateral amplification is defined by test scores of 5% correct or less on monosyllabic consonant-nucleus-consonant (CNC) words in quiet when tested in the ear to be implanted alone.</li> <li>• For ages between 5 and 18 years-old, insufficient functional access to sound in the ear to be implanted must be determined by aided speech perception test scores of 5% or less on developmentally appropriate monosyllabic word lists when tested in the ear to be implanted alone</li> <li>• At least 1 month experience wearing a Contra Lateral Routing of Signal (CROS) hearing aid or other relevant device and not show any subjective benefit</li> </ul>
<b>HYBRID COCHLEAR IMPLANTS</b>	
<b>Cochlear®</b> <ul style="list-style-type: none"> <li>• Nucleus® Hybrid™ L24 Cochlear Implant (Nucleus 6)</li> </ul>	<p style="text-align: right;"><u>Adults:</u></p> <ul style="list-style-type: none"> <li>• ≥ 18 years old</li> <li>• Residual low-frequency hearing sensitivity</li> <li>• Severe to profound high-frequency sensorineural hearing loss</li> <li>• Limited benefit from appropriately fit bilateral hearing aids</li> </ul>
<b>Med EI®</b> <ul style="list-style-type: none"> <li>• Med EL EAS™</li> </ul>	<p style="text-align: right;"><u>Adults:</u></p> <ul style="list-style-type: none"> <li>• ≥ 18 years old</li> <li>• Residual low-frequency hearing sensitivity</li> <li>• Severe to profound high-frequency sensorineural hearing loss</li> <li>• Candidates should go through a suitable hearing aid trial, unless already appropriately fit with hearing aids</li> </ul>
<b>RECENTLY FDA-APPROVED DEVICES</b>	
<ul style="list-style-type: none"> <li>• New devices that come onto the market are added to the policy at policy updates. In the interim, new devices may be approved for coverage for FDA-approved indications when applicable criteria are met.**</li> </ul>	

\*Note: Cochlear, Ltd. voluntarily recalled the Nucleus CI500 range in September 2011 for device malfunction in the CI512 implant. The external Nucleus 5 sound processor is not a part of the recall. Advanced Bionics HiRes90K was voluntarily recalled in November 2010 and given FDA-approval for re-entry to market the device in September 2011.

\*\* FDA-approved indications can be found by searching by device name in the FDA [510\(k\) Premarket Notification Database](#) or the [De Novo Database](#) and viewing the Summary.

While cochlear implants have typically been used mono laterally, in recent years, interest in bilateral cochlear implantation has arisen. The proposed benefits of bilateral cochlear implants are to improve understanding of speech in noise and localization of sounds. Improvements in speech intelligibility may occur with bilateral cochlear implants through binaural summation; i.e., signal processing of sound input from two sides may provide a better representation of

sound and allow one to separate out noise from speech. Speech intelligibility and localization of sound or spatial hearing may also be improved with head shadow and squelch effects, i.e., the ear that is closest to the noise will be received at a different frequency and with different intensity, allowing one to sort out noise and identify the direction of sound. Bilateral cochlear implantation may be performed independently with separate implants and speech processors in each ear or with a single processor. However, no single processor for bilateral cochlear implantation has been FDA approved for use in the United States. In addition, single processors do not provide binaural benefit and may impair localization and increase the signal to noise ratio received by the cochlear implant.

In March 2014, FDA approved the Nucleus® Hybrid™ L24 Cochlear Implant System (Cochlear Corporation) through the premarket approval process.<sup>[1]</sup> This system is a hybrid cochlear implant and hearing aid, with the hearing aid integrated into the external sound processor of the cochlear implant. It is indicated for unilateral use in patients aged 18 years and older who have residual low-frequency hearing sensitivity and severe to profound high-frequency sensorineural hearing loss, and who obtain limited benefit from appropriately fit bilateral hearing aid. The electrode array inserted into the cochlea is shorter than conventional cochlear implants. According to the FDA's premarket approval notification, labeled indications for the device include:

- Preoperative hearing in the range from normal to moderate hearing loss (HL) in the low frequencies (thresholds no poorer than 60 dB HL up to and including 500 Hz).
- Preoperative hearing with severe to profound mid- to high-frequency hearing loss (threshold average of 2000, 3000, and 4000 Hz  $\geq 75$  dB HL) in the ear to be implanted.
- Preoperative hearing with moderately severe to profound mid- to high-frequency hearing loss (threshold average of 2000, 3000, and 4000 Hz  $\geq 60$  dB HL) in the contralateral ear.
- Consonant-Nucleus-Consonant (CNC) word recognition score between 10% to 60% (inclusively) in the ear to be implanted in the preoperative aided condition and in the contralateral ear equal to or better than that of the ear to be implanted but not more than 80% correct.

In September 2016, FDA approved the Med EL EAS™ (Electric Acoustic Stimulation) Hearing Implant System (Med EL Corp.).<sup>[2]</sup> This system is a hybrid cochlear implant and hearing aid, with the hearing aid integrated into the external sound processor of the cochlear implant. It is the combination of the SYNCHRONY cochlear implant and the SONNET EAS audio processor. According to the FDA's premarket approval notification:<sup>[3]</sup>

The MED-EL EAS System is indicated for partially deaf individuals aged 18 years and older who have residual hearing sensitivity in the low frequencies sloping to a severe/profound sensorineural hearing loss in the mid to high frequencies, and who obtain minimal benefit from conventional acoustic amplification. Typical preoperative hearing of candidates ranges from normal hearing to moderate sensorineural hearing loss in the low frequencies (thresholds no poorer than 65 dB HL up to and including 500 Hz) with severe to profound mid- to high-frequency hearing loss (no better than 70 dB HL at 2000 Hz and above) in the ear to be implanted. For the non-implanted ear, thresholds may be worse than the criteria for the implanted ear, but may not be better. The CNC word recognition score in quiet in the best-aided condition will be 60% or less, in the ear to be implanted and in the contralateral ear. Prospective candidates should go through a suitable hearing aid trial, unless already appropriately fit with hearing aids.

## EVIDENCE SUMMARY

Cochlear implants (CI) are recognized effective treatment of sensorineural deafness in select patient, as noted in a 1995 National Institutes of Health Consensus Development conference, which offered the following conclusions:<sup>[4]</sup>

- Cochlear implantation has a profound impact on hearing and speech reception in postlingually deafened adults with positive impacts on psychological and social functioning.
- The results are more variable in children. Benefits are not realized immediately but rather are manifested over time, with some children continuing to show improvement over several years.
- Prelingually deafened adults may also benefit, although to a lesser extent than postlingually deafened adults. These individuals achieve minimal improvement in speech recognition skills. However, other basic benefits, such as improved sound awareness, may meet safety needs.
- Training and educational intervention are fundamental for optimal post implant benefit.
- Cochlear implants in children under two years old are complicated by the inability to perform detailed assessment of hearing and functional communication. However, a younger age of implantation may limit the negative consequences of auditory deprivation and may allow more efficient acquisition of speech and language. Some children with post-meningitis hearing loss have been implanted under the age of two years due to the risk of new bone formation associated with meningitis, which may preclude a cochlear implant at a later date.

### ENLARGED VESTIBULAR AQUEDUCTS (EVA)

Enlarged vestibular aqueduct (also known as enlarged vestibular aqueduct syndrome (EVAS), large vestibular aqueduct, large vestibular aqueduct syndrome (LVAS), or dilated vestibular aqueduct) is a condition which is associated with childhood hearing loss. According to the NIH National Institute on Deafness and other Communication Disorders (NIDCD):<sup>[5]</sup> most children with enlarged vestibular aqueducts (EVA) will develop some amount of hearing loss, and approximately 5-15% of children with sensorineural hearing loss (hearing loss caused by damage to sensory cells inside the cochlea) have EVA.

### Systematic Reviews

In 2014, Xu conducted a systematic review in Chinese to assess the efficacy and safety of cochlear implantation in deaf patients with inner ear malformations compared to deaf patients with normal inner ear structure, including 11 RTCs (N=655 patients).<sup>[6]</sup> In terms of postoperative complications, electrode impedance, behavior T-level, hearing abilities and speech discrimination; patients with mixed inner ear malformations, Mondini syndrome or EVA were not significantly different than controls. However, the reviewers concluded that additional larger controlled studies with longer follow-up may help to evaluate the efficacy of cochlear implantation for deaf patients with inner ear malformation more reliably.

In 2012, Pakdaman conducted a systematic review to determine if abnormal cochleovestibular anatomy influences surgical and audiologic outcomes following cochlear implant (CI) surgery in children, including 22 studies.<sup>[7]</sup> Out of the 311 children included, 89 (29%) were diagnosed with EVA, considered to be a mild/moderate anomaly. Outcomes of CI surgery were analyzed based on the severity of the ear malformation (mild/moderate anomaly versus severe), and subgroup analyses were not performed based on the different malformations observed. The

reviewers reported that severe inner ear dysplasia was associated with increased surgical difficulty and lower speech perception.

## **Nonrandomized Studies**

There have been a number of case series and retrospective analyses published on the efficacy of cochlear implants in patients with EVA, all generally reporting an improvement of outcomes including various clinical scores for hearing improvement and scores measuring quality of life. These studies range in size from three to 47 cases.<sup>[8-18]</sup> Some of these studies have focused on pediatric patients, while others have included mixed patient populations and have not analyzed pediatric patients from adults in terms of outcomes. Overall, these studies report that outcomes in EVA patients are comparable to cochlear implant patients with no malformations, including similar risk of cerebrospinal fluid (CSF) gusher during cochlear implantation.

There is research indicating that the age of cochlear implantation for patients with EVA affects health outcomes. In 2013, Ko conducted a study (1) to assess health outcomes of Mandarin-speaking patients with EVA after cochlear implantation (CI); (2) to compare their performance with a group of CI users without EVA; (3) to understand the effects of age at implantation and duration of implant use on the CI outcomes.<sup>[19]</sup> Forty-two patients with EVA participating in this study were divided into two groups: the early group received CI before five years of age and the late group after five years of age. The patients with EVA with more than five years of implant use (18 cases) achieved a mean score higher than 80% on the most recent speech perception tests and reached the highest level on the CAP/SIR scales. The early group developed speech perception and intelligibility steadily over time, while the late group had a rapid improvement during the first year after implantation. The two groups, regardless of their age at implantation, reached a similar performance level. These patients do not necessarily need to wait until their hearing thresholds are higher than 90 dB HL or PB word score lower than 40% to receive CI. Similar results have been reported in small pediatric case series, indicating that if patients receive cochlear implants prior to becoming severely to profoundly deaf, that residual hearing is preserved.<sup>[8,20]</sup>

In contrast to studies reporting favorable outcomes, one small retrospective study performed by Bichy in 2002 that reported better hearing outcomes in patients with EVA using hearing aid than those who had undergone cochlear implantation.<sup>[21]</sup> The analysis in this study included 16 children and adults with EVA that had undergone cochlear implantation and 10 children and adults undergoing treatment of progressive or fluctuant sensorineural hearing loss with the use of a hearing aid alone. Although the hearing aid group had a better mean pure-tone average (70.8 dB; SD 24.4) versus (107.0 dB; SD 21.7) for the cochlear implant group, the use of health utility indexes determined that greater net health benefit (including quality of life) was derived from cochlear implantation over hearing aids.

## **INFANTS UNDER AGE 12 MONTHS**

The literature review focused on studies comparing the impact on hearing, speech development and recognition, and complication rates of implantation in infants younger than 12 months with those of older age groups. This includes the question of whether any early benefits that may occur in these very young patients later converge with those in older patients.

## **Systematic Reviews**

Two systematic reviews were identified that addressed CI in children under 12 months of age. The reviews, summarized below, reported few studies of CI in this age group compared with CI in children over one year of age. Both systematic reviews ranked the available studies as poor to fair due to heterogeneity in study participants and study designs, and high risk for potential bias. In addition, differences in outcomes between the age groups did not reach statistical significance. Therefore, it remains unclear whether the benefits of early cochlear implantation outweigh the risk of surgery and anesthesia in these very young patients.

In 2011 Forli reported similar findings in seven studies comparing CI implanted prior to one year of age with implantations performed after one year of age.<sup>[22]</sup> The studies precluded meta-analysis due to heterogeneity of age ranges analyzed and outcomes evaluated. While studies suggested improvements in hearing and communicative outcomes in children receiving implants prior to one year of age, between-group differences did not reach statistical significance. In addition, it is not certain whether any improvements were related to duration of cochlear implant usage rather than age of implantation. Nor is it clear whether any advantages of early implantation are retained over time.

In 2010, Vlastarakos conducted a systematic review of studies on bilateral cochlear implants in a total of 125 children implanted before one year of age.<sup>[23]</sup> The authors noted that follow-up times ranged from a median duration of 6 to 12 months and, while results seemed to indicate accelerated rates of improvement in implanted infants, the evidence available was limited and of lower quality. Additionally, the lack of reliable outcome measures for infants demonstrated the need for further research before cochlear implantation prior to one year of age becomes widespread.

## **Nonrandomized Studies**

In March 2020, the FDA approved an expansion of the indications for Cochlear Americas' Nucleus 24 cochlear implant system for infants aged 9 to 12 months of age with bilateral profound sensorineural deafness who demonstrate limited benefit from appropriate binaural hearing aids. Previously, this device was approved for ages 12 months and older. According to the FDA's summary of safety and effectiveness data, approval was based on supporting evidence from a comprehensive literature review and a clinical feasibility study. The clinical feasibility study was a retrospective clinical analysis of 84 subjects implanted with cochlear implants between the ages of 9 and 12 months. Descriptive statistics were reported for time under anesthesia (unilateral: 2hrs 34min, bilateral: 4hrs 15min), estimated blood loss (unilateral: 10.75 cc, bilateral: 19.88 cc), time in recovery (unilateral: 2hr 18min, bilateral: 1hr 59min), and adverse events (Percent of subjects: 2.4% cerebral spinal fluid leak; 2.4% facial weakness; 2.4% infection; 7.1% minor post-op complication; 3.6% minor skin irritation; 3.6% otitis media; 2.4% seroma; 7.1% temperature regulation during procedure).

The supporting literature review identified 49 articles including 750 total (not necessarily unique) patients implanted with cochlear implants prior to 12 months of age. Safety results were reported on a per-study basis with no meta-analysis. Complication rates were reported between 1.5% and 10% except for two studies. One reported a rate of 29%, and the other reported on two techniques, one of which had a rate of 20.6% and the other 61.5%. Two studies compared complications across different age ranges. One reported similar complication rates across ages and the other reported higher rates for younger ages. The summary section states that the study findings support that the safety profile for cochlear implantation in pediatric patients who are implanted between 9 and 12 months of age is

comparable to that of the currently approved population of age 12 months and older. Effectiveness results were reported on a per-study basis with no meta-analysis. No study reported worse hearing outcomes for the early-implanted group and many reported significantly better outcomes for this group.

A 2017 retrospective study by Kalejaiye assessed surgical complications, operative times, and reoperation rates in 73 patients under one year of age.<sup>[25]</sup> They compared these patients, identified from the American College of Surgeons National Surgical Quality Improvement Program Pediatric database (2012-2013), with pediatric patients in the database above the age of one. They found that the patients under one year had higher readmission rates (6.9% vs. 2.7%) and longer mean operative times (191 minutes vs. 160 minutes), but no significant differences were noted in complication rate, postoperative length of stay, or reoperation rate.

In 2015, Guerzoni conducted a prospective study of 28 children with profound sensorineural hearing loss who were implanted early with cochlear implants (mean age at device activation: 13.3 months).<sup>[26]</sup> The investigators reported that at one-year follow-up, assertiveness and responsiveness scores were within the normal range of normal-hearing age-matched peers. Age at cochlear implant activation exerted a significant impact, with the highest scores associated to the youngest patients.

In 2011, Colletti reported on the 10-year results comparing 19 children with cochlear implants received between the ages of 2 to 11 months to 21 children implanted between 12-23 months and 33 children implanted between 24 to 35 months.<sup>[27]</sup> Within the first six months post-implantation, there was no significant difference among groups in Category of Auditory Performance testing but differences became significantly better in the infant group (early implantation) at the 12 and 36 month testing. Previously, Colletti reported on findings from 13 infants who had implants placed before 12 months.<sup>[28]</sup> The procedures were performed between 1998 and 2004. In this small study, the rate of receptive language growth for these early implant infants overlapped scores of normal-hearing children. This overlap was not detected for those implanted at 12 to 23 or 24 to 36 months.

In 2009 Ching published an interim report on early language outcomes of children with cochlear implants.<sup>[29]</sup> This study evaluated 16 children who had implants before 12 months of age compared to 23 who had implants after 12 months (specific time of implantation was not provided). The preliminary results demonstrated that children who received an implant before 12 months of age developed normal language skills at a rate comparable to normal-hearing children, while those with later implants performed at two standard deviations below normal. The authors noted that these results are preliminary, as there is a need to examine the effect of multiple factors on language outcomes and the rate of language development.

Johr (2008) highlighted the surgical and anesthetic considerations when performing cochlear implant surgery in very young infants.<sup>[30]</sup> This was an observational study and literature review by pediatricians at a tertiary children's hospital in Switzerland. Surgical techniques and anesthetic management aspects of elective surgeries in small infants were analyzed in patients younger than one year of age undergoing cochlear implant surgeries. The results demonstrated that the age of the patient and the pediatric experience of the anesthesiologist, but not the duration of the surgery, are relevant risk factors. The authors concluded, "Further research is needed to provide more conclusive evidence that the performance outcome for children implanted before 12 months of age does not converge with the results of children implanted between 12 and 18 months."

## ADULTS AND CHILDREN OVER AGE 12 MONTHS

Since there is sufficient evidence that bilateral and unilateral cochlear implants are safe and lead to improvements in health outcomes in adults and children over the age of twelve months with bilateral severe to profound pre- or postlingual (sensorineural) hearing loss, the evidence reviewed below will be focused on systematic reviews and randomized studies. Nonrandomized studies will not be described in detail.

### Systematic Reviews

The following is a summary of the most recent systematic reviews related to CI. These reviews included a critical analysis of the quality of the included studies. While noting the heterogeneity of the studies, and the potential for bias, these reviews found that the studies consistently reported beneficial outcomes for both bilateral and unilateral CI in select children and adults compared with no hearing devices or with conventional hearing aids.

#### Adults

A technology assessment published by Health Quality Ontario in 2018 evaluated bilateral cochlear implantation in adults and children in separate analyses.<sup>[31]</sup> The literature search conducted through March 2017 identified 10 studies on bilateral cochlear implantation in adults: three RCTs and seven prospective observational studies. Two of the three RCTs included data from a single RCT and compared simultaneous bilateral with unilateral cochlear implantation for severe bilateral sensorineural hearing loss. The third RCT randomized 24 adult patients with severe bilateral sensorineural hearing loss to receive bilateral implantation immediately or after a six-month waiting period. The observational studies performed within- or between-patient comparisons of bilateral cochlear implantation with unilateral cochlear implantation with or without hearing aids in the nonimplanted ear. Study quality was evaluated using the GRADE system. The quality of the RCTs was high, medium, and low and the quality of the prospective observational studies ranged from very low to low. The GRADE of evidence for adults overall was rated moderate to high. Overall, the authors concluded that bilateral cochlear implantation improved sound localization, speech perception in noise, and subjective benefits of hearing and that the safety profile was acceptable.

In a meta-analysis, McRackan (2018) examined the impact of cochlear implantation on quality of life (QOL).<sup>[32]</sup> From 14 articles with 679 CI patients who met the inclusion criteria, pooled analyses of all hearing-specific QOL measures revealed a very strong improvement in QOL after cochlear implantation (SMD=51.77). Subset analysis of CI-specific QOL measures also showed very strong improvement (SMD=51.69). Thirteen articles with 715 patients met the criteria to evaluate associations between QOL and speech recognition. Pooled analyses showed a low positive correlation between hearing-specific QOL and word recognition in quiet ( $r=0.213$ ), sentence recognition in quiet ( $r=0.241$ ), and sentence recognition in noise ( $r=0.238$ ). A subset analysis of CI-specific QOL showed similarly low positive correlations with word recognition in quiet ( $r=0.213$ ), word recognition in noise ( $r=0.241$ ), and sentence recognition in noise ( $r=0.255$ ) between QOL and speech recognition ability. Using hearing-specific and CI-specific measures of QOL, patients report significantly improved QOL after cochlear implantation. This study is limited in that widely used clinical measures of speech recognition are poor predictors of patient-reported QOL with CIs.

In another meta-analysis, McRackan (2018) aimed to determine the change in general health-related quality of life (HRQOL) after cochlear implantation and association with speech recognition.<sup>[33]</sup> Twenty-two articles met criteria for meta-analysis of HRQOL improvement, but 15 (65%) were excluded due to incomplete statistical reporting. From the seven articles with 274 CI patients that met inclusion criteria, pooled analyses showed a medium positive effect of cochlear implantation on HRQOL (SMD=0.79). Subset analysis of the HUI-3 measure showed a large effect (SMD=0.84). Nine articles with 550 CI patients met inclusion criteria for meta-analysis of correlations between non-disease specific PROMs and speech recognition after cochlear implantation (word recognition in quiet [r=0.35], sentence recognition in quiet [r=0.40], and sentence recognition in noise [r=0.32]). Some limitations are, though regularly used, HRQOL measures are not intended to measure nor do they accurately reflect the complex difficulties facing CI patients. Only a medium positive effect of cochlear implantation on HRQOL was observed along with a low correlation between non-disease specific PROMs and speech recognition. The use of such instruments in this population may underestimate the benefit of cochlear implantation.

In 2013, the authors of the 2011 AHRQ technology assessment reported the following findings of an updated systematic review of studies published through May 2012:<sup>[34]</sup>

- Unilateral cochlear implants

Sixteen (of 42) studies were of unilateral cochlear implants. Most unilateral implant studies showed a statistically significant improvement in mean speech scores as measured by open-set sentence or multi-syllable word tests. A meta-analysis of four studies revealed a significant improvement in cochlear-implant relevant quality of life (QOL) after unilateral implantation. However, these studies varied in design and there was considerable heterogeneity observed across studies, making it difficult to compare outcomes across studies.

- Bilateral cochlear implants

Thirteen studies reported improvement in communication-related outcomes with bilateral implantation compared with unilateral implantation and additional improvements in sound localization compared with unilateral device use or implantation only. The risk of bias varied from medium to high across studies. Based on results from at least two studies, the QOL outcomes varied across tests after bilateral implantation. A meta-analysis was not performed because of heterogeneity in design between the studies.

In 2012 and 2013 Crathorne and van Schoonhoven, respectively, published updated systematic reviews for the National Institute for Health and Care Excellence (NICE). Included studies were from the U.S. and Europe and compared bilateral with unilateral cochlear implants. In two studies the unilateral implant group also had an acoustic hearing aid for the contralateral ear. Neither systematic review was able to conduct a meta-analysis due to the heterogeneity of the studies and the level of evidence of the studies which was rated as moderate-to-poor.

In October 2011, Berrettini published results of a systematic review of unilateral and bilateral cochlear implant effectiveness in adults.<sup>[35]</sup>

- Unilateral cochlear implants

Eight articles on unilateral cochlear implants in advanced age patients were included. All of the studies reported benefits with cochlear implantation despite advanced age at time of implant (age 70 years or older). In six studies, results were not significantly different between younger and older patients. However, two studies reported statistically significant inferior perceptive results (e.g., hearing in noise test and consonant nucleus consonant test) in older patients. This systematic review also examined three studies totaling 56 adults with pre-lingual deafness who received unilateral cochlear implants. The authors concluded unilateral cochlear implants provided hearing and quality-of-life benefits in prelingually deaf patients, but results were variable.

- Bilateral cochlear implants

Thirteen articles on bilateral cochlear implants were reviewed. Sound localization improved with bilateral cochlear implants compared with monaural hearing in six studies. Significant improvements in hearing in noise and in quiet environments with bilateral implants compared with unilateral implants were reported in ten studies and seven studies, respectively. Five of the studies reviewed addressed simultaneous implantation, five studies reviewed sequential implantation, and three studies included a mix of simultaneous and sequential implantation. However, no studies compared simultaneous to sequential bilateral implantation results, and no conclusions could be made on the timing of bilateral cochlear implantation.

In June 2011 the most recent technology assessment, by the Tufts Evidence-based Practice Center for the Agency for Health Care Research and Quality (AHRQ), reported the following findings on the effectiveness of unilateral and bilateral cochlear implants (CIs) in adults:<sup>[36]</sup>

- Unilateral cochlear implants

The assessment examined 22 studies with 30 or more patients and concluded that, while the studies reviewed were rated as poor to fair quality, unilateral cochlear implants are effective in adults with sensorineural hearing loss. Pre- and post-cochlear implant scores on multi-syllable tests and open-set sentence tests demonstrated significant gains in speech perception regardless of whether a contralateral hearing aid was used along with the cochlear implant. Additionally, the assessment found generic and disease-specific health-related quality of life improved with unilateral cochlear implants. However, the available evidence was insufficient to draw conclusions on improvements in open-set sentence test scores (i.e., >40% and ≤50% or >50% and ≤60%), and any relationship between pre-implantation patient characteristics and outcomes [e.g., age, duration of hearing impairment, Hearing in Noise Test (HINT) scores and pre- or post-linguistic deafness.]

- Bilateral cochlear implants

The technology assessment examined 16 studies published since 2004 which were determined to be of fair to moderate quality. The assessment concluded that bilateral cochlear implants provided greater benefits in speech perception test scores, especially in noise, when compared with unilateral cochlear implants with or without contralateral hearing aids. Significant binaural head shadow benefits were noted along with some benefit in binaural summation, binaural squelch effects, and sound localization with bilateral cochlear implants. However, it was unclear if these benefits were experienced under quiet

conditions, although benefits increased with longer bilateral cochlear implant usage indicating a need for longer term studies. Hearing-specific quality of life could not be assessed because only one study evaluated this outcome. Additionally, although gains were experienced in speech perception using open-set sentences or multi-syllable tests compared with unilateral cochlear implants or unilateral listening conditions, the evidence available on simultaneous bilateral implantation was found to be insufficient. The assessment noted longer term studies are needed to further understand the benefits with bilateral cochlear implantation and identify candidacy criteria given the risks of a second surgery and the destruction of the cochlea preventing future medical intervention.

## Children

The technology assessment published by Health Quality Ontario in 2018 discussed above regarding its findings on adult implantation identified 14 studies (all prospective observational studies) on bilateral cochlear implantation in children.<sup>[31]</sup> Two studies included both sequential and simultaneous bilateral implantation while the rest evaluated sequential only. As for adults, overall, the authors concluded that bilateral cochlear implantation improved sound localization, speech perception in noise, and subjective benefits of hearing and that the safety profile was acceptable (GRADE of evidence: moderate to high). The authors additionally concluded that bilateral cochlear implantation allowed for better language development and more vocalization in preverbal communication in children (GRADE of evidence: moderate).

In a 2015 systematic review, Fernandes evaluated 18 published studies and two dissertations that reported hearing performance outcomes for children with ANSD and cochlear implants.<sup>[37]</sup> Studies included four nonrandomized controlled studies considered high quality, five RCTs considered low quality, and 10 clinical outcome studies. Most studies (n=14) compared the speech perception in children with ANSD and cochlear implants with the speech perception in children with sensorineural hearing loss and cochlear implants. Most of these studies concluded that children with ANSD and cochlear implants developed hearing skills similar to those with sensorineural hearing loss and cochlear implants; however, these types of studies do not allow comparisons of outcomes between ANSD patients treated with cochlear implants and those treated with usual care.

In a 2014 systematic review, Lammers summarized the evidence on the effectiveness of bilateral cochlear implantation compared with unilateral implantation among children with sensorineural hearing loss.<sup>[38]</sup> The authors identified 21 studies that evaluated bilateral cochlear implantation in children, with no RCTs identified. Due to the limited number of studies, heterogeneity in outcomes and comparison groups, and high risk for bias in the studies, the authors were unable to perform pooled statistical analyses, so a best-evidence synthesis was performed. The best-evidence synthesis demonstrated that there was consistent evidence indicating the benefit of bilateral implantation for sound localization. One study demonstrated improvements in language development, although other studies found no significant improvements. The authors noted that the currently available evidence consisted solely of cohort studies that compared a bilaterally implanted group with a unilaterally implanted control group, with only one study providing a clear description of matching techniques to reduce bias.

In 2013, Eze published a systematic review comparing outcomes for cochlear implantation for children with developmental disability with those without developmental disability.<sup>[39]</sup> The authors noted that while approximately 30% to 40% of children who receive cochlear implants have developmental disability and that evidence about outcomes in this group was limited.

Their review included 13 studies that compared receptive or expressive language outcomes in children with cochlear implants with and without developmental disability. The included studies were heterogeneous in terms of comparator groups and outcome measures, precluding data pooling and meta-analysis. In a structured systematic review, the authors reported that seven of the eligible studies demonstrated a significantly poor cochlear implant outcome in children with developmental disability, while the remaining studies reported no significant difference in outcomes between the groups.

Humphriss (2013) published a systematic review evaluating outcomes after cochlear implantation among pediatric patients with auditory neuropathy spectrum disorder (ANSD), a sensorineural hearing disorder characterized by abnormal auditory brainstem response with preserved cochlear hair cell function as measured by otoacoustic emissions testing.<sup>[40]</sup> The authors identified 27 studies that included an evaluation of cochlear implantation in patients with ANSD, including 15 noncomparative studies, one that compared children with ANSD who received a cochlear implant with children with ANSD with hearing aids, and 12 that compared children with ANSD who received a cochlear implant with children with severe sensorineural hearing loss who received a cochlear implant. Noncomparative studies were limited in that most (11/15) did not include a measure of speech recognition before cochlear implantation. Among the comparative studies, those comparing cochlear implantation to “usual care”, typically a hearing aid, provided the most information about effectiveness of cochlear implantation among patients with ANSD; the one small study that used this design found no significant differences between the groups. Overall, the authors suggested that further RCT evidence is needed.

The 2011 Forli systematic review noted above also addressed the effect of bilateral versus unilateral cochlear implants on verbal perception in children. Bilateral CI improved verbal perception in noise, and sound localization compared with unilateral implants in 19 of 20 studies reviewed.<sup>[22]</sup> However, none of the studies compared learning development and language in bilateral versus unilateral cochlear implant recipients. Simultaneous versus sequential bilateral cochlear implantation results were not examined in any of the studies reviewed. Seven studies were reviewed that examined cochlear implant outcomes in children with associated disabilities. In this population, cochlear implant outcomes were inferior and occurred more slowly but were considered to be beneficial.

In a 2011 systematic review of 38 studies, Black sought to identify prognostic factors for cochlear implantation in pediatric patients.<sup>[41]</sup> A quantitative meta-analysis was not able to be performed due to study heterogeneity. However, four prognostic factors: age at implantation, inner ear malformations, meningitis, and Connexin 26 (a genetic cause of hearing loss), consistently influenced hearing outcomes.

Pakdaman conducted a systematic review of cochlear implants in children with cochleovestibular anomalies in 2011.<sup>[42]</sup> Anomalies included inner ear dysplasia such as large vestibular aqueduct and anomalous facial nerve anatomy. Twenty-two studies were reviewed totaling 311 patients. The authors found implantation surgery was more difficult and speech perception was lower in patients with severe inner ear dysplasia. However, heterogeneity in the studies limited interpretation of these findings.

In another 2011 systematic review, Roush examined the audiologic management of children with auditory neuropathy spectrum disorder.<sup>[43]</sup> The review included 15 studies that addressed cochlear implantation in these patients. All of the studies reported auditory benefit with

cochlear implantation in children with auditory neuropathy spectrum disorder. However, the studies were noted to be limited methodologically and further research is needed in this population.

## **Randomized Trials**

In 2016, Smulder conducted a small prospective multi-center randomized trial to evaluate the benefits of bilateral implants compared to unilateral implants in adults with postlingual deafness, including 38 patients.<sup>[44]</sup> At one-year follow-up, there were no significant differences between groups on the speech-in-noise or the consonant-vowel-consonant test. The bilaterally implanted group performed significantly better when noise came from different directions ( $p < 0.001$ ) and was better able to localize sounds ( $p < 0.001$ ) compared to the unilaterally implanted group. These results were consistent with the patients' self-reported hearing capabilities. The results were consistent at a two year follow up, reported in 2017.<sup>[45]</sup>

## **Nonrandomized Studies**

### Adults

Numerous case series have been published on adult patients with bilateral cochlear implants.<sup>[46-54]</sup> Most but not all studies report slight to modest improvements in sound localization and speech intelligibility with bilateral cochlear implants especially with noisy backgrounds but not necessarily in quiet environments. In addition, depression scores improved in cochlear implant patients from pre-implantation to 12 months post-treatment (geriatric depression scale improvement: 31%, 95% CI 10% to 47%) in a prospective observational study including 113 patients with postlingual hearing loss, of whom 50 were treated with cochlear implants and 63 with hearing aids.<sup>[55]</sup>

When reported, the combined use of binaural stimulation improved hearing in the range of one to four decibels or 1%–2%. While this improvement seems slight, any improvement in hearing can be considered beneficial in the deaf. However, this improvement may not outweigh the significant risks of a second implantation. In addition, similar binaural results can be achieved with a contralateral hearing aid, assuming the contralateral ear has speech recognition ability. A number of studies have reported benefits for patients with a unilateral cochlear implant with hearing aid (HA) in the opposite ear.

### Children

Several recent publications have evaluated bilateral cochlear implants in children.<sup>[56-58]</sup> These studies, ranging in size from 91 to 961 patients, generally report improved speech outcomes with bilateral implantation, compared with unilateral implantation. In a retrospective case series of 73 children and adolescents who underwent sequential bilateral cochlear implantation with a long (>five year) interval between implants, performance on the second implanted side was worse than the primary implanted side, with outcomes significantly associated with the interimplant interval.<sup>[49,53,59-65]</sup>

### Adults and Children

Ching (2006) subsequently reported on 29 children and 21 adults with unilateral cochlear implant and a contralateral hearing aid.<sup>[47]</sup> They noted that both children and adults localized sound better with bilateral inputs.

## UNILATERAL HEARING LOSS WITH OR WITHOUT TINNITUS

The use of cochlear implants in patients with unilateral hearing loss is an off-label use of these devices. As noted in the 2011 AHRQ technology assessment, a number of narrative literature reviews<sup>[66-68]</sup> and small ( $n \leq 30$ ) observational studies (described below) conducted primarily in adult patients have been published. However, these studies have included small numbers of patients ( $n \leq 30$ ) and had risk of reporting bias.

### Systematic Reviews

A 2019 SR published by Peter identified 13 studies that met inclusion criteria and evaluated the influence of cochlear implantation on tinnitus in patients with single-sided deafness.<sup>[69]</sup> All identified studies were cohort studies. They mainly reported tinnitus questionnaire scores using the Tinnitus Handicap Inventory. Overall, of the 153 included patients, 34.2% demonstrated complete suppression, 53.7% demonstrated an improvement, 7.3% demonstrated a stable value, and 4.9% showed an increase of tinnitus. No patients reported an induction of tinnitus

In 2015, van Zon published a systematic review of studies evaluating cochlear implantation for single-sided deafness or asymmetric hearing loss.<sup>[70]</sup> The authors reviewed 15 studies, nine of which ( $n=112$  patients) were considered high enough quality to be included in data review. The authors identified no high-quality studies of cochlear implantation in this population. Data were not able to be pooled for meta-analysis due to high between-study heterogeneity, but the authors conclude that studies generally report improvements in sound localization, quality of life scores, and tinnitus after cochlear implantation, with varying results for speech perception in noise.

In 2014, Vlastarakos published a systematic review of the evidence related to cochlear implantation for single-sided deafness.<sup>[71]</sup> The authors included 17 studies, including prospective and retrospective comparative studies, case series and case reports that included 108 patients. The authors report that sound localization is improved after cochlear implantation, although statistical analysis was not included in some of the relevant studies. In most patients (95%), unilateral tinnitus improved. The authors note that most of the studies included had short follow-up times, and evaluation protocols and outcome measurements were heterogeneous.

In 2014, Blasco and Redleaf published a systematic review and meta-analysis of studies evaluating cochlear implantation for unilateral sudden deafness.<sup>[72]</sup> The review included nine studies with a total of 36 patients. In pooled analysis, subjective improvement in tinnitus occurred in 96% of patients (of 27 assessed), subjective improvement in speech understanding occurred in 100% of patients (of 16 assessed), and subjective improvement in sound localization occurred in 87% of patients (of 16 assessed). However, the small number of patients in which each outcome was assessed limits any conclusions that may be drawn.

### Nonrandomized Studies

In 2019, Dillon published a clinical update reporting on the prevalence of low-frequency hearing preservation with the use of standard long electrode arrays (MED-EL Corporation) in a subset of 25 patients (12 with unilateral hearing loss) from earlier cohorts.<sup>[73]</sup> Unaided hearing thresholds at 125 Hz were compared between the preoperative and initial activation intervals in 24 participants to assess the change in low-frequency hearing. At activation, a significant elevation in the unaided hearing thresholds at 125 Hz was noted ( $p < 0.001$ ), with the majority of

subjects (n=16) demonstrating no response to stimulus. The remaining nine participants maintained an unaided low-frequency hearing threshold of  $\leq 95$  dB, and 5/9 participants met the fitting criterion of  $\leq 80$  dB for electric-acoustic stimulation (EAS) at initial activation. An additional three participants demonstrated improvement in unaided low-frequency hearing thresholds at latter monitoring intervals. It is uncertain whether identifying patients with preservation of low-frequency hearing can help predict individuals that may benefit from EAS vs standard cochlear implants.

Galvin III (2019) reported data from an FDA-approved study of cochlear implantation in 10 patients with SSD.<sup>[74]</sup> Patients were implanted with the MED-EL Concerto Flex 28 device. Speech perception in quiet and noise, localization, and tinnitus severity were measured prior to implantation at one, three, and six months postactivation. Performance was assessed with both ears (binaural), with the implanted ear alone, and the normal hearing alone. No patient had previous experience with a contralateral routing of signal (CROS) or bone conduction device (BCD) system. Mean improvement for consonant-nucleus-consonant (CNC) word recognition vs baseline was 66.8%, 76.0%, and 84.0% at one, three, and six months postactivation, respectively. The normal hearing ear performed significantly better compared to the implanted ear for all outcome measures at all intervals ( $p < 0.05$ ). Audiological performance of the implanted ear at one, three, and six months postactivation was significantly better compared to baseline ( $p < 0.05$ ), with no significant difference across postactivation intervals ( $p > 0.05$ ). The change in root mean square error (RMSE) in localization with binaural listening postactivation reduced by 6.7, 7.6, and 11.5 degrees at one, three, and six months postactivation. Binaural performance was significantly improved compared to the normal hearing ear alone at all postactivation time intervals ( $p < 0.05$ ). Tinnitus visual analog scale (VAS) scores significantly decreased with the implant on at all postactivation time intervals ( $p < 0.05$ ). Significant improvements on SSQ scores were reported for the Speech ( $p = 0.003$ ), Spatial ( $p < 0.001$ ), and Quality ( $p = 0.034$ ) subtests. Global scores were not reported. Adverse events were reported in 5/10 participants, including facial nerve stimulation, periorbital edema, mild postoperative balance disturbance, postauricular pain, and unresolved taste disturbance. The study is limited by small sample size.

Peter (2019) published the results of a Swiss multicenter study assessing cochlear implantation for use in adult patients in post-lingual single-sided deafness, defined as a hearing loss of 70 dB hearing level (HL) in the mean thresholds of 0.5, 1, 2, and 4 kHz in the affected ear, and 25 dB HL or better in the frequencies from 125 to 2 kHz and 35 dB HL or better from 4 to 8 kHz in the normally hearing contralateral ear.<sup>[75]</sup> A total of 10 patients were evaluated. Two years post-implantation, 90% of patients used their implant regularly for an average of more than 11 hours per day. Twelve months postactivation, speech from the front and noise at the healthy ear achieved a 2.7 dB improvement ( $p = 0.0029$ ). Speech to the implanted ear and noise from the front achieved a 1.5 dB improvement ( $p = 0.018$ ). The mean sound localization error of all participants was improved by 10.2 degrees ( $p = 0.030$ ) at 12 months postactivation. One participant experienced a loss in low-frequency residual hearing from surgery, resulting in poorer localization performance after surgery with an increased error of 11.3 degrees. Tinnitus severity decreased significantly 12 months postactivation from 41.2 points (SD 26.5) preoperatively to 23.0 points (SD 17.5;  $p = 0.004$ ) on the Tinnitus Handicap Inventory (THI). Quality of life measures showed a significant improvement on the global subscale of the WHO Quality of Life questionnaire ( $p = 0.007$ ). The Speech, Spatial, and Qualities of Hearing Scale questionnaire (SSQ) indicated a significant improvement from 4.2 to 6 ( $p = 0.004$ ) in speech comprehension and from 3 to 5.3 ( $p = 0.009$ ) in spatial hearing. No significant difference was noted in the subscale qualities of hearing (6.2 to 6.9;  $p = 0.13$ ). The

scores of the patient's on the three subscales were significantly lower than for the normal hearing control group, with an average speech comprehension score of 8.7 ( $p=0.001$ ), an average spatial hearing of 8.6 ( $p<0.001$ ), and an average qualities of hearing score of 9.1 ( $p=0.005$ ). Adverse events were not reported.

Poncet-Wallet (2019) reported on audiological and tinnitus outcomes of cochlear implantation in adults with single-sided deafness (SSD) and tinnitus.<sup>[76]</sup> Twenty-six patients with SSD and incapacitating tinnitus (THI score > 58) underwent cochlear implantation. Masking white noise stimulation was delivered for the first month post-implantation, after which standard cochlear implant stimulation was provided. Catastrophic handicaps (grade 5, THI 78-100) were noted for 31% of participants and severe handicaps (grade 4, THI 58-76) were noted for 69% of participants. The first month of white noise stimulation provided a significant improvement in THI scores ( $72 \pm 9$  to  $55 \pm 20$ ;  $p<0.05$ ). No change was observed for the other measures at this time point. After one year of standard stimulation, 23 patients (92%) completed the final 13-month visit with 0% of participants reporting catastrophic handicaps, 4% reporting severe handicaps, and 26% reporting moderate handicaps (grade 3, THI 38-56), 30% reporting mild handicaps (grade 2, THI 18-36), and 39% reporting slight or no handicaps (grade 1, THI 0-16) ( $p<0.05$ ). All 23 patients attending the 13-month visit reported improvement of tinnitus on at least two of four tinnitus questionnaires.

In July 2019, the FDA approved to expand the indication for the MED-EL Cochlear Implant System to include individuals aged five years and older with single-sided deafness (SSD) or asymmetric hearing loss (AHL). According to the FDA's summary of safety and effectiveness data, approval was based on supporting evidence from a comprehensive literature review and a clinical feasibility study conducted at the University of North Carolina at Chapel Hill under IDE# G140050 in patients treated between 2014 and 2019. In this prospective, non-blinded, repeated measures study, 40 subjects were implanted with the MED-EL CONCERT or SYNCHRONY Cochlear Implant System. Twenty patients each were enrolled into the SSD and AHL groups. All 20 patients completed testing in the SSD group. One patient withdrew from the AHL group and one patient had not yet completed follow-up at the time of data analysis. Patients were required to have previous experience of at least one month in duration with a conventional hearing aid, bone conduction device, or CROS device. Exclusion criteria included Meniere's disease with intractable vertigo, tinnitus as the primary concern for cochlear implantation, and severe or catastrophic score on the THI. Aided word recognition in the ear to be implanted was required to be 60% or less as measured with a 50-word CNC word list. Speech perception and localization were evaluated at baseline and at 1, 3, 6, 9, and 12 months post-operatively utilizing CNC word recognition and AzBio sentence tests. For patients in the AHL group, soundfield testing was completed with a hearing aid in the contralateral ear. Quality of life measures included the SSQ, THI, and Abbreviated Profile of Hearing Aid Benefit (APHAB) scales. Primary effectiveness measures were comparisons of speech perception and localization performance between the bilateral, preoperative, unaided/best-aided condition and the bilateral, 12-month post-operative cochlear implant (CI) + normal hearing (NH) or hearing aid (HA) condition. Study results are summarized in Table 1. Nine device- or procedure-related adverse events were reported. Most frequently reported adverse events included vertigo/dizziness/imbalance (22.5%) and unrelated infection (7.5%). The data from the is limited by its small sample size in adult subjects only. Effectiveness endpoints were not prespecified.

**Table 1. Feasibility Study Results for MED-EL Cochlear Implant System for SSD and AHL**

<b>Outcome</b>	<b>SSD (n=20)</b>			<b>AHL (n=18)</b>		
<b>Speech Perception in Quiet</b>	<b>Baseline, unaided</b>	<b>12-mo, unaided</b>	<b>12-mo, CI-on</b>	<b>Baseline, unaided</b>	<b>12-mo, unaided</b>	<b>12-mo, CI-on</b>
Implant Ear CNC, Mean (SD) Range	3.5 (-6.68) 0 to 22	NA	54.6 (-18.15) 10 to 84	6.3 (-7.98) 0 to 22	NA	56.2 (-18.41) 28 to 86
Contralateral Ear CNC, Mean (SD) Range	99.3 (-2.27) 90 to 100	99.8 (-0.62) 98 to 100	NA	92.7 (8.68) 78 to 100	92.7 (8.68) 72 to 100	NA
Soundfield, Binaural AzBio, Mean (SD) Range	99.0 (1.56) 95 to 100	NA	99.5 (1.19) 95 to 100	87.4 (13.96) 50 to 99	NA	94.3 (8.38) 72 to 100
	<b>SSD (n=20)</b>			<b>AHL (n=17)</b>		
<b>Speech Perception in Noise</b>	<b>Baseline, Unaided</b>	<b>Baseline, Best-Aided (BCHA)</b>	<b>12-mo, CI-On</b>	<b>Baseline, Unaided</b>	<b>Baseline, Best-Aided (BCHA)</b>	<b>12-mo, CI-On</b>
Noise Front AzBio, Mean (SD) Range	37.5 (10.98) 20 to 64	31.5 (16.56) 0 to 59	47.2 (10.72) 29 to 68	22.7 (13.95) 0 to 47	20.5 (12.86) 0 to 47	33.5 (22.10) 3 to 85
Noise at CI AzBio, Mean (SD) Range	83.4 (9.51) 59 to 94	61.25 (27.92) 0 to 98	85.0 (11.04) 60 to 97	44.2 (17.70) 9 to 78	30.5 (18.23) 1 to 70	44.6 (24.74) 5 to 94
Noise at Contralateral AzBio, Mean (SD) Range	16.5 (12.78) 0 to 45	18.3 (13.50) 0 to 59	52.6 (21.43) 8 to 86	6.3 (9.49) 0 to 36	11.3 (16.69) 0 to 66	29.4 (22.59) 1 to 95

	<b>SSD (N=20)</b>			<b>AHL (N=18)</b>		
<b>Localization Performance</b>	<b>Baseline, Unaided</b>	<b>Baseline, Best-Aided (BCHA)</b>	<b>12-mo, CI- On</b>	<b>Baseline, Unaided</b>	<b>Baseline, Best-Aided (BCHA)</b>	<b>12-mo, CI- On</b>
Mean RMS Error (SD) Range	66.5 (20.47) 42.9 to 109.1	69.6 (18.71) 45.3 to 106.1	26.7 (6.32) 13.6 to 38.4	76.5 (19.23) 43.8 to 105.3	77.2 (18.89) 45.6 to 106.5	40.1 (10.65) 26.6 to 73.6
<b>Quality of Life</b>	<b>SSQ (Speech)</b>	<b>SSQ (Spatial)</b>	<b>SSQ (Qualities)</b>	<b>APHAB (Global)</b>	<b>APHAB (EC, RV, BN, AV)</b>	<b>THI</b>
SSD (N=20) Baseline: Mean (SD); Range 12-mo: Mean (SD); Range	3.7 (1.34); 0.6 to 7.2 7.1 (0.99); 5.4 to 8.9	2.4 (1.2); 0.5 to 4.5 6.5 (1.86); 2.8 to 8.9	5.6 (2.09); 0.5 to 9.8 7.7 (1.28); 5.6 to 9.8	49.8 (18.65); 20.3 to 86.3 17.9 (8.91); 6.1 to 36.7	EC: 31.6 (21.06); 2.8 to 81.0 8.7 (6.15); 1.0 to 24.8 BN: 70.1 (17.32); 39.3 to 95.0 25.2 (11.95); 10.2 to 56.2 RV: 47.5 (21.96); 18.7 to 87.0 19.7 (12.43); 2.8 to 41.7 AV: 43.1 (28.64); 1.0 to 93.0 26.7 (24.83); 1.0 to 91.0	NR

AHL (N=18) Baseline: Mean (SD); Range 12-mo: Mean (SD); Range	3.2 (1.48); 0.4 to 6.0 5.8 (1.50); 3.6 to 8.9	2.6 (1.26); 0.3 to 4.7 6.0 (1.62); 3.1 to 8.5	4.6 (1.77); 0.2 to 8.3 6.8 (1.20); 4.4 to 8.7	54.1 (16.21); 20.0 to 92.3 28.1 (10.49); 11.3 to 54.1	EC: 42.9 (24.67); 10.2 to 91.0 16.6 (13.01); 1.0 to 54.0 BN: 63.5 (16.84); 14.5 to 95.0 39.3 (17.10); 14.5 to 66.3 RV: 56.0 (18.30); 14.2 to 97.0 28.3 (11.96); 12.0 to 54.2 AV: 43.1 (35.04); 1.0 to 99.0 42.4 (29.21); 1.0 to 97.0	NR
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AHL: asymmetric hearing loss; APHAB: Abbreviated Profile of Hearing Aid Benefit; AV: Aversiveness subscale; BCHA: bone conduction hearing aid; BKB-SIN: Bench-Kowal-Banford Speech in Noise Test; BN: Background Noise subscale; CI: cochlear implant; CNC: consonant-nucleus-consonant; EC: Ease of Communication subscale; NA: not applicable; NR: not reported; RMS: root mean square; RV: Reverberation subscale; SD: standard deviation; SSD: single-sided deafness; SSQ: Speech, Spatial, and Qualities of Hearing Scale; THI: Tinnitus Handicap Inventory.

The FDA decision was further supported by a literature search yielding six publications comprising a total of 58 adults with SSD (n=50 of which implanted with MED-EL devices) and a total of 52 adults with AHL (n=37 of which implanted with MED-EL devices). The candidacy criterion of ages five and older was based on a literature search yielding five publications comprising a total of 26 children with SSD (n=5 of which implanted with a MED-EL device) and a total of nine children with AHL. While the overall benefits of CI in children with SSD and AHL included improved performance in speech perception in quiet and noise, sound localization, and subjective measures of quality of life – these results are limited to primarily case series with small sample sizes, heterogeneous in methodology and outcome assessment, and at high risk of bias in self-reported measures. The FDA has required MED-EL to conduct a post-marketing study to continue to assess the safety and efficacy of the implant in a new enrollment cohort of adults and children.

Buss (2018) published the results of an FDA clinical trial that investigated the potential benefit of cochlear implant (CI) for use in adult patients with moderate-to-profound unilateral sensorineural hearing loss and normal to near-normal hearing on the other side.<sup>[79]</sup> The study population was 20 CI recipients with one normal or near-normal ear (NH) and the other met criterion for implantation (CI). All subjects received a MED-EL standard electrode array, with a full insertion based on surgeon report. They were fitted with an OPUS 2 speech processor. This group was compared to 20 normal hearing persons (control group) that were age-matched. Outcome measures included: sound localization on the horizontal plane; word recognition in quiet with the CI alone, and masked sentence recognition when the masker was presented to the front or the side of normal or near-normal hearing. The follow-up period was 12-months. While the majority of CI recipients had at least one threshold  $\leq 80$ dB prior to implantation, only three subjects had these thresholds after surgery. For CI recipients, scores on consonant-nucleus-consonant (CNC) words in quiet in the impaired ear rose an average of 4% (0-24%) at the postoperative test to a mean of 55% correct (10%-84%) with the CI alone at the 12-month test interval.

In a 2017 prospective study, Sladen examined speech recognition and self-perceived health-related quality of life in a cohort of 20 adults and children with unilateral hearing loss.<sup>[80]</sup> Improvements were observed in speech recognition, both in quiet and noise, and self-perceived benefit with disease-specific instruments. Pure tone audiometry improved with air conduction in the implanted ear. CNC scores in quiet improved from 4.8% (SD 9.0%) in the preoperative period to 42.3% (SD 14.8%) at the six-month post-activation check in the patients who reached that follow-up.

A 2016 study also from Sladen reported on a retrospective review of prospectively-collected data of short-term (six-month) follow-up for 23 adults and children with single-sided deafness from a variety of mechanisms who received a cochlear implant.<sup>[81]</sup> In the implanted ear, CNC word recognition improved significantly from pre-implantation to three months post-activation ( $P=0.001$ ). However, for AzBio sentence understanding in noise (+5 dB signal-to-noise [SNR]), there was no significant improvement from pre-implantation to six months post-activation.

Also in 2016, Rahne reported on a retrospective review of four children and 17 adults with single-sided deafness treated with cochlear implants and followed for 12 months.<sup>[82]</sup> Sound localization with aided hearing improved from pre-implantation to aided hearing for all individuals. The Speech recognition threshold in noise (signal-to-noise) ratio improved from -1.95 dB (CI off, SD: 2.7 dB) to -4.0 dB after three months (SD 1.3 dB,  $P<0.05$ ), with continued improvements through six months.

In 2016, Mertens reported a case series including 23 individuals who received cochlear implants for single-sided deafness with tinnitus.<sup>[83]</sup> Eligible patients had either single-sided deafness or asymmetric hearing loss and ipsilateral tinnitus. Subjects had a mean eight years of experience with their cochlear implant (range, 3 to 10 years). Patients demonstrated improvements in VAS from baseline (mean score, 8) to one month (mean score: 4;  $p<0.01$  vs baseline) and three months (mean score: 3;  $p<0.01$  vs baseline) after the first fitting. Tinnitus scores improved from baseline to three months post fitting (55 vs 31,  $p<0.05$ ) and were stable for the remainder of follow-up.

In 2015, Ramos Macias reported results of a prospective multicenter study with repeated measures related to tinnitus, hearing, and quality of life, among 16 individuals with unilateral hearing loss and severe tinnitus who underwent cochlear implantation.<sup>[84]</sup> All patients had a

severe tinnitus handicap (THI score  $\geq 58\%$ ). Eight (62%) of the 13 patients who completed the six-month follow-up visit reported a lower tinnitus handicap on the THI score. Perceived loudness/annoyingness of the tinnitus was evaluated with a 10-point VAS. When the CI was on, tinnitus loudness decreased from 8.4 preoperatively to 2.6 at the six-month follow-up; 11 of 13 patients reported a change in score of three or more.

In 2015, Arndt reported outcomes for 20 children who underwent cochlear implantation for single-sided deafness, which represented a portion of their center's cohort of 32 pediatric patients with single-sided deafness who qualified for cochlear implants.<sup>[85]</sup> Repeated-measure analyses of hearing data sets were available for 13 implanted children, excluding five who had undergone surgery too recently to be evaluated and two children who were too young to be evaluated for binaural hearing benefit. There was variability in the change in localization ability across the tested children. Self- (or child-) reported hearing benefit was measured with the Speech, Spatial and Qualities of Hearing Scale (SSQ). Significant improvements were reported on the child and parent evaluations for the scale's three subcategories: speech hearing, spatial hearing, hearing quality, and total hearing.

In 2013, Hansen reported results of a prospective study of cochlear implantation for severe-to-profound single-sided sensorineural hearing loss in 29 patients, 10 of whom had single-sided deafness due to Meniere's disease.<sup>[86]</sup> Performance was compared pre- to post-implant within each subject; outcomes were measured at three-, six-, and 12-months postoperatively. Patients showed significant improvements in CNC word and AzBio sentence scores showed improvement in the implanted ear pre-and post-implant. For the 19 patients with pre- and post-operative data available, the average improvement on CNC word score was 28% (range: -26% to 64%). The average AzBio score improvement was 40% (range: -57% to 92%).

Tavora-Vieira (2013) reported results of a prospective case series that included nine post-lingually deaf subjects with unilateral hearing loss, with or without tinnitus in the ipsilateral ear, with functional hearing in the contralateral ear, who underwent cochlear implantation.<sup>[87]</sup> Speech perception was improved for all subjects in the "cochlear implant on" state compared with the "cochlear implant off" state, and subjects with tinnitus generally reported improvement.

Arndt published a pilot study in 2010 of 11 adult patients with unilateral hearing loss of various causes.<sup>[88]</sup> The aim was to evaluate the use of unilateral electrical stimulation with normal hearing on the contralateral side and after a period of six months compared with the preoperative unaided situation, conventional contralateral routing of signal or bone-anchored hearing aid hearing aids. Ten patients also suffered from tinnitus. Two tests were used to assess speech comprehension, localization was assessed using an array of multiple speakers, and QOL was evaluated using three questionnaires. The study results were presented as p-values without adjustment for multiple testing. The authors reported that cochlear implantation improved hearing abilities in these study patients and was superior to the above alternative treatment options. The use of the cochlear implant did not interfere with speech understanding in the normal-hearing ear.

The application of cochlear implants for tinnitus relief in patients with unilateral deafness has also been described in previous studies. For example, van de Heyning published a study in 2008 of 21 patients with unilateral hearing loss accompanied by severe tinnitus for at least two years who underwent cochlear implants at a university center in Belgium.<sup>[89]</sup> The majority of patients demonstrated a significant reduction in tinnitus loudness based on a visual analogue

scale (two years after implantation,  $2.5 \pm 1.9$ ; before implantation,  $8.5 \pm 1.3$ ). Three patients showed complete tinnitus relief.

## Section Summary

The available evidence for the use of cochlear implants in improving outcomes for patients with unilateral hearing loss, with or without tinnitus, is limited by small sample sizes, and heterogeneity in evaluation protocols and outcome measurements. A small feasibility study in adults with SSD or AHL demonstrated improvements in sound perception, sound localization, and subjective measures of quality of life compared to baseline conditions. However, studies assessing outcomes compared to best-aided hearing controls across multiple time points are lacking. An ongoing post-marketing study in adults and children may further elucidate outcomes.

## COCHLEAR RESTORATION

The optimal timing of cochlear implantation in children is of particular interest given the strong associations between hearing and language development. While there is current research investigating the ability to restore hearing by stimulating cochlear hair cell regrowth, cochlear implantation damages the cochlea and eliminates the possibility of cochlear restoration. However, the potential to restore cochlear function is not foreseeable in the near future; therefore, if implantation of cochlear implants is felt to be most beneficial at a younger age when the nervous system is “plastic”, this potential development seems too far in the future to benefit young children who are current candidates for a cochlear implant.

## HYBRID COCHLEAR IMPLANTATION

### Systematic Review

Santa Maria (2014) conducted a systematic review and meta-analysis of hearing outcomes after various types of hearing-preservation cochlear implantation, including implantation hybrid devices, cochlear implantation with surgical techniques designed to preserve hearing, and the use of post-operative systemic steroids.<sup>[90]</sup> The study included 24 studies, but only two studies focused specifically on a hybrid cochlear implant system, and no specific benefit from a hybrid system was reported.

### Nonrandomized Studies

The pivotal trial for the Med-EL EAS system was a prospective, multi-center, non-randomized, non-blinded, repeated measures clinical study of 73 subjects at 14 U.S. sites, implanted with either SONATA FLEX24 or a PULSAR FLEX24.<sup>[3]</sup> Final outcomes were reported in 2018 by Pillsbury.<sup>[91]</sup> Sixty-seven of 73 subjects (92%) completed outcome measures at 3, 6, and 12 months postactivation. A 30 dB or less low-frequency pure-tone average shift was experienced by 79% and 97% were able to use the acoustic unit at 12 months postactivation. In the EAS condition, 94% of subjects performed similarly or demonstrated improvement (85%) compared to preoperative performance on City University of New York sentences in noise at 12 months. Ninety-seven percent of subject performed similarly or improved (85%) on CNC words in quiet. Improvements in speech perception scores were statistically significant ( $p < 0.001$ ). The Abbreviated Profile of Hearing Aid Benefit (APHAB) was administered preoperatively and at 12 months postactivation; 60 subjects completed the APHAB assessment at each time point. The mean score on the APHAB Global Scale improved by 30.2%, demonstrating a significant reduction in perceived disability ( $p < 0.001$ ). Thirty-five device-related adverse events were

reported for 29 of 73 subjects (39.7%). The most frequently observed adverse event was profound/total loss of residual hearing, which occurred in 8 of 73 subjects (11.0%).

The pivotal trial for the Nucleus® Hybrid™ L24 Cochlear Implant System, published by Roland in 2016, was a prospective, multi-center, one-arm, non-randomized, non-blinded, repeated-measures clinical study of 50 subjects at 10 U.S. sites.<sup>[92]</sup> Performance was compared pre- to post-implant within each subject; outcomes were measured at three-, six-, and 12-months postoperatively. Post-operatively, patients' hearing was evaluated in three states: Hybrid (simultaneous electric and acoustic stimulation in the implanted ear via the Hybrid L24 including the acoustic component), Bimodal (electric stimulation only using the Hybrid L24 minus the acoustic component with contralateral acoustic stimulation), and Combined (electric and acoustic stimulation via the Hybrid L24 and contralateral acoustic stimulation). Results from the Bimodal and Combined conditions were grouped into an "Everyday Listening" category, which was not prospectively defined by the manufacturer. All 50 subjects enrolled underwent device implantation and activation. One subject had the device explanted and replaced with a standard cochlear implant between the three- and six- month follow up visit due to profound loss of low frequency hearing; an additional subject was explanted before the 12-month follow up visit and two additional subjects were explanted after 12 months. For the two primary effectiveness endpoints, CNC word-recognition score and AzBio sentence-in-noise score, a measure of sentence understanding in noisy environments, there were significant within-subject improvements from baseline to six-month follow up. The mean improvement in CNC word score was 35.7% (95% confidence interval [CI] 27.8% to 43.6%); for AzBio score, the mean improvement was 32.0% (95% CI 23.6% to 40.4%) For safety outcomes, 71 adverse events were reported, most commonly profound/total loss of hearing (occurring in 44% of subjects) with at least one adverse event occurring in 34 subjects (68%).

Five-year outcomes for the pivotal trial were reported by Roland in 2018.<sup>[93]</sup> Thirty-two out of 50 subjects (64%) enrolled in the postapproval study. Out of the 18 subjects who did not participate, six had been explanted and reimplanted with a long electrode array, two discontinued for unrelated medical reasons, two withdrew for other reasons, four declined to continue follow-up evaluations, and four chose not to participate in the postapproval study. At five years postactivation, 94% of subjects had measurable hearing and 72% continued to use electric-acoustic stimulation with functional hearing in the implanted ear, and 6% had a total loss. Changes from pre-operate hearing to six months were statistically significant ( $p < 0.001$ ), but changes six months through five years postactivation were not statistically different ( $p > 0.05$ ). Acoustic component amplification was utilized by 84% and 81% of patients at 12 and three years postactivation, respectively. Mean CNC word recognition in quiet scores were significantly improved over the preoperative condition at each postactivation interval ( $p < 0.001$ ). However, mean scores did not significantly differ after 12 months postactivation. At five years postactivation, 94% performed the same or better in unilateral CNC word scores, whereas 6% demonstrated a decline in performance. For bilateral CNC word scores, 97% performed the same or better, whereas one subject showed a decline in performance. The Speech, Spatial, and Qualities of Hearing Questionnaire (SSQ) was implemented to measure subjective implant satisfaction and benefit. Scores significantly improved and remained stable through all postactivation intervals ( $p < 0.001$ ).

In 2016, Gantz published outcomes from a multicenter, longitudinal study evaluating outcomes with the Nucleus Hybrid S8 featuring a shorter cochlear array.<sup>[94]</sup> Eighty-seven subjects received an implant. At 12 months postactivation, five subjects had total hearing loss, whereas functional hearing was maintained by 80%. CNC word scores demonstrated 82.5% of subjects

had experience a significant improvement in the hybrid condition. Improvement in speech understanding in noise were demonstrated in 55% of subjects. Fourteen patients requested implant explantation due to various reasons of dissatisfaction with the device. These patients were re-implanted with a standard-length Nucleus Freedom cochlear implant. CNC scores prior to loss of residual hearing were missing for six subjects. CNC scores following re-implantation were missing for two additional subjects. Similar or better CNC scores following re-implantation were observed in five of the six remaining subjects.

In 2015, Friedmann conducted a retrospective review that included 22 subjects implanted with a cochlear implant with either a standard electrode (n=12) or the Nucleus Hybrid L24 electrode (n=10).<sup>[95]</sup> At one year post-implant, 30% patients with the Hybrid-L and 58% patients with the standard electrode lost residual acoustic hearing resulting in a profound hearing loss in the implanted ear. The authors reported that while hearing preservation rates with the hybrid electrode tended to be better, among recipients who lost residual hearing, speech perception was better in those with the longer standard electrode.

Lenarz (2013) reported results of a prospective multi-center European study evaluating the Nucleus Hybrid™ L24 system.<sup>[96]</sup> The study enrolled 66 adults with bilateral severe-to-profound high frequency hearing loss. At one year post-operatively, 65% of subjects had significant gains in speech recognition in quiet and 73% had significant gains in noisy environments. Compared with the cochlear implant hearing alone, residual hearing significantly increased speech recognition scores.

Gifford (2013) compared hearing outcomes pre- and post-implantation for 44 adult cochlear implant recipients with preserved low-frequency hearing in two test conditions: cochlear implant plus low-frequency hearing in the contralateral plus low-frequency hearing in the contralateral ear (bimodal condition) and cochlear implant plus low-frequency hearing in both ears (best-aided condition).<sup>[97]</sup> The authors reported that there were small but statistically significant differences in improvements in adaptive sentence recognition and speech recognition in a noisy “restaurant” environment, suggesting that the presence of residual hearing is beneficial.

A small number of studies in a small number of patients suggest that a hybrid cochlear implant system is associated with improvements in hearing of speech in quiet and noise. However, there are currently no available studies that compare the use of a standard hearing aid with a hybrid cochlear implant, which would be an appropriate comparison to determine if a hybrid device improves outcomes for patients who currently have hearing loss, but might not be candidate for a cochlear implant. In addition, there is only limited data to suggest that the preservation of residual hearing associated with a hybrid device is associated with improved outcomes compared with a standard cochlear implant.

## Section Summary

Prospective and retrospective studies using a single-arm, within-subjects comparison pre- and postintervention have suggested that a hybrid cochlear implant system is associated with improvements in hearing of speech in quiet and noise. For patients who have high-frequency hearing loss but preserved low-frequency hearing, the available evidence has suggested that a hybrid cochlear implant improves speech recognition better than a hearing aid alone. Some studies have suggested that a shorter cochlear implant insertion depth may be associated with preserved residual low-frequency hearing, although there is uncertainty about the potential

need for reoperation following hybrid cochlear implantation if there is a loss of residual hearing. Studies reporting on long-term outcomes and results of re-implantation are lacking.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN ACADEMY OF OTOLARYNGOLOGY- HEAD AND NECK SURGERY

In 2014, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) published a revised position statement on cochlear implants. The Academy “considers unilateral and bilateral cochlear implantation as appropriate treatment for adults and children with severe to profound hearing loss. Based on extensive literature demonstrating that clinically selected adults and children can significantly perform better with two cochlear implants rather than one, bilateral cochlear implantation is accepted medical practice.”<sup>[98]</sup>

In 2020, the AAO-HNS published a position statement on pediatric cochlear implants.<sup>[99]</sup> The Academy states that “there is ample evidence that early cochlear implantation of children with sensorineural hearing loss (SNHL) for whom hearing aids provide inadequate access to sound is advantageous.” The statement goes on to say that “Children with bilateral severe to profound SNHL (4-frequency PTA > 80 dB HL or 2-frequency PTA > 85) will not receive adequate benefit from amplification and are candidates for bilateral cochlear implantation. Children with this degree of SNHL, including infants between 6 and 12 months, should receive cochlear implants as soon as practicable.”

### AMERICAN ACADEMY OF AUDIOLOGY

In July 2019, the American Academy of Audiology published clinical practice guidelines on cochlear implants.<sup>[100]</sup> These guidelines include recommendations regarding cochlear implant evaluation. They recommend determining unaided air conduction and bone conduction thresholds using developmentally appropriate assessment measures. They additionally recommend determining auditory speech perception using appropriately fit amplification using developmentally appropriate assessment measures. Other recommendations are included regarding non-audiologic evaluation prior to implantation, and surgical and post-surgical roles for the audiologist.

## SUMMARY

There is enough research to show that cochlear implants improve health outcomes, specifically, speech reception (especially in noise) and sound localization, for some patients who have severe to profound bilateral sensorineural hearing loss. Therefore, cochlear implants may be considered medically necessary in specific patients with bilateral hearing loss who meet the policy criteria.

The current research on cochlear implantation in patients diagnosed with enlarged vestibular aqueducts (EVA) has limitations. Despite these limitations, there is enough research to show that cochlear implants improve health outcomes, specifically, speech recognition, for patients for patients with EVA. In addition, early placement of cochlear implants avoids atrophy and preserves hearing patients with EVA with moderate hearing loss. Therefore, cochlear implants may be considered medically necessary in patients with EVA when policy criteria are met.

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The current research on hybrid cochlear implant/hearing aid systems has limitations. Despite these limitations, there is enough research to show that hybrid cochlear implant/hearing aid systems improve health outcomes, specifically, speech recognition, for patients aged 18 years or older who have high frequency sensorineural hearing loss with preserved low frequency hearing. Therefore, hybrid cochlear implant/hearing aid systems may be considered medically necessary in specific patients with high frequency sensorineural hearing loss with preserved low frequency hearing who meet the policy criteria.

There are currently no cochlear implants that have approval from the U.S. Food and Drug Administration (FDA) for use in patients who are younger than 9 months of age. There is not enough research to show that cochlear implants improve health outcomes in patients younger than 9 months of age and it is unclear that the benefits of early cochlear implantation outweigh the risk of surgery and anesthesia in these very young patients. In addition, there are no clinical practice guidelines from U.S. professional societies that recommend cochlear implantation in these very young patients. Therefore, cochlear implantation in patients younger than 9 months of age is considered not medically necessary

In all other situations, cochlear implants and hybrid cochlear implant/hearing aid systems do not improve health outcomes. Therefore, cochlear implants and hybrid cochlear implant/hearing aid systems are considered not medically necessary when the policy criteria are not met, including but not limited to unilateral hearing loss with or without tinnitus.

Implant replacement, including replacement parts or upgrades to existing cochlear implants and/or components may be considered medically necessary only in those patients whose response to the existing device is inadequate to the point of interfering with activities of daily living, including school or work. Replacement of an existing cochlear implant device is considered not medically necessary when the policy criteria are not met.

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101. BlueCross BlueShield Association Medical Policy Reference Manual "Cochlear Implant." Policy No. 7.01.05

## CODES

Codes	Number	Description
CPT	69930	Cochlear device implantation, with or without mastoidectomy
	92601	Diagnostic analysis of cochlear implant, patient younger than 7 years of age; with programming
	92602	;subsequent reprogramming
	92603	Diagnostic analysis of cochlear implant, age 7 years or older; with programming
	92604	;subsequent reprogramming
	92630	Auditory rehabilitation; pre-lingual hearing loss
	92633	Auditory rehabilitation; post-lingual hearing loss
HCPCS	L8614	Cochlear device, includes all internal and external components
	L8615	Headset/headpiece for use with cochlear implant device, replacement
	L8616	Microphone for use with cochlear implant device, replacement
	L8617	Transmitting coil for use with cochlear implant device, replacement
	L8618	Transmitter cable for use with cochlear implant device or auditory osseointegrated device, replacement
	L8619	Cochlear implant external speech processor and controller, integrated system, replacement
	L8621	Zinc air battery for use with cochlear implant device and auditory osseointegrated sound processors, replacement, each
	L8622	Alkaline battery for use with cochlear implant device, any size, replacement, each
	L8623	Lithium ion battery for use with cochlear implant device speech processor
	L8624	Lithium ion battery for use with cochlear implant or auditory osseointegrated device speech processor, ear level, replacement, each
	L8625	External recharging system for battery for use with cochlear implant or auditory osseointegrated device, replacement only, each
	L8627	Cochlear implant, external speech processor, component, replacement
L8628	Cochlear implant, external controller component, replacement	
L8629	Transmitting coil and cable, integrated, for use with cochlear implant device, replacement	

**Date of Origin:** January 1996

## Cosmetic and Reconstructive Surgery

**Effective:** September 1, 2020

**Next Review:** May 2021

**Last Review:** July 2020

### IMPORTANT REMINDER

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

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

### DESCRIPTION

Cosmetic surgery is performed to reshape normal body structures in order to improve appearance.

Reconstructive surgery is primarily performed to improve or correct a functional impairment.

**NOTE: This policy is not intended to address treatment of gender dysphoria which is addressed in the [Gender Affirming Interventions for Gender Dysphoria medical policy, Medicine, Policy No. 153](#), which may be applicable.**

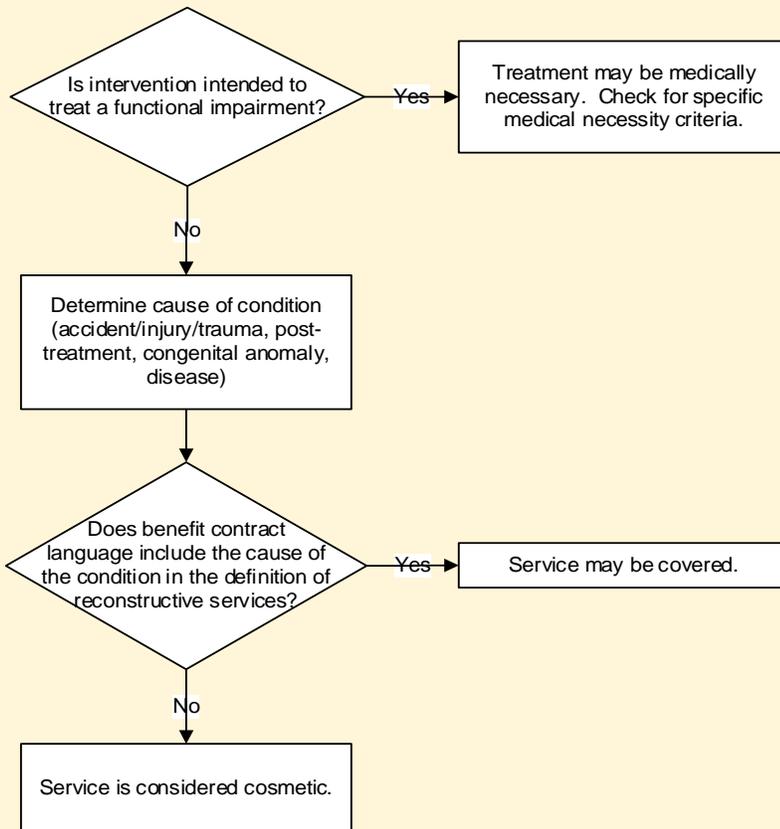
### MEDICAL POLICY CRITERIA

#### Notes:

- Many member contracts have very specific language regarding covered reconstructive services and excluded cosmetic procedures. Specific member contract language has precedence over medical policy, and requests for coverage of potentially cosmetic services should be reviewed by applicable member contract language.
- Specific services may be addressed in separate medical policies. Please see cross references below.

- I. The following criteria may be applied when member contract language is not specific:
  - A. If the intervention is intended to treat a functional impairment and if no other contract exclusions apply, it may be considered **medically necessary**.
  - B. If the intervention is not intended to treat a functional impairment, the cause of the condition must be determined, for example, accident/injury/trauma, post-treatment, congenital anomaly, disease. If the cause is included in the definition of reconstructive services in the benefits contract language, then the treatment may be covered.

The following flow chart may be used as a guide to interpreting benefits language.



## CROSS REFERENCES

1. [Gender Affirming Interventions for Gender Dysphoria](#), Medicine, Policy No. 153
2. [Endometrial Ablation](#), Surgery, Policy No. 01
3. [Panniculectomy](#), Surgery, Policy No. 12.01
4. [Pectus Excavatum](#), Surgery, Policy No. 12.02
5. [Ventral Hernia Repair](#), Surgery, Policy No. 12.03
6. [Dermabrasion or Microdermabrasion](#), Surgery, Policy No. 12.04
7. [Blepharoplasty and Brow Ptosis Repair](#), Surgery, Policy No. 12.05
8. [Mastectomy as a Treatment of Gynecomastia Cosmetic Services](#), Surgery, Policy No. 12.06
9. [Rhinoplasty](#), Surgery, Policy No. 12.28
10. [Laser Treatment for Port Wine Stains](#), Surgery, Policy No. 12.34
11. [Chemical Peels](#), Surgery, Policy No. 12.50
12. [Reconstructive Breast Surgery/Management of Breast Implants](#), Surgery, Policy No. 40
13. [Reduction Mammoplasty](#), Surgery, Policy No. 60

14. [Varicose Vein Treatment](#), Surgery, Policy No. 104
15. [Orthognathic Surgery](#), Surgery, Policy No. 137
16. [Autologous Fat Grafting to the Breast and Adipose-derived Stem Cells](#), Surgery, Policy No. 182

## REFERENCES

None

## CODES

Codes	Number	Description
CPT	11920	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.0 sq cm or less
	11921	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.1 to 20.0 sq cm
	11922	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; each additional 20.0 sq cm, or part thereof
	11950	Subcutaneous injection of filling material (eg, collagen); 1 cc or less
	11951	Subcutaneous injection of filling material (eg, collagen); 1.1 to 5.0 cc
	11952	Subcutaneous injection of filling material (eg, collagen); 5.1 to 10.0 cc
	11954	Subcutaneous injection of filling material (eg, collagen); over 10.0 cc
	15775	Punch graft for hair transplant; 1 to 15 punch grafts
	15776	Punch graft for hair transplant; more than 15 punch grafts
	15769	Grafting of autologous soft tissue, other, harvested by direct excision (eg, fat, dermis, fascia)
	15771	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; 50 cc or less injectate
	15772	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; each additional 50 cc injectate, or part thereof (List separately in addition to code for primary procedure)
	15773	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; 25 cc or less injectate
	15774	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; each additional 25 cc injectate, or part thereof (List separately in addition to code for primary procedure)
	15819	Cervicoplasty
	15824	Rhytidectomy; forehead
	15825	Rhytidectomy; neck with platysmal tightening (platysmal flap, P-flap)
	15826	Rhytidectomy; glabellar frown lines
	15828	Rhytidectomy; cheek, chin and neck
	15829	Rhytidectomy; superficial musculoaponeurotic system (SMAS) flap
	15832	Excision, excessive skin and subcutaneous tissue (includes lipectomy); thigh
	15833	Excision, excessive skin and subcutaneous tissue (includes lipectomy); leg
	15834	Excision, excessive skin and subcutaneous tissue (includes lipectomy); hip
	15835	Excision, excessive skin and subcutaneous tissue (includes lipectomy); buttock
	15836	Excision, excessive skin and subcutaneous tissue (includes lipectomy); arm
	15837	Excision, excessive skin and subcutaneous tissue (includes lipectomy); forearm or hand
	15839	Excision, excessive skin and subcutaneous tissue (includes lipectomy); other area
	15876	Suction assisted lipectomy; head and neck

	15877	Suction assisted lipectomy; trunk
	15878	Suction assisted lipectomy; upper extremity
	15879	Suction assisted lipectomy; lower extremity
	17380	Electrolysis epilation, each 30 minutes
	17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue
	19355	Correction of inverted nipples
	21137	Reduction forehead; contouring only
	21138	Reduction forehead; contouring and application of contouring material or bone graft (includes obtaining autograft)
	21139	Reduction forehead; contouring and setback of anterior frontal sinus wall
	21244	Reconstruction of mandible, extraoral, with transosteal bone plate (eg, mandibular staple bone plate)
	21245	Reconstruction of mandible, or maxilla, subperiosteal implant; partial
	21246	Reconstruction of mandible, or maxilla, subperiosteal implant; complete
	21248	Reconstruction of mandible or maxilla, endosteal implant (eg, blade, cylinder); partial
	21249	Reconstruction of mandible or maxilla, endosteal implant (eg, blade, cylinder); complete
	21270	Malar augmentation, prosthetic material
	21280	Medial canthopexy
	21282	Lateral canthopexy
	21295	Reduction of masseter muscle and bone (eg, for treatment of benign masseteric hypertrophy); extraoral approach
	21296	Reduction of masseter muscle and bone (eg, for treatment of benign masseteric hypertrophy); intraoral approach
	26590	Repair macrodactylia, each digit
	31830	Revision of tracheostomy scar
	41510	Suture of tongue to lip for micrognathia (Douglas type procedure)
	49250	Umbilectomy, omphalectomy, excision of umbilicus
	54360	Plastic operation on penis to correct angulation
	67999	Unlisted procedure, eyelids
	69090	Ear piercing
	69300	Otoplasty, protruding ear, with or without size reduction
	67950	Canthoplasty
HCPCS	G0429	Dermal filler injection(s) for the treatment of facial lipodystrophy syndrome (LDS) (e.g., as a result of highly active antiretroviral therapy)
	J0591	Injection, deoxycholic acid, 1 mg
	Q2026	Injection, Radiesse, 0.1 ML
	Q2028	Injection, Sculptra, 0.5 mg

**Date of Origin:** January 1996

## ***Panniculectomy***

**Effective:** August 1, 2020

**Next Review:** May 2021

**Last Review:** June 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Panniculectomy refers to the removal of excess skin and subcutaneous tissue typically from the abdominal area.

### **MEDICAL POLICY CRITERIA**

**Note:** Member contract language takes precedent over medical policy. Member contracts for covered services vary and may exclude weight loss surgery and all associated, services, supplies, and/or complications.

- I. Panniculectomy may be considered **medically necessary** when all of the following Criteria (A.-D.) are met:
  - A. Submission of photographs documenting significant pannus which hangs below the level of the pubis; and
  - B. The pannus causes a chronic and persistent skin condition (e.g., intertriginous dermatitis, panniculitis, cellulitis or skin ulcerations) that is refractory to at least 3 months of medical treatment and associated with at least one episode of cellulitis requiring systemic antibiotics (oral and/or intravenous). In addition to good

hygiene practices, treatment should also include topical antifungals, topical and/or systemic corticosteroids; and

- C. The pannus causes functional physical impairment documented to interfere with activities of daily living (see Policy Guidelines); and
- D. Stable weight for at least 6 months and if following bariatric surgery, at least 18 months after the surgery.

II. Panniculectomy which does not meet the above Criteria I. is considered **cosmetic**.

III. Abdominoplasty with or without panniculectomy is considered **cosmetic**.

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

## POLICY GUIDELINES

Activities of Daily Living (ADLs) Definition: Instrumental ADLs are defined as feeding, bathing, dressing, grooming, meal preparation, household chores, and occupational tasks that are required as a daily part of job functioning.

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- The specific functional physical impairment caused by the pannus
- Front and lateral view photographs demonstrating redundant/excessive skin and the size of the pannus
- Clinical documentation about the nature and extent of the chronic and persistent skin condition that is refractory to at least three months of medical treatment [at least one episode of cellulitis requiring systemic antibiotics (oral and/or intravenous) and good hygiene practices including topical antifungals, topical and/or systemic corticosteroids]
- Any bariatric surgery procedure performed within the past three years, including date of procedure
- Clinical documentation of stable weight for at least six months or at least 18 months after bariatric surgery

## CROSS REFERENCES

1. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12

## BACKGROUND

This procedure is often performed after substantial weight loss as a result of bariatric surgery or diet. According to the American Society of Plastic Surgeons, “abdominoplasty and panniculectomy are typically performed for purely cosmetic indications such as unacceptable appearance due to fat maldistribution or contour deformities caused by pregnancy, stretch marks, contracted scars and loose hanging skin after weight loss.”<sup>[1]</sup> Similar to abdominoplasty, panniculectomy involves the removal of skin in a transverse or vertical wedge, but does not include muscle plication, neoumbilicoplasty or flap elevation.<sup>[1]</sup> There is limited evidence and

clinical practice guidelines which indicate when panniculectomy may be appropriate due to functional impairment.<sup>[2,3]</sup> Typically no functional impairment is associated with pannus development.

## REFERENCES

1. American Society of Plastic Surgeons (ASPS): Recommended Insurance Coverage Criteria for Third-Party Payers; Abdominoplasty and Panniculectomy Unrelated to Obesity or Massive Weight Loss. [cited 5/19/2020]; Available from: <http://www.plasticsurgery.org/Documents/medical-professionals/health-policy/insurance/Abdominoplasty-and-Panniculectomy.pdf>
2. American Society for Metabolic & Bariatric Surgery, American Association of Clinical Endocrinologists, and The Obesity Society: Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient. [cited 5/19/2020]; Available from: <https://asmbs.org/resources/clinical-practice-guidelines-for-the-perioperative-nutritional-metabolic-and-nonsurgical-support-of-the-bariatric-surgery-patient>
3. Pestana, IA, Campbell, D, Fearmonti, RM, Bond, JE, Erdmann, D. "Supersize" panniculectomy: indications, technique, and results. *Annals of plastic surgery*. 2014 Oct;73(4):416-21. PMID: 23722576

## CODES

Codes	Number	Description
CPT	15830	Excision, excessive skin and subcutaneous tissue (includes lipectomy); abdomen, infraumbilical panniculectomy
	15838	Excision, excessive skin and subcutaneous tissue (includes lipectomy); submental fat pad
	15847	Excision, excessive skin and subcutaneous tissue (includes lipectomy), abdomen (eg, abdominoplasty) (includes umbilical transposition and fascial plication) (List separately in addition to code for primary procedure)
	17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue
HCPCS	None	

**Date of Origin:** August 2018

## ***Pectus Excavatum***

**Effective:** September 1, 2020

**Next Review:** May 2021

**Last Review:** July 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Pectus excavatum, commonly referred to as "funnel chest," is a chest wall malformation in which the sternum is depressed inward, causing midline narrowing of the thoracic cavity.

### **MEDICAL POLICY CRITERIA**

- I. Surgical repair of pectus excavatum may be considered **medically necessary** in children or adults when at least two of the following medical necessity criteria are met:
  - A. Documented progression of the deformity with associated symptoms.
  - B. Pulmonary function studies indicate components of restrictive airway disease.
  - C. Haller Computerized Tomography (CT) scan index greater than 3.25 at end-inspiration. This Haller CT index is the ratio derived from a chest CT scan by dividing the transverse diameter by the anterior-posterior diameter.
  - D. Cardiac evaluation (electrocardiogram [EKG], chest CT, and/or echocardiogram) demonstrates compression-caused mitral valve prolapse, abnormal rhythm, conduction abnormalities, or significant cardiac deformity.
- II. Surgical repair of pectus excavatum that does not meet at least two of the criteria in I.A. – I. D. above is considered **not medically necessary**.

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

## CROSS REFERENCES

1. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12

## BACKGROUND

Although pectus excavatum may be visually prominent, in most cases the loss of volume is not significant and does not interfere with ventilation. Pectus excavatum is occasionally associated with upper or lower airway obstruction; however, when this condition is successfully treated or resolves spontaneously, the pectus deformity may lessen or disappear. Pectus excavatum may also be associated with segmental bronchomalacia, and in some patients, cardiac function may be adversely affected. In many children, the heart is shifted leftward, and in the rare patient, cardiac function may be adversely affected.

Surgical correction of pectus excavatum is not physiologically beneficial for the vast majority of patients; surgery is most often sought due to psychological and cosmetic concerns. However, for some patients with extreme deformity, operative interventions may be indicated for functional reasons.

## REFERENCES

None

## CODES

Codes	Number	Description
CPT	21740	Reconstructive repair of pectus excavatum or carinatum; open
	21742	Reconstructive repair of pectus excavatum or carinatum; minimally invasive approach (Nuss procedure), without thoracoscopy
	21743	Reconstructive repair of pectus excavatum or carinatum; minimally invasive approach (Nuss procedure), with thoracoscopy
HCPCS	None	

**Date of Origin:** August 2018

## ***Ventral Hernia Repair***

**Effective:** June 1, 2020

**Next Review:** May 2021

**Last Review:** April 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Ventral hernias occur in the abdomen and develop when a portion of the lining of the peritoneum pushes through a weak area of the abdominal wall fascia. This results in a protrusion which can be filled with intra-abdominal fat or intestine.

### **MEDICAL POLICY CRITERIA**

- I. Surgical repair of a ventral hernia may be considered **medically necessary** in symptomatic patients when there is documentation that one or more of the following Criteria are met:
  - A. Hernia associated pain; or
  - B. Bowel obstruction or strangulation; or
  - C. Incarceration; or
  - D. Thinning of the overlying skin; or
  - E. Loss of abdominal domain (see Policy Guidelines).
- II. Surgical repair of ventral hernias using the component separation technique (CST) may be considered **medically necessary** for the following indications (see Policy Guidelines):

- A. Initial repair is for a large (defined as width greater than or equal to 10 cm) abdominal wall defect that cannot be closed primarily; or
- B. Repair is for a recurrent ventral hernia.
- III. Surgical repair of ventral hernias is considered **not medically necessary** when Criterion I. is not met.
- IV. Surgical repair of ventral hernias using the component separation technique (CST) is considered **not medically necessary** when Criterion II. is not met.
- V. Surgical repair of asymptomatic ventral hernias, including ventral hernias found incidentally during surgery, is considered **not medically necessary**.
- VI. Surgical repair of diastasis recti is considered **cosmetic**.
- VII. Abdominoplasty, and related procedures, including but not limited to fascial plication, surgical imbrication, and tightening of lax fascia, are considered **cosmetic**.

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

## POLICY GUIDELINES

- Loss of abdominal domain is defined as 50% of the abdominal viscera reside outside the abdominal cavity.<sup>[1]</sup>
- A defect width greater than or equal to 10 cm is classified as a large hernia.<sup>[2]</sup>

## 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 and description of associated functional physical impairment if applicable
- Diagnostic testing results as applicable to request and associated policy criteria
- Photographs as applicable to request and associated policy criteria
- Documentation of stable weight loss as applicable to associated criteria
- If the component separation technique is being performed, specify if the surgical repair is for an initial or recurrent hernia and for initial repairs, indicate the size of the hernia in centimeters.

## CROSS REFERENCES

1. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12

## BACKGROUND

Ventral hernias are usually acquired when pressure is applied to an area of the abdomen which is weakened. They can occur spontaneously, known as a primary hernia, or at the site of

a previous surgical incision, known as an incisional hernia.

Abdominal wall hernias (Epigastric, Umbilical, Lumbar and Spigelian) are defined by their anatomical location. Patients who are obese, older, under-weight, pregnant, have ascites or other factors which increase intra-abdominal pressure may be predisposed to developing abdominal hernias. Most hernias are acquired; however, the occurrence of umbilical hernias in infants is considered a congenital defect which usually resolves before the age of two. Children with persistent symptoms may require surgical repair.

Diastasis recti is defined as increased distance between the right and left rectus abdominis muscles that is created by the stretching of the collagen sheath (the linea alba) connecting the two rectus abdominis muscles. Diastasis recti is not considered a hernia as there is no fascial defect.

In general, small, asymptomatic hernias do not require surgical repair. Adults with larger symptomatic hernias should be considered for ventral hernia repair. Over time, hernia symptoms may develop and include pain, bowel obstruction, incarceration, thinning of the overlying skin, strangulation and displacement of abdominal contents into the hernia itself, known as loss of abdominal domain.

## LOSS OF ABDOMINAL DOMAIN

Loss of abdominal domain is defined as 50% of the abdominal viscera reside outside the abdominal cavity.<sup>[1]</sup>

## COMPONENT SEPARATION TECHNIQUE

The component separation technique (CST) is a surgical method that may be used to repair large, complicated ventral hernias using a rectus abdominis muscle advancement flap. A defect width greater than or equal to 10 cm is classified as a large hernia by the European Hernia Society.<sup>[2]</sup> Mesh reinforcement is often used in recurrent repairs where the abdominal defect is too large and there is a large amount of tension on the CST repair. CST is not typically used as an initial surgical approach for small primary ventral hernia repairs.

### Note:

- CPT states, “select the name of the procedure or service that accurately identifies the service performed”; therefore, an abdominal wall hernia with a specific CPT code (i.e. **epigastric, umbilical, spigelian, or lumbar** hernia repair) should not be coded as a ventral hernia repair.
- A ventral hernia at the site of a prior surgery is considered an incisional hernia.

## SUMMARY

There is enough evidence to show that the surgical repair of a ventral hernia improves health outcomes for symptomatic patients meeting criteria. Therefore, surgical repair of a ventral hernia may be considered medically necessary in symptomatic patients when policy criteria are met.

The component separation technique is a method that may be used to repair large, complicated ventral hernias and is not typically used for the initial surgical approach to

ventral hernia repair of less than 10 cm in width. Therefore, surgical repair of recurrent or very large (greater than or equal to 10 cm in width) ventral hernias using the component separation technique may be considered medically necessary. Surgical repair of initial ventral hernias less than 10 cm in width using the component separation technique is considered not medically necessary.

There is not sufficient evidence that surgical repair of asymptomatic ventral hernias improves health outcomes. Therefore, surgical repair of asymptomatic ventral hernias is considered not medically necessary. Surgical repair of diastasis recti, abdominoplasty, and related procedures, including but not limited to fascial plication, surgical imbrication, and tightening of lax fascia, are considered cosmetic.

## REFERENCES

1. Mancini, GaL, Hien. Loss of Abdominal Domain: Definition and Treatment Strategies; 2016, pp. 361-370.
2. Muysoms, FE, Miserez, M, Berrevoet, F, et al. Classification of primary and incisional abdominal wall hernias. *Hernia : the journal of hernias and abdominal wall surgery*. 2009 Aug;13(4):407-14. PMID: 19495920

## CODES

Codes	Number	Description
CPT	15734	Muscle, myocutaneous, or fasciocutaneous flap; trunk
	49560	Repair initial incisional or ventral hernia; reducible
	49565	Repair recurrent incisional or ventral hernia; reducible
	49652	Laparoscopy, surgical, repair, ventral, umbilical, spigelian or epigastric hernia (includes mesh insertion, when performed); reducible
	49654	Laparoscopy, surgical, repair, incisional hernia (includes mesh insertion, when performed); reducible
	49656	Laparoscopy, surgical, repair, recurrent incisional hernia (includes mesh insertion, when performed); reducible
HCPCS	None	

**Date of Origin:** May 2010

## ***Blepharoplasty, Repair of Blepharoptosis, and Brow Ptosis Repair***

**Effective:** October 1, 2020

**Next Review:** May 2021

**Last Review:** May 2020

### **IMPORTANT REMINDER**

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

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### **DESCRIPTION**

Blepharoplasty is a surgical procedure performed on the upper and/or lower eyelids to remove or repair excess tissue that obstructs the field of vision. Blepharoptosis repair involves repair of drooping of the eyelid and can include shortening or advancement of the elevator muscle of the eyelid. These procedures may also be performed for cosmetic purposes in the absence of visual field obstruction.

### **MEDICAL POLICY CRITERIA**

**Note:** Blepharoplasty CPT codes and policy criteria do not apply to eyelid retraction.

- I. Blepharoplasty and repair of blepharoptosis may be considered **medically necessary** when one or more of the following Criteria (A. or B.) is met:
  - A. Trichiasis, ectropion or entropion for an affected upper or lower lid when documented by lateral and full-face photographs clearly showing the affected lid(s); or

- B. Anophthalmia when there is clinical documentation that the upper eyelid position interferes with the fit of a prosthesis in the socket.
- II. Unilateral or bilateral upper lid blepharoplasty or repair of blepharoptosis may be considered **medically necessary** for reconstructive purposes when all of the following Criteria (A.- E.) are met:
- A. Any related disease process, such as myasthenia gravis or a thyroid condition, is documented as stable; and
  - B. Documentation of clinically decreased vision with functional impairment due to visual field loss; and
  - C. Prior to manual elevation of redundant upper eyelid skin (taping), the superior visual field, in at least one eye is less than or equal to 20 degrees. Examinations may be either automated or hand drawn, but need to clearly document specific visual points seen and not seen; and
  - D. With taping of the eyelids, in at least one eye, superior visual fields improve by at least 12 degrees; and
  - E. Photographs taken in the pupillary plane with a primary gaze (looking straight ahead) that demonstrate pupillary obstruction.
- III. Brow ptosis repair including open and endoscopic procedures may be considered **medically necessary** for reconstructive purposes when both of the following Criteria (A. and B.) are met:
- A. At least one eye meets either Criterion I. or II above; and
  - B. Frontal and lateral facial photographs demonstrate the eyebrow is below the supraorbital rim.
- IV. Surgical session
- A. One surgical session for either unilateral or bilateral blepharoplasty, repair of blepharoptosis, and/or brow ptosis repair may be **medically necessary**, when Criteria I., II. and/or III. are met.
  - B. Surgical session(s) in excess of one, for unilateral or bilateral blepharoplasty, repair of blepharoptosis, and/or brow ptosis repair is considered **not medically necessary**.
- V. Unilateral or bilateral upper lid blepharoplasty, repair of blepharoptosis, and brow ptosis repair is considered **not medically necessary** when Criteria I., or II., or III. above are not met.
- VI. Blepharoplasty of the lower lids for excessive skin is considered **not medically necessary**.

## LIST OF INFORMATION NEEDED FOR REVIEW

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

## Trichiasis, ectropion or entropion

- Any congenital or anatomical issue causing issues with vision
- Lateral and full-face photographs

## Anophthalmia

- Clinical documentation that the upper eyelid position interferes with the fit of a prosthesis in the socket

## Blepharoplasty for all other reasons

- Any disease process that can affect vision (e.g. myasthenia gravis or thyroid condition) or documentation to support absence of such disease process
- Clinical documentation of functional impairment due to vision loss
- Clinical documentation of visual field testing and examinations including 0-20 degrees as well as above 20 degrees, documenting:
  - Specific visual points seen and not seen, and
  - Proof that taping improves vision enough to meet criteria guidelines
- Clear direct frontal and lateral photographs in the pupillary plane with gaze in the primary position (looking straight ahead) that are consistent with the above visual fields and examinations
- Clinical documentation that surgical repair will be completed in one session (surgery)
- Clinical documentation to support the procedure is for the upper lid only

## Brow Ptosis

- Photographs demonstrate the eyebrow is below the supraorbital rim

## CROSS REFERENCES

1. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12

## BACKGROUND

Functional visual impairment occurs when excess upper eyelid tissue overhangs the upper eyelid margin and results in significant superior visual field obstruction. Visual field studies are used to determine the degree of obstruction. Visual field studies should be measured both with and without elevation of the excess tissue to determine the extent of visual field defect at rest and the amount of improvement that may be obtained from blepharoplasty.

Cahill (2011) published a report by the American Academy of Ophthalmology, on functional indications for upper eyelid ptosis and blepharoplasty surgery.<sup>[1]</sup> Thirteen studies were included. The authors stated that there are certain indicators that predict surgery outcomes, including margin reflex distance of 1 (MRD(1)) of 2mm or less and superior visual field loss of at least 12 degrees or 24%.

## REFERENCES

1. Cahill, KV, Bradley, EA, Meyer, DR, et al. Functional indications for upper eyelid ptosis and blepharoplasty surgery: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2011 Dec;118(12):2510-7. PMID: 22019388

## CODES

Codes	Number	Description
CPT	15820	Blepharoplasty, lower eyelid;
	15821	Blepharoplasty, lower eyelid; with extensive herniated fat pad
	15822	Blepharoplasty, upper eyelid;
	15823	Blepharoplasty, upper eyelid; with excessive skin weighting down lid
	67900	Repair of brow ptosis (supraciliary, mid-forehead or coronal approach)
	67901	Repair of blepharoptosis; frontalis muscle technique with suture or other material (eg, banked fascia)
	67902	Repair of blepharoptosis; frontalis muscle technique with autologous fascial sling (includes obtaining fascia)
	67903	Repair of blepharoptosis; (tarso) levator resection or advancement, internal approach
	67904	Repair of blepharoptosis; (tarso) levator resection or advancement, external approach
	67906	Repair of blepharoptosis; superior rectus technique with fascial sling (includes obtaining fascia)
	67908	Repair of blepharoptosis; conjunctivo-tarso-Muller's muscle-levator resection (eg, Fasanella-Servat type)
	67909	Reduction of overcorrection of ptosis
	67999	Unlisted procedure, eyelids
	67911	Correction of lid retraction
	67916	Repair of ectropion; excision tarsal wedge
	67917	Repair of ectropion; extensive (eg, tarsal strip operations)
	67923	Repair of entropion; excision tarsal wedge
67924	Repair of entropion; extensive (eg, tarsal strip or capsulopalpebral fascia repairs operation)	
	67950	Canthoplasty (reconstruction of canthus)
HCPCS	None	

**Date of Origin:** August 2018

## Rhinoplasty

**Effective:** August 1, 2020

**Next Review:** May 2021

**Last Review:** June 2020

### IMPORTANT REMINDER

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

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### DESCRIPTION

Rhinoplasty surgery reshapes the nose and is usually considered cosmetic. Reconstructive rhinoplasty may be performed to improve nasal respiratory function and/or to correct anatomic abnormalities caused by birth defects, disease or trauma.

### MEDICAL POLICY CRITERIA

#### Notes:

- Member contracts for covered services vary. Member contracts may have specific language defining congenital and developmental anomalies. Member contract language takes precedence over medical policy.
  - A congenital anomaly is defined as an anomaly that is present at birth (e.g., cleft palate).
  - Developmental anomalies are conditions that develop some time after birth.

- I. Rhinoplasty may be considered **medically necessary** for reconstruction of a nasal deformity in only **one or more** of the following circumstances:
  - A. Secondary to a congenital anomaly, including but not limited to facial cleft; or
  - B. After tumor resection; or

- C. After trauma which causes significant functional impairment, including but not limited to displaced nasal bone fracture severe enough to cause symptomatic nasal airway obstruction; or
  - D. Symptomatic nasal airway obstruction (i.e., difficulty breathing related to nasal passage obstruction) when **all** of the following are met:
    1. The nasal deformity is documented by **all** of the following:
      - a. Photographs of the anatomical abnormality, including frontal, lateral and inferior views (e.g., nasal base); and
      - b. There is significant bony obstruction of one or both nares, documented by an advanced imaging modality permitting visualization of the bony obstruction, such as computed tomography (CT) or magnetic resonance imaging (MRI); and
    2. Septoplasty, vestibular stenosis, alar collapse, and/or turbinectomy surgeries are not expected to resolve the nasal deformity or have been performed and failed to improve functional impairment; and
    3. Nasal airway obstruction is poorly responsive to a documented six-week trial of conservative medical management (e.g., topical/nasal corticosteroids, antihistamines).
- II. Rhinoplasty is considered a **cosmetic** procedure unless Criterion I. is met.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- Condition causing the need for rhinoplasty
- If not caused by congenital anomaly, including but not limited to facial cleft or tumor:
  - Photographs of the anatomical abnormality, including frontal, lateral and inferior views (e.g., nasal base)
  - Computed tomography (CT), magnetic resonance imaging (MRI) or other advanced imaging documenting significant obstruction of one or both nares
  - Conservative medical management provided, timeline and outcomes

Any surgeries performed, with outcomes or documentation why septoplasty, vestibular stenosis, alar collapse, and/or turbinectomy surgeries alone are not expected to resolve the nasal deformity.

## CROSS REFERENCES

1. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12
2. [Absorbable Nasal Implant for Treatment of Nasal Valve Collapse](#), Surgery, Policy No. 209

## REFERENCES

None

## CODES

Codes	Number	Description
CPT	30120	Excision or surgical planing of skin of nose for rhinophyma
	30400	Rhinoplasty, primary; lateral and alar cartilages and/or elevation of nasal tip
	30410	Rhinoplasty, primary; complete, external parts including bony pyramid, lateral and alar cartilages, and/or elevation of nasal tip
	30420	Rhinoplasty, primary; including major septal repair
	30430	Rhinoplasty secondary; minor revision (small amount of nasal tip work)
	30435	Rhinoplasty secondary; intermediate revision (bony work with osteotomies)
	30450	Rhinoplasty secondary; major revision (nasal tip work and osteotomies)
	30460	Rhinoplasty for nasal deformity secondary to congenital cleft lip and/or palate, including columellar lengthening; tip only
	30462	Rhinoplasty for nasal deformity secondary to congenital cleft lip and/or palate, including columellar lengthening; tip, septum, osteotomies
HCPCS	None	

**Date of Origin:** August 2018

## ***Laser Treatment for Port Wine Stains***

**Effective:** July 1, 2020

**Next Review:** May 2021

**Last Review:** May 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Port wine stain (PWS) is a capillary malformation that begins as a pale pink flat area (macular lesion) in childhood and grows as the patient ages.

### **MEDICAL POLICY CRITERIA**

- I. Laser treatment may be considered **medically necessary** for port wine stains.
- II. Destruction of cutaneous vascular lesions for removal of telangiectasias (spider veins) is considered **cosmetic**.

### **LIST OF INFORMATION NEEDED FOR REVIEW**

#### **REQUIRED DOCUMENTATION:**

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

Medical records related to history and physical/chart notes documenting presence of port wine stain.

## CROSS REFERENCES

1. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12

## BACKGROUND

Common areas for port wine stains (PWS) to appear are on the face over the areas of the first and second trigeminal nerves and the eyes or mouth. It is common to see a PWS overlying an arteriovenous, arterial or venous malformation. The abnormal blood vessels within the PWS become progressively more dilated in size, which results in the lesion becoming dark purple and elevated in some instances. Nodules and hypertrophy may develop in the soft tissue underlying the PWS. Nodules may continue to grow and can bleed easily if traumatized. PWS persists into adult life and is associated with systemic abnormalities such as glaucoma.

Treatment of a PWS in its macular stage will prevent the development of the hypertrophic component of the lesion. Laser treatment of a PWS diminishes the existing blood vessels making them smaller, fewer in number, and less likely to progress in size.

## REFERENCES

None

## CODES

Codes	Number	Description
CPT	17106	Destruction of cutaneous vascular proliferative lesions (eg, laser technique); less than 10 sq cm
	17107	Destruction of cutaneous vascular proliferative lesions (eg, laser technique); 10.0 to 50.0 sq cm
	17108	Destruction of cutaneous vascular proliferative lesions (eg, laser technique); over 50.0 sq cm
HCPCS	None	

**Date of Origin:** August 2018

## Chemical Peels

**Effective:** September 1, 2020

**Next Review:** May 2021

**Last Review:** July 2020

### IMPORTANT REMINDER

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

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

## DESCRIPTION

A chemical peel refers to a controlled removal of varying layers of the epidermis and superficial dermis with the use of a 'wounding' agent, such as phenol or trichloroacetic acid (TCA).

## MEDICAL POLICY CRITERIA

### EPIDERMAL CHEMICAL PEELS

- I. Epidermal chemical peels with 50 - 70% alpha hydroxy acids may be considered **medically necessary** as a treatment of active acne that has failed to respond to a trial of topical and/or oral antibiotic acne therapy.
- II. Epidermal chemical peels with 50 - 70% alpha hydroxy acids are considered **not medically necessary** as a first-line treatment of active acne.
- III. Epidermal chemical peels for the treatment of photoaged skin, wrinkles, or acne scarring are considered **cosmetic**.

### DERMAL CHEMICAL PEELS

- I. Dermal chemical peels may be considered **medically necessary** to treat numerous (>10) actinic keratoses or other premalignant skin lesions, when treatment of the individual lesions becomes impractical.

- II. Dermal chemical peels are considered **not medically necessary** to treat less than 10 actinic keratoses or other premalignant skin lesions.
- III. Dermal chemical peels as treatments of end-stage acne scarring are considered **cosmetic**.

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

## CROSS REFERENCES

1. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12

## BACKGROUND

The most common indication for chemical peeling is as a treatment of photoaged skin, correcting pigmentation abnormalities, solar elastosis, and wrinkles. However, chemical peeling has also been used as a treatment for various stages of acne and multiple actinic keratoses when treatment of individual lesions is not feasible.

An epidermal peel may be used to remove fine, subtle lines, soften the appearance of enlarged pores, improve the skin texture and lighten hyper-pigmentary disorders. Multiple epidermal peels (also referred to as chemical exfoliation) may also be used in patients with active acne.

Dermal peels may be used to treat deep wrinkling, actinic damage, or actinic keratoses. Acne scarring has also been treated with dermal peels.

## REFERENCES

1. BlueCross BlueShield Association Medical Policy Reference Manual "Chemical Peels." Policy No. 8.01.16

## CODES

Codes	Number	Description
CPT	15788	Chemical peel, facial; epidermal
	15789	Chemical peel; facial; dermal
	15792	Chemical peel; nonfacial; epidermal
	15793	Chemical peel; nonfacial; dermal
	17360	Chemical exfoliation for acne (eg, acne paste, acid)
HCPCS	None	

**Date of Origin:** August 2018

## ***Implantable Cardioverter Defibrillator***

**Effective:** July 1, 2020

**Next Review:** April 2021

**Last Review:** June 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

The automatic implantable cardioverter defibrillator (ICD) is a device designed to monitor a patient's heart rate, recognize ventricular fibrillation (VF) or ventricular tachycardia (VT), and deliver an electric shock to terminate these arrhythmias to reduce the risk of sudden cardiac death. Indications for ICD implantation can be broadly subdivided into 1) primary prevention, i.e., their use in patients who are considered at high risk for sudden cardiac death but who have not yet experienced life-threatening VT or VF; and 2) secondary prevention, i.e., their use in patients who have experienced a potentially life-threatening episode of VT (near sudden cardiac death).

### **MEDICAL POLICY CRITERIA**

- I. Transvenous or subcutaneous implantable cardioverter defibrillator (ICD) implantation in pediatric patients (less than 18 years of age) may be considered **medically necessary**.
- II. The use of a transvenous automatic implantable cardioverter defibrillator (ICD) may be considered **medically necessary** in adult patients (age 18 and older) who are not candidates for a cardiac revascularization procedure (coronary artery bypass graft

[CABG] or percutaneous transluminal coronary angioplasty [PTCA]) and who meet one of the following criteria (A. or B.):

- A. For *primary* prevention when one or more of the following criteria are met:
1. Ischemic cardiomyopathy with New York Heart Association (NYHA) functional Class I symptoms (See Policy Guidelines) when both of the following criteria (a. and b.) are met:
    - a. History of myocardial infarction at least 40 days before ICD treatment;  
and
    - b. Left ventricular ejection fraction of 30% or less.
  2. Ischemic cardiomyopathy with NYHA functional Class II or Class III symptoms (See Policy Guidelines) when both of the following criteria (a. and b.) are met:
    - a. History of myocardial infarction at least 40 days before ICD treatment;  
and
    - b. Left ventricular ejection fraction of 35% or less.
  3. Nonischemic cardiomyopathy, including arrhythmogenic right ventricular cardiomyopathy, or neuromuscular disorders when one or more of the following criteria are met:
    - a. Syncope presumed due to ventricular arrhythmia; or
    - b. All of the following criteria are met:
      - i. Left ventricular ejection fraction of 35% or less; and
      - ii. Reversible causes have been excluded; and
      - iii. Response to optimal medical therapy has been adequately determined.
  4. Heart failure with left ventricular ejection fraction of 40% or less, who are awaiting heart transplantation and will be discharged home
  5. Nonhospitalized heart failure patients with NYHA Class IV symptoms (see Policy Guidelines) that are candidates for a left ventricular assist device (LVAD) or cardiac transplantation
  6. Hypertrophic cardiomyopathy (HCM) at high risk for sudden cardiac death with at least one of the following major risk factors:
    - a. History of premature HCM-related sudden death in one or more first-degree relatives younger than 50 years; or
    - b. Left ventricular hypertrophy greater than 30 mm; or
    - c. One or more runs of nonsustained ventricular tachycardia at heart rates of 120 beats per minute or greater on 24-hour Holter monitoring; or
    - d. Prior unexplained syncope inconsistent with neurocardiogenic origin
    - e. Abnormal blood pressure response to exercise.
  7. Documented *LMNA* gene mutations (lamin A/C deficiency) in patients with at least one of the following conditions:

- a. Cardiomyopathy; or
  - b. Symptomatic cardiac arrhythmias; or
  - c. Left ventricular ejection fraction less than 45%; or
  - d. Nonsustained ventricular tachycardia; or
  - e. Nonsense *LMNA* variant.
8. Diagnosis of long QT syndrome (LQTS) with at least one of the following:
- a. Prior cardiac arrest; or
  - b. Recurrent syncope events while on beta blocker therapy.
9. Diagnosis of Brugada syndrome (BrS) with at least one of the following:
- a. Prior cardiac arrest; or
  - b. Spontaneous sustained ventricular tachycardia (VT) with or without syncope; or
  - c. Spontaneous diagnostic type 1 ECG with a history of syncope, seizure, or nocturnal agonal respiration after noncardiac causes have been excluded; or
  - d. Development of ventricular fibrillation (VF) during programmed electrical stimulation.
10. Diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) with at least one of the following:
- a. Prior cardiac arrest; or
  - b. Recurrent syncope; or
  - c. Polymorphic/bidirectional VT that is nonresponsive to medical management, or left cardiac sympathetic denervation.
11. Diagnosis of short QT syndrome (SQTS) with at least one of the following:
- a. Prior cardiac arrest; or
  - b. Symptomatic and have documented spontaneous VT with or without syncope; or
  - c. Family history of sudden cardiac death.
12. Diagnosis of cardiac sarcoidosis with at least one of the following:
- a. Prior cardiac arrest; or
  - b. Sustained VT; or
  - c. Left ventricular ejection fraction of 35% or less.
13. Diagnosis of adult congenital heart disease with hemodynamically unstable VT or VF.
14. Patients with a left ventricular assist device (LVAD) and sustained ventricular arrhythmia
- B. For *secondary* prevention in patients who meet one or more of the following:

1. History of a life-threatening clinical event associated with ventricular arrhythmic events such as sustained ventricular tachyarrhythmia, after reversible causes (e.g., acute ischemia) have been excluded; or
  2. Diagnosis of nonischemic cardiomyopathy or ischemic heart diseases with at least one of the following:
    - a. Hemodynamically unstable ventricular tachycardia; or
    - b. Stable ventricular tachycardia not due to reversible causes (e.g., acute ischemia).
- III. The use of the transvenous ICD is considered **investigational** for adult patients when Criterion II. is not met and including, but not limited to, patients with one or more of the following:
- A. Have had an acute myocardial infarction (i.e., less than 40 days before ICD treatment); or
  - B. Have New York Heart Association (NYHA) Class IV (See Policy Guidelines) congestive heart failure (unless patient is eligible to receive a combination cardiac resynchronization therapy ICD device); or
  - C. Have had a cardiac revascularization procedure in the past 3 months (coronary artery bypass graft [CABG] or percutaneous transluminal coronary angioplasty [PTCA]) or are candidates for a cardiac revascularization procedure; or
  - D. Have noncardiac disease that would be associated with life expectancy less than one year.
- IV. The use of the subcutaneous ICD may be considered **medically necessary** in adult patients (age 18 years and older) who meet all of the following criteria (A.-C.):
- A. Applicable medical necessity criteria for transvenous ICD is met (Criterion II.); and
  - B. Have no indication for antibradycardia pacing; and
  - C. Do not have ventricular arrhythmias that are known or anticipated to respond to antitachycardia pacing.
- V. The use of the subcutaneous ICD is considered **investigational** for adult patients when Criteria IV. are not met.
- VI. Revision(s) or replacement(s) of a transvenous or subcutaneous ICD may be considered **medically necessary** after the device has been placed.
- VII. The use of ICDs with an ST-segment monitoring feature in patients is considered **investigational** for all indications.
- VIII. The use of extravascular (substernal lead) ICDs is considered **investigational** for all indications.

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

## POLICY GUIDELINES

### New York Heart Association Classes

- NYHA Class I = No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
- NYHA Class II = Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
- NYHA Class III = Marked limitation of physical activity; less than ordinary activity leads to symptoms
- NYHA Class IV = Inability to carry on any activity without symptoms; symptoms may be present at rest

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and Physical/Chart Notes
- Documentation of symptoms, associated diagnoses and treatments
- Type of ICD being requested

## CROSS REFERENCES

1. [Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy](#), Genetic Testing, Policy No. 72
2. [Intracardiac Ischemia Monitoring](#), Surgery, Policy No. 208
3. [Leadless Cardiac Pacemakers](#), Surgery, Policy No. 217

## BACKGROUND

The standard ICD involves placement of a generator in the subcutaneous tissue of the chest wall. Transvenous leads are attached to the generator and threaded intravenously into the endocardium. The leads sense and transmit information on cardiac rhythm to the generator which analyzes the rhythm information and produces an electrical shock when a malignant arrhythmia is recognized.

A totally subcutaneous ICD (S-ICD®) has also been developed. This device does not employ transvenous leads, and thus avoids the need for venous access and complications associated with the venous leads. Rather, a subcutaneous electrode is implanted adjacent to the left sternum. The electrodes sense the cardiac rhythm and deliver countershocks through the subcutaneous tissue of the chest wall.

ICDs with a built-in ST-segment monitoring feature, also called ICD-based ischemia monitors, are currently being studied. ST segment monitoring may also be referred to as intracardiac ischemia monitoring. The continuous ST-segment monitoring provided by this added feature is intended to detect changes in the patient's ST-segment as a possible indicator of an ischemic cardiac event. If an ST segment shift meets or exceeds a preprogrammed threshold, the device stores the event data (e.g., date, time, heart rate, maximum ST shift, duration of the event). The device has a patient notifier feature that vibrates to alert the patient that an ST episode has occurred.

Extravascular (EV) ICDs have been developed, which have lead placement under the sternum. These devices are designed to provide the benefits of transvenous ICDs while avoiding the complications associated with intravascular lead placement.

## REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) has approved a number of ICDs through the premarket approval (PMA) process. The FDA-labeled indications generally include patients who have experienced life-threatening ventricular tachyarrhythmia associated with cardiac arrest or ventricular tachyarrhythmia associated with hemodynamic compromise and resistance to pharmacologic treatment.

The following are examples of FDA-approved transvenous ICDs:

- Devices manufactured by Boston Scientific include Dynagen, Inogen, Origen, and Teligen.
- Medtronic produces the Evera Family of devices (originally: Virtuosos/Entrust/Maximo/Intrinsic/Marquis family).
- St. Jude Medical, Inc. devices include the Ellipse / Fortify Assura Family and the Current Plus ICD (originally: Cadence Tiered Therapy Defibrillation System).
- Other devices with similar approval language include devices from Biotronik, Boston Scientific, and Sorin CRM USA.

The following are examples of FDA-approved subcutaneous ICDs:

- The Subcutaneous Implantable Defibrillator (S-ICD®) System (Cameron Health, Inc., acquired by Boston Scientific, Inc.) received FDA approval on September 28, 2012 for “defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous frequently recurring ventricular tachycardia that is reliably terminated with antitachycardia pacing.” The electrode is called the Q-TRAK® and the electrode insertion tool is called the Q-Guide™.
- The Emblem S-ICD™ (Boston Scientific, Inc.), which is smaller and longer-lasting than the original S-ICD, was cleared for marketing through a PMA supplement.

Currently, there are no FDA-approved EV ICDs.

**Note:** This policy addresses only initial ICD implantation; it does not address ICD removal or replacement.

## EVIDENCE SUMMARY

### TRANSVENOUS IMPLANTABLE CARDIAC DEFIBRILLATOR (ICD)

The scientific evidence evaluating the use of automatic ICDs on health outcomes consists of several technology assessments and clinical trials. Evidence from well-conducted randomized controlled trials (RCTs) shows consistent associations between use of ICDs and improved health outcomes among specific groups of patients with symptomatic ischemic or nonischemic dilated cardiomyopathy and those with history of prior arrhythmogenic events.

### ICDS FOR HEART FAILURE AND CARDIOMYOPATHY

#### Systematic Reviews

In 2016, results from the Danish Study were published. This was a multi-center RCT comparing ICD to standard management in patients with non-ischemic heart failure, described in more detail below.<sup>[1]</sup> While the trial demonstrated a significantly lower risk of sudden cardiac

death (SCD) with ICD, there was no difference seen in overall mortality. After this article was published, several systematic reviews evaluated the evidence from RCTs on ICD use in patients with nonischemic cardiomyopathy.

A 2018 Cochrane review included six RCTs (n=3,128) and reported that ICD use plus optimal medical therapy had a survival benefit compared with optimal medical therapy alone (hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.66 to 0.92), but the authors noted that ICD use likely increases the risk of adverse events.<sup>[2]</sup> Wolff (2015) meta-analyzed five RCTs, with a total of 2,992 dilated cardiomyopathy patients, that compared ICD therapy with medical therapy for primary prevention.<sup>[3]</sup> They found a significant reduction in mortality and sudden cardiac death with ICD therapy (odds ratio [OR] 0.77, 95% CI 0.64 to 0.93, p=0.006 and OR 0.43, 95% CI 0.27 to 0.69, p = 0.0004, respectively).

Similarly, Luni (2017) performed a meta-analysis of six RCTs evaluating ICD use for primary prevention in patients with nonischemic cardiomyopathy.<sup>[4]</sup> While they reported a significant survival benefit with ICD therapy, this benefit was no longer significant when the analysis was restricted to trials which had adequate beta blocker, ACE/ARB and aldosterone receptor blocker use. A meta-analysis by Al-Khatib (2017) included only four RCTs, as they included only trials that compared ICD to medical therapy that had at least 100 nonischemic cardiomyopathy patients and follow-up periods of at least 12 months.<sup>[5]</sup> This analysis also reported a significant mortality reduction with ICD therapy (hazard ratio [HR] 0.75, 95% CI 0.61-0.93, p=0.008). A meta-analysis by Siddiqui (2018), which included six RCTs, similarly reported a lower mortality rate with ICD compared to medical therapy (OR 0.74, 95% CI 0.62 to 0.90, p=0.002), and compared to amiodarone treatment (OR 0.66, 95% CI 0.44 to 0.98, p=0.04).<sup>[6]</sup> Other meta-analyses have shown similar results.<sup>[7,8]</sup>

Gracieux (2014) published the results of a systematic review of nine RCTs of adults aged 19 years or older with ischemic cardiomyopathy to determine the incidence and predictors of appropriate ICD therapy delivery.<sup>[9]</sup> Only four of the nine RCTs that met inclusion criteria reported the clinical characteristics of patients who received appropriate shocks. These characteristics included male sex, advanced NYHA class, nonsustained ventricular tachycardia, and lower serum creatinine. These patients were also less likely to be on beta-blocker medications. LVEF was not a significant factor. The authors noted that predictors of appropriate shocks were not adequately studied in large trials and recommended further large prospective studies.

A 2013 technology assessment from the Agency for Healthcare Research and Quality (AHRQ) assessed the evidence published through December 4, 2012 for ICDs for primary prevention of sudden cardiac death.<sup>[10]</sup> Included studies were RCTs or comparative cohort studies comparing ICD to no ICD or to different ICD interventions, a minimum of 10 participants per study group, and concurrent controls in the cohort studies. Patients in the ICD groups must have been followed from the time of ICD implantation. Key questions were well defined and focused on the following:

- Outcomes of 1) ICD vs. no ICD, 2) ICD with antitachycardia pacing (ATP) vs. ICD alone, and 3) ICD with cardiac resynchronization therapy (CRT) vs. ICD alone
- Variations in outcomes and adverse events among subgroups of participants, ICD devices, clinicians, and facilities
- Eligibility criteria and methods for evaluation of participants in comparative trials

- Likelihood of SCD or ventricular tachyarrhythmia (VT) as measured by total shocks in patients with ICDs or SCD episodes in patients without ICDs.

Ten RCTs (18 articles<sup>[11-27]</sup>) and four cohort studies<sup>[28-31]</sup> of adults met inclusion criteria.; no studies of ICDs in children met inclusion criteria. All included studies conducted intention-to-treat analyses. In studies comparing ICD to no ICD the strength of evidence for all-cause mortality and SCD was rated as high. These studies found reduced risk of all-cause mortality three to seven years after ICD implantation and SCD two to six years after implantation (HR 0.69 and 0.37, respectively). There was indirect evidence across studies that ICD provided no benefit for patients with recent myocardial infarction (MI), defined as <30-40 days. No significant difference was found for all-cause mortality or SCD across subgroups by patient sex or age or by the facilities in which the ICDs were placed. The evidence for quality of life in these studies was rated as low and failed to show consistent effects of ICD placement. No studies reported the effect of adding ATP in ICD patients. Four RCTs<sup>[32-35]</sup> that compared ICD alone to ICD with CRT (CRT-D) met inclusion criteria, but the strength of evidence was rated as insufficient due to discordant findings.

Eligibility criteria for ICD implantation in 13 of the 14 studies included both ischemic or nonischemic dilated cardiomyopathy (DCM) and left ventricular ejection fraction (LVEF)  $\leq 35\%$ . Most of the studies excluded adults over 70 to 80 years of age. Heart failure (HF) class varied between studies. While most RCTs tested ICD patients for nonsustained VT, different diagnostic tools were used. Only one RCT used electrophysiology studies (EPS) in all participants. Coronary angiography or exercise testing for coronary stenosis was tested in four of the RCTs. Limitations of the included studies were high attrition rates (>20%), differential attrition and/or crossover rates between study groups, and between-group differences in concurrent beta blocker use and control treatments. In addition, outcome assessors were not blinded. The authors concluded that there was high strength evidence in favor of ICD therapy compared to no ICD therapy for primary prevention of SCD in certain patients with reduced LVEF and ischemic or non-ischemic cardiomyopathy (NICM).

Chen (2013) analyzed eight RCTs<sup>[32,36-54]</sup> that compared the safety and effectiveness of ICD alone with cardiac resynchronization therapy and ICD (CRT-D) in patients with heart failure.<sup>[55]</sup> The study quality was rate as high in four RCTs with follow-up of more than six months. The quality of the other four RCTs was down-graded slightly due to short-term follow-up of less than six months. CRT-D showed significantly superior outcomes compared to ICD alone for cardiac function, improved clinical condition, fewer hospitalizations, and lower all-cause mortality 12 months or more after implantation, though not during the initial three to six months after implantation. However, CRT-D had a significantly higher rate of serious adverse events (e.g., pneumothorax, hemothorax, lead dislodgement, coronary sinus dissection). There were a number of methodological limitations of the meta-analysis and the included RCTs. The limitations included the between-study differences in follow-up duration noted above. In addition, some studies included primarily NYHA class I and II heart failure patients while others focused on class III and IV patients. The authors also noted that the enrolled patients were younger than the general population of candidates for ICD or CRT-D which could result in an overestimation of benefit since older patients would be expected to have more comorbidities that could negatively impact clinical outcomes.

Shinkel (2012) reported the results of a systematic review and meta-analysis<sup>[56-58]</sup> of patients with ICDs for hypertrophic cardiomyopathy (HCM).<sup>[59]</sup> Mean age was 42 years and mean follow-up was 3.7 years. The majority of the studies were for primary prevention ICDs.

Risk factors for SCD included left ventricular wall thickness  $\geq 30$  mm, family history of SCD, nonsustained ventricular tachycardia, syncope, and abnormal blood pressure response. The rate of appropriate ICD therapy was 14%, with annualized rate of 3.3%. Inappropriate shocks occurred in 20% of the 1966 patients in the 13 studies that reported this outcome. The annualized rate of inappropriate therapy was 4.8%. Mortality rates were reported in 13 studies and included 3% from cardiac death and 2% from noncardiac death. Nine studies reported adverse events which occurred in 15% of patients. The most frequent complications were lead malfunction (7%) or displacement (3%) and infection (3%). Limitations of the meta-analysis included the use of data from observational studies, and the potential risk of heterogeneity of participant clinical characteristics and SCD risk profiles when pooling data from different studies. Limitations of the included studies were the lack of clear information on the clinical decision strategy and risk factors for ICD placement, lack of long-term data on ICD-related complications in the general practice setting, younger age of participants than would be expected in the general clinical setting, and insufficient consideration of the psychological and behavioral aspects of ICD therapy in HCM patients. This latter limitation is important because many HCM patients who are candidates for ICD are otherwise healthy, asymptomatic young individuals.

### **Randomized Controlled Trials (RCTs)**

A study by Biton (2018) evaluated the impact NYHA class on long-term survival with ICD therapy in patients from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II).<sup>[60]</sup> There were 1,164 patients in the study, 442 were NYHA I, 425 were NYHA II, and 297 were NYHA III. All had a documented prior MI. After eight years of follow-up, mortality was lower for the ICD treatment group compared with non-ICD therapy, regardless of HF symptoms (NYHA I HR 0.63, 95% CI 0.46 to 0.85,  $p=0.003$ ; NYHA II HR 0.68, 95% CI 0.50 to 0.93,  $p=0.017$ ; NYHA III HR 0.68, 95% CI 0.50 to 0.94,  $p=0.018$ ).

Kober (2013) reported results from the Danish Study in 2016,<sup>[1]</sup> which was included in several of the recent systematic reviews described above. This unblinded trial included 556 patients with NICM, enrolled between 2008 and 2014 from multiple centers in Denmark, to compare ICD therapy to usual clinical care. As many patients with heart failure are not treated with CRT, the randomization of patients was stratified such that both ICD and control groups had a similar proportion of CRT patients (58%). The primary outcome of the study was death from any cause, and secondary outcomes included sudden cardiac death, cardiovascular death and non-fatal MIs. The median follow-up time was 67.6 months (interquartile range, 49-85 months). There were 120 patients (21.6%) in the ICD group and 131 patients in the control group that died during follow-up (4.4 and 5.0 deaths/100 person-years, respectively), which was not significantly different. Subgroup analysis showed no difference in ICD effect between patients receiving CRT and those who did not, but younger patients ( $< \text{age } 59$ ) did demonstrate a survival benefit with ICD (HR 0.51, 95% CI 0.29 to 0.92). The risk for cardiovascular death was also not significantly different between groups (HR for ICD group vs. control, 0.77, 95% CI 0.57 to 1.05,  $p=0.10$ ). However, sudden cardiac death was far less frequent in the ICD group than in controls (HR 0.50, 95% CI 0.31 to 0.82). The lack of benefit with IDC therapy for overall survival seen in this study differs from previous findings. The authors concluded that recent advances in heart failure treatment, including CRT, have reduced the potential benefit from ICD therapy, except in select patients.

### **Non-randomized Studies**

## Ischemic or Dilated Cardiomyopathy

Zabel (2020) published results of the European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter-Defibrillators (EU-CERT-ICD) study, a multicenter controlled cohort study evaluating ICD use for primary prevention in patients with ischemic or dilated cardiomyopathy.<sup>[61]</sup> Of the 2,327 patients that were recruited for the study, 2,247 had sufficient data for analysis: 1,516 who had ICD implantation and 731 controls who did not have ICD implantation. After a mean follow-up of 2.4 years, mortality was significantly lower in the ICD group after adjustment for other mortality predictors, such as age and LVEF (HR 0.731, 95% CI 0.569 to 0.938,  $p=0.014$ ). ICDs did not appear to benefit patients with diabetes or those above age 75.

## Nonischemic Cardiomyopathy

A multi-center study using data from the German Device Registry was published by Frommeyer (2019).<sup>[62]</sup> This registry includes 5,451 patients with one year of follow-up who had a device implanted. Of these, 779 were patients with NICM and a LVEF of 35% or less. Among these 779 patients, 56% received a cardiac resynchronization therapy defibrillator system, 33% received a single-chamber ICD, and 11% received a dual-chamber ICD. After a median follow-up of 16.1 months, 9.3% of the patients had died. Mortality was significantly higher in patients aged 68 years and above (7.9%) compared with patients aged 59 to 68 years (2.5%) or below age 59 (3.8%,  $p<0.015$ ).

Amara (2017) compared ICD therapy for the prevention of sudden cardiac death in patients with NICM and ischemic cardiomyopathy (ICM) enrolled in the multicenter Défibrillateur Automatique Implantable-Prévention Primaire (DAI-PP) study.<sup>[63]</sup> A total of 5,485 patients participated in the study: 2,181 (39.8%) with NICM and 3,304 (60.2%) with ICM. The mean follow-up was  $3.1 \pm 2.2$  years. Patients with ICM were significantly older ( $63.7 \pm 10.3$  vs.  $60.6 \pm 12.2$  years,  $p<0.0001$ ) and had a higher prevalence of sinus rhythm (77.3% vs. 74.0%,  $p=0.009$ ), a higher ejection fraction (27% vs. 25%,  $p<0.0001$ ), and a narrower QRS (37.3% vs. 21.4% with QRS  $<120$ ,  $p<0.0001$ ) than those with NICM. Mortality during follow-up was significantly higher in ICM patients, at 52.3 events/1000 person-years vs. 48.6 events/1000 person-years for NICM patients ( $p=0.008$ ). This difference was primarily due to increased non-cardiovascular mortality, as cardiovascular mortality rates were similar between groups. The authors noted that inappropriate therapies were more frequent in those with NICM (7.94 vs. 5.96%,  $p=0.005$ ).

Results from subjects with nonischemic dilated cardiomyopathy (NIDCM) included in SCD-HeFT and DEFINITE studies suggested a mortality benefit from ICD therapy, although statistical significance that was not achieved in these studies was likely related to insufficient power.

## Hypertrophic Cardiomyopathy

Magnusson (2015) reported outcomes for 321 patients with HCM treated with an ICD enrolled in a Swedish registry.<sup>[64]</sup> Over a mean 5.4 years of follow-up, appropriate ICD discharges in response to ventricular tachycardia or fibrillation occurred in 77 patients (24%), corresponding to an annual rate of appropriate discharges of 5.3%. At least one inappropriate shock occurred in 46 patients (14.3%), corresponding to an annualized event rate of 3.0%. Ninety-two patients (28.7%) required at least one surgical intervention for an ICD-related complication, with a total

of 150 ICD-related reinterventions. Most reinterventions (n=105, 70%) were related to lead dysfunction.

## **ICDS IN PATIENTS WITH *LMNA* GENE MUTATION**

In a systematic review for GeneReviews®, Hershberger (2016) concluded, “Because risk for sudden cardiac death in *LMNA*-related DCM accompanies heart block and bradyarrhythmias, ICD use (rather than just pacemaker use) has been recommended for all indications.”<sup>[65]</sup>

Pasotti (2008) conducted a retrospective longitudinal study with 94 individuals with mutations in the *LMNA* gene.<sup>[66]</sup> Subjects were observed for a median follow-up time of 57 months. During follow-up, 20 patients received a pacemaker and 16 received an ICD implantation. Twelve appropriate ICD interventions detected by the device (eight ventricular fibrillation and four sustained VT). None of the subjects with ICDs died from sudden cardiac death, whereas the pacemaker did not appear to protect from SCD.

## **ICDS IN PATIENTS WITH CARDIAC ION CHANNELOPATHIES**

ICDs have been used for both primary and secondary prevention in patients with a number of disorders that predispose to ventricular arrhythmias and sudden cardiac death, including long QT syndrome (LQTS), Brugada syndrome (BrS), short QT syndrome (SQTS), and catecholaminergic polymorphic ventricular tachycardia (CPVT). Some of these conditions are extremely rare, but the use of ICDs has been described in small cohorts of patients with BrS, LQTS, and SQTS. These small cohort studies are listed below:

### **Long QT Syndrome**

Horner (2010) reported on outcomes for 51 patients with genetically confirmed LQTS treated with an ICD from 2000 to 2010 who were included in a single-center retrospective analysis of 459 patients with genetically confirmed LQTS.<sup>[67]</sup> Of the patients treated with ICDs, 43 (84%) received the device as primary prevention. Twelve patients (24%) received appropriate ventricular fibrillation or torsades de pointes-terminated ICD shocks. Factors associated with appropriate shocks included secondary prevention indications (p=0.008), QT corrected (QTc) duration greater than 500 ms (p=0.0008), non-LQT3 genotype (p=0.02), documented syncope (p=0.05), documented torsades de pointes (p=0.003), and a negative sudden family death history (p=0.0001). Inappropriate shocks were delivered in 15 patients (29%). Patients with the LQT3 genotype had only received inappropriate shocks.

### **Brugada Syndrome**

A systematic review by Kusumoto (2018) compared ICD outcomes for asymptomatic Brugada syndrome (BrS) patients with and without inducible ventricular arrhythmia on electrophysiology study.<sup>[68]</sup> A meta-analysis of five studies reported OR of 2.3 (95% CI 0.63 to 8.66, p=0.2) for major arrhythmic events in those with inducible ventricular arrhythmia compared to those without. The authors noted that there was a low overall event rate in this asymptomatic population.

Hernandez-Ojeda (2017) reported on results from a single-center registry of 104 patients with BrS who were treated with ICDs. Ten (9.6%) patients received an ICD for secondary prevention and in 94 (90.4%) patients received an ICD for primary prevention. During the average 9.3-year follow-up, 21 (20.2%) patients received a total of 81 appropriate shocks. In multivariate analysis, type 1 electrocardiogram with syncope and secondary prevention

indication were significant predictors of appropriate therapy. Nine (8.7%) patients received 37 inappropriate shocks. Twenty-one (20.2%) patients had other ICD-related complications.

Conte (2015) described outcomes for a cohort of 176 patients with spontaneous or drug-induced Brugada type 1 electrocardiographic findings who received an ICD at a single institution and were followed for at least six months.<sup>[69]</sup> Before ICD implantation, 14.2% of subjects had a history of aborted SCD due to sustained spontaneous ventricular arrhythmias, 59.7% had at least one episode of syncope, and 25.1% were asymptomatic. Over a mean follow up of 83.8 months, 30 patients (17%) had spontaneous sustained ventricular arrhythmias detected. Sustained ventricular arrhythmias were terminated by ICD shocks or antitachycardia pacing in 28 patients (15.9%) and two patients (1.1%), respectively. However, 33 patients (18.7%) experienced inappropriate shocks. Eight patients (4.5%) died during follow up, three of whom died of cardiac causes.

Dores (2015) reported results of a Portuguese registry that included 55 patients with BrS, 36 of whom were treated with ICDs for either primary or secondary prevention.<sup>[70]</sup> Before ICD implantation, 52.8% of subjects were asymptomatic, 30.6% had a history of syncope with suspected arrhythmic cause, and 16.7% had a history of aborted SCD. Over a mean follow up of 74 months, seven patients experienced appropriate shocks, corresponding to an incidence of 19.4% and an annual event rate of 2.8%. In multivariate analysis, predictors of appropriate shocks were a history of aborted SCD (HR 7.87, 95% CI 1.27 to 49.6,  $p=0.027$ ) and nonsustained ventricular tachycardia during follow up (HR 6.73, 95% CI 1.27 to 35.7,  $p=0.025$ ).

In data from a US cohort of 33 patients with BrS treated with ICDs, Steven (2011) reported that two of three patients with a prior history of aborted SCD received appropriate shocks over a mean 7.9 years of follow up, while none of the 30 patients without a history of aborted SCD had an arrhythmia detected.<sup>[71]</sup> In a smaller registry that included 25 patients with BrS treated with ICDs, over an average follow up of 41.2 months, appropriate shocks were delivered in three patients, all of whom had prior cardiac arrest.<sup>[72]</sup>

### **Catecholaminergic Polymorphic Ventricular Tachycardia**

A systematic review by Roston (2018) assessed the use of ICDs in patients with CPVT and included 53 studies (total  $n=1,429$ ).<sup>[73]</sup> There were 503 patients that received an ICD in these studies, with 47.3% of the patients receiving the device for primary prevention. Only 12.8% were prescribed optimal antiarrhythmic therapy. More than 40% of the ICD patients had at least one appropriate shock during follow-up, while 20.8% had at least one inappropriate shock, 19.6% had electrical storm, and seven patients died (four due to an ICD-associated electrical storm). Other ICD complications were seen in 32.4% of the patients.

Roston (2015) published the results of a multicenter retrospective cohort study that included 226 patients with catecholaminergic polymorphic ventricular tachycardia.<sup>[74]</sup> Implantable cardioverter defibrillators were placed in 121 (54%) most often for history of cardiac arrest (67 patients [55%]). One or more treatment failure events while on beta blockers were documented in 42 patients (35%). Appropriate shocks were experienced by 56 patients (46%) and inappropriate shocks occurred in 21 patients (22%). Arrhythmia was terminated after appropriate shock in 31 patients (55%), but nine (16%) had poor response to appropriate shocks. Electrical storm occurred in 22 patients (18%). ICD-related complications occurred in 28 patients (23%), usually manifesting as lead problems in 16 (57%). There were no differences in number of appropriate shocks, success of shocks, or incidence of electrical storm between patients with and without history of cardiac arrest. Death occurred in three

patients (2%) despite ICD placement, one of which was associated with electrical storm. Fifty-eight patients (48%) were asymptomatic after ICD placement; however, 30 (25%) had persistent ventricular ectopy, 13 (11%) experienced syncope, and 13 (11%) had subsequent cardiac arrest.

Roses-Noguer (2014) reported results of a small retrospective study of 13 patients with CPVT who received an ICD.<sup>[75]</sup> The indication for ICD therapy was syncope despite maximal beta-blocker therapy in 6 patients (46%) and aborted SCD in seven patients (54%). Over a median follow-up of 4.0 years, 10 patients (77%) received a median four shocks. For 96 shocks, 87 electrocardiograms (ECGs) were available for review; of those, 63 (72%) were appropriate and 24 (28%) were inappropriate. Among appropriate shocks, 20 (32%) were effective in restoring sinus rhythm.

## ICDS AND ADVERSE EVENTS

Ezzat (2015) published a systematic review and meta-analysis of adverse events (AEs) following ICD implantation, comparing rates of AEs reported in clinical trials of ICDs with those reported in the U.S. National Cardiovascular Data Registry.<sup>[76]</sup> The review included 18 RCTs with a total of 6,796 patients. In pooled analysis, the overall AE rate was 9.1% (95% CI 6.4 to 12.6%). Rates of access-related complications, lead-related complications, generator-related complications, and infection were 2.1% (95% CI 1.3 to 3.3%), 5.8% (95% CI 3.3 to 9.8%), 2.7% (95% CI 1.3 to 5.7%), and 1.5% (95% CI 0.8 to 2.6%), respectively. Complication rates in the RCTs were higher than those in the U.S. registry, which reports only in-hospital complications (9.1% in the RCTs vs. 3.08%,  $p < 0.01$ ). The overall complication rate was similar to that reported by Kirkfelt (2014) in a population-based cohort study including all Danish patients who underwent a cardiac implantable electronic device procedure from 2010 to 2011 (562/5918 patients [9.5%] with at least one complication).<sup>[77]</sup>

Persson (2014) published a systematic review and meta-analysis of AEs following ICD implantation.<sup>[78]</sup> The authors included data from 35 cohort studies, reported in 53 articles. In-hospital serious AE rates ranged from 1.2% to 1.4%, most frequently pneumothorax (0.4%-0.5%) and cardiac arrest (0.3%). Posthospitalization complication rates were variable: device-related complications occurred in 0.1% to 6.4%; lead-related complications in 0.1% to 3.9%; infection in 0.2% to 3.7%; thrombosis in 0.2% to 2.9%; and inappropriate shock in 3% to 21%.

The 2013 AHRQ technology assessment summarized above identified 14, 33, and 22 studies that reported early (up to 30 days after ICD implantation) AEs, late AEs, and inappropriate ICD shock, respectively.<sup>[10]</sup> The rate of early adverse events was 2.8% to 3.6% during hospitalization, of which 1.2% to 1.35% were considered serious events (strength of evidence high). The most common early AEs were lead dislodgement and hematoma. Higher early AE rates were found with dual chamber ICDs, in older patients, in women, and in patients with end-stage renal disease (ESRD). The most common late AEs were device-related AEs that occurred in <0.1% to 6.4% of ICD patients during follow-up ranging from 2 to 49 months (strength of evidence low). Lead malfunction, infection, and thrombosis were also reported. Inappropriate shocks at one to five years follow-up occurred in 3% to 21% of patients, with more occurring in younger patients. There was inconsistent evidence related to the rate of inappropriate shocks for single and dual chamber ICDs.

A systematic review and meta-analysis by Auricchio (2017) focused on inappropriate shocks from both single chamber ICDs (VR-ICDs) and subcutaneous ICDs (S-ICDs).<sup>[79]</sup> The review included 16 articles, which showed that an average of 6.4% (95% CI 5.1 to 7.9%) of patients

with these ICDs received an inappropriate shock per year. There was evidence that this proportion was lower in more recent studies and in studies with longer follow-up.

In contrast to patients requiring ICDs for secondary prevention or for primary prevention after acute MI, patients with hereditary arrhythmia syndromes are more likely to potentially require ICDs for primary prevention. Olde Nordkamp (2016) reported on a systematic review and meta-analysis of studies reporting on ICD complications in individuals with inherited arrhythmia syndromes.<sup>[80]</sup> The review included 63 cohort studies with a total of 4,916 patients (710 [10%] with arrhythmogenic right ventricular tachycardia; 1,037 [21%] with BrS; 28 [0.6%] with CPVT; 2,466 [50%] with hypertrophic cardiomyopathy; 162 [3.3%] with lamin A/C gene mutations; 462 [9.4%] with LQTS; and 51 [1.0%] with SQTS). Overall, inappropriate shocks occurred in 20% over a mean follow up of 51 months, corresponding to an inappropriate shock rate of 4.7% per year (95% CI 4.2 to 5.3%). Over a mean follow up of 55 months, ICD-related complications occurred in 22%, most commonly lead malfunction (10.3% of patients). The pooled rate of ICD-related complications was 4.4% per year (95% CI 3.6 to 5.2%).

## SUBCUTANEOUS ICDS

Totally subcutaneous ICDs (S-ICDs) are a less invasive alternative to the conventional transvenous ICD, and are intended for patients who do have standard indications for an ICD, but who do not require pacing for bradycardia or antitachycardia overdrive pacing for VT. The S-ICD has also been proposed to be of particular benefit for patients with limited vascular access, including patients undergoing renal dialysis or children; or those who have had complications with transvenous ICDs. Evaluating the safety and efficacy of S-ICDs requires comparisons with transvenous ICDs in large, long-term, randomized, controlled trials. These comparisons are necessary to determine whether any benefits of S-ICDs outweigh risks and whether they offer advantages over transvenous ICDs with respect to the rate of adverse effects, successful termination of life-threatening arrhythmias, and unnecessary shocks.

### RANDOMIZED CONTROLLED TRIALS

No randomized controlled trials of S-ICDs have been published.

### NONRANDOMIZED STUDIES

#### Comparative Studies

Kobe (2013) published a prospective study that followed 69 patients who received S-ICD.<sup>[81]</sup> These were compared with a group of 69 sex- and age-matched patients with conventional ICD who were randomly selected from an ICD database. Fifty-four patients were followed-up over a minimum of two years. The successful conversion rate was 89.5% for S-ICD and 90.8% for transvenous ICD ( $p=0.81$ ). The rate of perioperative AEs was similar for the two groups, as were the rate of inappropriate shocks ( $p=0.745$ ) during short-term follow-up.

The Subcutaneous versus Transvenous Arrhythmia Recognition Testing (START) study compared the performance of a subcutaneous ICD with a transvenous ICD for detecting arrhythmias in the electrophysiology lab.<sup>[82]</sup> The patient population included 64 patients who were scheduled for ICD implantation. All patients had a transvenous ICD placed as well as subcutaneous electrodes attached to a subcutaneous ICD. Arrhythmias were induced and the sensitivity and specificity of detection by each device was compared. For ventricular arrhythmias, sensitivity of detection was 100% for the subcutaneous ICD and 99% for the

transvenous ICD. Specificity was 98.0% for the subcutaneous ICD device compared to 76.7% for the transvenous device ( $p < 0.001$ ).

### Non-comparative Studies

A single-center registry study published by Mithani (2018) compared outcomes between patients implanted with S-ICD ( $n=91$ ) and a matched control group implanted with a transvenous single-chamber ICD.<sup>[83]</sup> Control matching was based on gender, age, and dialysis status. The patients who received an S-ICD were more likely to be on chronic dialysis, have higher creatinine levels, and have had prior device infections compared to transvenous ICD patients. No significant difference was seen in implant complication rates or death in the six months after implantation.

Lambiase (2016) evaluated the use of the S-ICD in patients with hypertrophic cardiomyopathy in the S-ICD System Clinical Investigation (S-ICD IDE Study) and the EFFORTLESS registry (both described below), reporting on 99 patients with hypertrophic cardiomyopathy, who were compared with 773 non-hypertrophic cardiomyopathy patients.<sup>[84]</sup> At the time of reporting, three episodes of ventricular arrhythmias had been identified in the hypertrophic cardiomyopathy cohort, all of which were successfully terminated. In the hypertrophic cardiomyopathy group, 12.5% of subjects had experienced an inappropriate shock at a mean follow up of 22.0 months, which did not differ significantly from the rate in non-hypertrophic cardiomyopathy patients (10.7%,  $p=NS$ ).

A follow-up publication by Boersma (2017) reported five-year outcomes for the EFFORTLESS S-ICD study. There were 82 patients that completed the five-year visit, with mean follow-up for the group of  $3.1 \pm 1.5$  years. The rate of inappropriate shock 8.1% at one year, and 11.7% at 3.1 years, while the rate of appropriate shock was 5.8% at one year and 13.5% at five years.<sup>[85]</sup>

Boersma (2016) reported outcomes for patients in the S-ICD IDE study and the EFFORTLESS registry stratified by whether patients had been previously treated with a transvenous ICD.<sup>[86]</sup> At the time of analysis, 866 patients were available for inclusion. Of those, 75 (8.7%) were implanted with an S-ICD following transvenous ICD extraction for a system-related infection and 44 (5.1%) were implanted following transvenous ICD extraction for reasons other than a system-related infection, while the remaining 747 (86.3%) were de novo implants. Patients explanted for infection were older than patients whose transvenous ICD was explanted for non-infection related events and the de novo implant patients (55.5, 47.8, and 49.9 years, respectively,  $p=0.01$ ), were more likely to have an ICD for secondary prevention (42.7%, 37.2%, and 25.6%, respectively,  $p < 0.0001$ ), and had a higher incidence of comorbidities. There were no significant differences in the rates of system- or procedure-related complications between patients whose transvenous ICDs were explanted for infection, those whose transvenous ICDs were explanted for non-infectious reasons, and the de novo S-ICD patients (10.7%, 6.8%, and 9.6%, respectively,  $p=0.078$ ).

Another subanalysis of the pooled S-ICD IDE study and EFFORTLESS registry data, which included 882 patients at the time of analysis, evaluated the effect of learning curves on implant time, procedure complications, and inappropriate shocks.<sup>[87]</sup> Rates of complications were significantly lower in patients treated by the least experienced providers than those treated with the most experienced (9.8% vs 5.4%,  $p=0.02$ ).

Theuns (2015) reported long term follow up of a cohort study.<sup>[88]</sup> Over a median follow up of 5.8 years, 26 devices (47%) were replaced and 5 (9%) were explanted. Four patients (7%)

required S-ICD explantation and replacement with a transvenous system, two due to a requirement for cardiac resynchronization therapy, one due to a requirement for bradycardia pacing, and one due to ineffective defibrillation testing. Most devices (81%) were replaced due to an elective replacement indication, at a median time to replacement of 5.0 years. Event-free rates for device replacement after 2, 4, and 6 years were 94%, 89%, and 30%, respectively. A total of 119 delivered shocks in 16 patients (29%) were recorded).

El-Chami (2015) reported on a single-center study of outcomes after S-ICD placement in patients with endstage renal disease (ESRD) undergoing chronic dialysis, which included 79 patients who underwent S-ICD placement, 27 of whom were on chronic dialysis.<sup>[89]</sup> This research was prompted by prior studies that suggested higher mortality rates for ESRD patients implanted with transvenous ICDs. The composite outcome (frequency of death, heart failure hospitalization, or appropriate S-ICD shocks) was nonsignificantly higher in the ESRD group (23.8%/year vs 10.9%/year,  $p=0.317$ ), a difference that was primarily driven by a significantly higher incidence of appropriate S-ICD shocks in the ESRD group (17.9%/year vs 1.4%/year,  $p=0.021$ ).

Burke (2015) published a pooled analysis of patients from the S-ICD IDE study and the EFFORTLESS registry, which included 882 patients.<sup>[90]</sup> The poolability of data across the two studies was assessed by analysis of complications, appropriate and inappropriate shocks, conversion efficacy, and mortality by study, with additional analyses for outcomes that differed by study. Patients were followed for a mean of 651 ( $\pm 345$ ) days. Most patients (63%) presented with a history of previous transvenous ICDs that required extraction due to infection. Within 30 days of the procedure, 4.5% of subjects experienced a complication, while 11.1% of subjects experienced a complication within three years of the procedure. The most common complication was infection requiring device removal/revision (17 events in 14 patients [1.7%]). Mortality was low: the annual mortality rate was 1.6% and the two-year mortality rate was 3.2%. The Kaplan-Meier incidence of time to first therapy for VT or VF was 5.3% at one year, 7.9% at two years, and 10.5% at three years. Excluding VT/VF storms, 111 discrete VT/VF events were treated, with 100 (90.1%) terminated with the first shock, and 109 (98.2%) terminated within the five shocks available. The Kaplan-Meier incidence of time to first inappropriate shock was 13.1% at three years. In patients with dual zone programming at the index procedure, the Kaplan-Meier incidence of inappropriate shock at three years was 11.7% compared with 20.5% with single-zone programming. A significant study effect was observed for inappropriate shocks ( $p=0.0209$ ), with a smaller proportion of inappropriate shocks in the EFFORTLESS group, but this effect was negated after correction for initially-programmed number of zones, shock zone rate, and conditional zone rate.

Gold (2014) published a subanalysis of patients in the S-ICD IDE study to evaluate a discrimination algorithm to reduce inappropriate shocks.<sup>[91]</sup> Patients in the study could receive one of two shock detection algorithms, a single- or double-zone configuration. In the single-zone configuration, shocks are delivered for detected heart rates above the programmed rate threshold. In the dual-zone configuration, arrhythmia discrimination algorithms are active in a lower rate zone up to a shockable heart rate threshold. At hospital discharge, dual-zone programming was used in 226 subjects (72%) and single-zone programming was used in the remaining 88 subjects (28%). Inappropriate shocks occurred on 23 of 226 (10.2%) subjects with dual-zone programming and 23 of 88 (26.1%,  $p<0.001$ ) subjects with single-zone programming. Freedom from appropriate shocks did not differ between groups.

Lambiase (2014) described patients in the EFFORTLESS-ICD registry, a multicenter European registry to report outcomes for patients treated with S-ICD.<sup>[92]</sup> At the time of analysis, the registry included 472 patients, 241 of whom (51%) were enrolled prospectively, at a median follow-up time of 498 days. Nine patients (2%) died during the reported period, none of the deaths, which were known to occur in the perioperative period, although the cause of death was unknown for one patient. A total of 317 spontaneous episodes in 85 patients were recorded during the follow-up, of which 169 episodes received therapy in 59 patients. Of the 145 classified untreated episodes, 93 were adjudicated as inappropriate sensing, 37 were nonsustained VT/VF, 12 were nonsustained SVT above discrimination zone, and three were unclassified. Of the VT/VF episodes, the first shock conversion efficacy was 88%, with 100% overall successful clinical conversion after a maximum of five shocks. A total of 73 inappropriate shocks were recorded in 32 patients over an average follow-up of 18 months (360-day inappropriate shock rate of 7%).

The S-ICD IDE Study was a multicenter series of 330 patients from several countries.<sup>[93]</sup> The S-ICD was successfully implanted in 314 of 330 patients (95.1%). Laboratory-induced VF was successfully terminated in more than 90% of patients, which was one of the primary outcomes of the study. The second primary outcome, greater than 99% freedom from complications at 180 days, was also met. Patients were followed for a mean duration of 11 months. There were 38 spontaneous episodes of VT in 21 patients (6.7%), and all were successfully terminated. Inappropriate shocks were received by 41 patients (13.1%).

A series of 118 patients from four centers in the Netherlands was published in 2013. Patients were followed for a mean of 18±7 months.<sup>[94]</sup> Device-related complications occurred in 14% of patients, including infection (5.9%), dislodgement of the device or leads (3.3%), skin erosion (1.7%), and battery failure (1.7%). In one patient, the S-ICD was replaced with a transvenous ICD because of the need for antitachycardia pacing. Over the entire follow-up period, eight patients experienced 45 appropriate shocks, with a first-shock conversion efficacy of 98%. Fifteen patients (13%) received a total of 33 inappropriate shocks. Two patients died, one due to cancer and one to progressive heart failure.

Aydin (2012) reported outcomes for 40 consecutive patients implanted with S-ICDs at three German centers.<sup>[95]</sup> Patients were considered for S-ICD if they met criteria for ICD implantation for primary or secondary prevention specified by the American College of Cardiology/American Heart Association/European Society of Cardiology, did not have symptomatic bradycardia, incessant ventricular tachycardia, or documented spontaneous, frequently-recurring ventricular tachycardia that was reliably terminated with antitachycardia pacing, and did not have pacemakers. Of the cohort, 25.0% had a prior transvenous ICD, and 57.5% received the S-ICD for secondary prevention. Over a median follow-up of 229 days, S-ICD activity was recorded in 10.0% of the patients, for whom a total of 25 episodes were retrieved. Of these, 21 shock episodes were correctly identified as ventricular tachyarrhythmia. The overall S-ICD shock efficacy was 96.4% (95% CI 12.8% to 100%).

Bardy (2010) described the development and testing of the device, including empiric evidence for the optimal placement of the subcutaneous electrode.<sup>[96]</sup> A total of 55 patients were tested in the electrophysiology lab for termination of induced arrhythmias and subsequently followed for a mean of 10.1 months for successful termination of detected arrhythmias and clinical outcomes. In the electrophysiology lab study, intraoperative VF was induced in 53 of 55. All episodes were correctly detected by the S-ICD. In 52 of 53 patients, two consecutive episodes of ventricular arrhythmia were successfully terminated. In the final patient, the arrhythmia was

terminated on one occasion but not on the other. In the cohort portion of this study, 54 of 55 patients were alive at last follow-up. The one death was due to renal failure, and this patient requested removal of the S-ICD before death. An infection at the generator site occurred in two patients, necessitating a revision procedure. Another three patients had lead dislodgement requiring repositioning. There were a total of 12 episodes of VT that were detected by the S-ICD; all 12 episodes were successfully terminated by countershock.

## **S-ICDS AND ADVERSE EVENTS**

The systematic review and meta-analysis by Auricchio (2017), described previously, evaluated inappropriate shocks in patients with single-chamber ICDs (VR-ICDs) and S-ICDs using data from 16 articles.<sup>[79]</sup> They found an overall rate of 6.4% of patients per year received an inappropriate shock, and this risk was no significant difference associated with the use of S-ICDs or ventricular tachycardia zone programming. The authors noted that one of the included studies had an anomalously low reported rate of inappropriate shocks (1.9%), which was not explained by the study design or covariates.

Olde Nordkamp (2015) used data from the EFFORTLESS-ICD registry to evaluate rates of inappropriate shocks associated with the S-ICD.<sup>[97]</sup> The patient population at the time of publication included 581 S-ICD recipients, 48 of whom (8.3%) experienced a total of 101 inappropriate shocks over a follow up period of 21.4 months. Most inappropriate shocks (73%) were related to T-wave oversensing.

Brisben (2015) described the development of an algorithm designed to reduce T-wave oversensing by S-ICDs.<sup>[98]</sup> The algorithm was developed using 133 episodes of T-wave oversensing and 70 episodes of appropriately treated VT or VF collected from S-ICD log files and 174 VT/VF recordings from an ECG signal library. It was validated using 164 episodes of T-wave oversensing from S-ICD log files and 137 and 328 recorded episodes, respectively, of VT/VF and supraventricular tachycardia from an ECG signal library. The revised algorithm was associated with a reduction in T-wave oversensing of 39.8% (95% CI 28.4% to 51.2%,  $p=0.001$  vs baseline.) Patient outcomes after the use of this algorithm have not been reported yet.

Groh (2014) evaluated an ECG screening test to determine patients who are potential S-ICD candidates who are at risk for T wave oversensing.<sup>[99]</sup> One hundred patients who had previously undergone transvenous ICD implantation and who were not receiving bradycardia pacing and did not have an indication for pacing were included. ECGs were obtained with lead placement to mimic the sensing vectors available on the S-ICD, and a patient was considered to qualify for S-ICD if the screening ECG template passed in any same lead supine and standing, at any gain, and without significant morphologic changes in QRS complexes. Of the included subjects who were potentially eligible for S-ICD, 8% were considered to fail based the ECG screening.

Kooiman (2014) reported inappropriate shock rates among 69 patients treated at a single center with an S-ICD between February 2009 and July 2012 who were not enrolled in one of two other concurrent trials.<sup>[100]</sup> Over a total follow-up of 1316 months (median per patient, 21 months), the annual incidence of inappropriate shocks was 10.8%. In eight patients, inappropriate shocks were related to T wave oversensing. After patients underwent adjustment of the sensing vector, no further inappropriate shocks occurred in 87.5% of patients with T wave oversensing.

## **ICDS WITH ST SEGMENT MONITORING**

The intent of ICDs with the capability for continuous ST segment monitoring is to detect possible myocardial ischemic events. Thus, the validation of this additional feature in ICDs focuses on evidence demonstrating the following:

- Technical performance of ICD-based ischemic monitoring compared with intermittent monitoring with conventional external ECG
- Diagnostic performance (i.e., sensitivity, specificity, and positive and negative predictive value), particularly the rate of false positive detections that could lead to unnecessary testing or invasive procedures
- Clinical utility, specifically evidence that demonstrates the ability of this monitoring to improve patient health outcomes.

There are currently no randomized controlled trials for ICD-based ischemia monitoring. Two preliminary nonrandomized comparative trials have been published. Baron (2006) compared surface ECG (SECG) with intrathoracic ECG (IT-ECG) in 22 patients undergoing PTCA.<sup>[101]</sup> IT-ECG was reported to be significantly more sensitive than SECG in early and overall ischemia assessment, with highest sensitivity of 85%. However, this study did not indicate how these tests results were used in patient management to improve health outcomes. More recently, Forleo (2012) compared ICDs with (n=53) versus without (n=50) ST-segment monitoring capability.<sup>[102]</sup> After at least six months follow-up, one patient in the ST monitoring group had an ST elevation myocardial infarction three weeks after implantation, but the algorithm had not yet been activated. Seven patients in the ST monitoring group had at least one episode (range 1 to 90) of false-positive ST events; the programmable features of the device helped overcome the problem in six patients. Unscheduled outpatient visits were significantly increased in ST monitored patients with a remote monitoring system (17 vs. 4, p=0.032). The authors concluded that ICD-based ST monitoring failed to provide a benefit over ICD alone and increased unscheduled evaluations in patients with remote follow-up.

## EXTRAVASCULAR (EV) ICDS

Recently, EV ICDs have been developed that rely on substernal leads for pacing. Feasibility studies have been published,<sup>[103,104]</sup> but these devices have not been approved by the FDA and clinical trials are underway.

## PRACTICE GUIDELINE SUMMARY

The following section includes the current evidence-based clinical practice guidelines for use of ICDs. Consensus statements are not included.

### THE AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION/HEART RHYTHM SOCIETY (ACC/AHA/HRS) GUIDELINES

In 2017, the American Heart Association (AHA,) American College of Cardiology (ACC) and Heart Rhythm Society (HRS) published practice guidelines on the management ventricular arrhythmia and prevention of sudden cardiac death. These guidelines made the recommendations on use of implantable cardioverter defibrillator (ICD) devices, including the the recommendations below, with a class of recommendation of I (strong recommendation) or IIa (moderate recommendation). The recommendations for use of an ICD apply only if meaningful survival is expected to be greater than one year.

Each recommendation is further classified as either A, B, or C, based on the weight of the evidence available.

- Level A is applied when data are from multiple, high-quality randomized clinical trials;
- Level B indicates data are from a moderate-quality randomized trials (B-R) or nonrandomized trials (B-NR); and
- Level C is applied when the recommendation is based lower quality evidence - either limited data (C-LD) or expert opinion (C-EO).

### Transvenous ICD recommendations

For primary prevention in ischemic heart disease:

- In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class II or III HF despite GDMT [guideline-directed medical therapy], an ICD is recommended (Class I, Level of Evidence [LOE]: A)
- In patients with LVEF of 30% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class I HF despite GDMT, an ICD is recommended (Class I, LOE: A)
- In patients with NSVT due to prior MI, LVEF of 40% or less and inducible sustained VT or VF at electrophysiological study, an ICD is recommended (Class I/ LOE: B-R)
- In nonhospitalized patients with NYHA class IV symptoms who are candidates for cardiac transplantation or an LVAD, an ICD is reasonable (Class IIa, LOE: B-NR)

For secondary prevention in ischemic heart disease:

- In patients with ischemic heart disease, who either survive SCA due to VT/VF or experience hemodynamically unstable VT (Class 1, LOE: B-R) or stable VT (Class I, LOE: B-NR) not due to reversible causes, an ICD is recommended
- In patients with ischemic heart disease and unexplained syncope who have inducible sustained monomorphic VT on electrophysiological study, an ICD is recommended (Class I, LOE: B-NR)
- In patients resuscitated from SCA due to coronary artery spasm in whom medical therapy is ineffective or not tolerated, an ICD is reasonable (Class IIa, LOE: B-NR)

For primary prevention in NICM:

- In patients with NICM, HF with NYHA class II–III symptoms and an LVEF of 35% or less, despite GDMT, an ICD is recommended (Class I, LOE: A)
- In patients with NICM due to a Lamin A/C mutation who have 2 or more risk factors (NSVT, LVEF <45%, nonmissense mutation, and male sex), an ICD can be beneficial (Class IIa, LOE: B-NR)

For secondary prevention in NICM:

- In patients with NICM who either survive SCA due to VT/VF or experience hemodynamically unstable VT (LOE: B-R) or stable VT (LOE: B-NR) not due to reversible causes, an ICD is recommended (Class I)

- In patients with NICM who experience syncope presumed to be due to VA and who do not meet indications for a primary prevention ICD, an ICD or an electrophysiological study for risk stratification for SCD can be beneficial (Class IIa, LOE: B-NR)

For hypertrophic cardiomyopathy:

- In patients with HCM who have survived an SCA due to VT or VF, or have spontaneous sustained VT causing syncope or hemodynamic compromise, an ICD is recommended (Class I, LOE: B-NR)
- In patients with HCM and 1 or more of the following risk factors, an ICD is reasonable: maximum LV wall thickness  $\geq 30$  mm (LOE: B-NR), SCD in 1 or more first-degree relatives presumably caused by HCM (LOE: C-LD), and 1 or more episodes of unexplained syncope within the preceding 6 months (LOE: C-LD) (Class IIa)
- In patients with HCM who have spontaneous NSVT (LOE: C-LD) or an abnormal blood pressure response with exercise (LOE: B-NR), who also have additional SCD risk modifiers or high risk features, an ICD is reasonable (Class IIa)

For cardiac sarcoidosis:

- In patients with cardiac sarcoidosis who have sustained VT or are survivors of SCA or have an LVEF of 35% or less, an ICD is recommended (Class I, LOE: B-NR)
- In patients with cardiac sarcoidosis and LVEF greater than 35% who have syncope and/or evidence of myocardial scar by cardiac MRI or positron emission tomographic (PET) scan, and/or have an indication for permanent pacing implantation of an ICD is reasonable (Class IIa, LOE: B-NR)
- In patients with cardiac sarcoidosis and LVEF greater than 35%, it is reasonable to perform an electrophysiological study and to implant an ICD, if sustained VA is inducible (Class IIa, LOE: C-LD)
- In patients with cardiac sarcoidosis who have an indication for permanent pacing, implantation of an ICD can be beneficial (Class IIa, LOE: C-LD)

For neuromuscular disorders:

- In patients with neuromuscular disorders, primary and secondary prevention ICDs are recommended for the same indications as for patients with NICM (Class I, LOE: B-NR)
- In patients with Emery-Dreifuss and limb-girdle type IB muscular dystrophies with progressive cardiac involvement, an ICD is reasonable (Class IIa, LOE: B-NR)

For cardiac channelopathies:

- In patients with a cardiac channelopathy and SCA, an ICD is recommended (Class I, LOE: B-NR)
- In high-risk patients with symptomatic long QT syndrome in whom a beta blocker is ineffective or not tolerated, intensification of therapy with additional medications (guided by consideration of the particular long QT syndrome type), left cardiac sympathetic denervation, and/or an ICD is recommended (Class I, LOE: B-NR)
- In patients with catecholaminergic polymorphic ventricular tachycardia and recurrent sustained VT or syncope, while receiving adequate or maximally tolerated beta blocker, treatment intensification with either combination medication therapy (e.g., beta blocker, flecainide), left cardiac sympathetic denervation, and/or an ICD is recommended (Class I, LOE: B-NR)

- In patients with Brugada syndrome with spontaneous type 1 Brugada electrocardiographic pattern and cardiac arrest, sustained VA or a recent history of syncope presumed due to VA, an ICD is recommended (Class I, LOE: B-NR)
- In patients with early repolarization pattern on ECG and cardiac arrest or sustained VA, an ICD is recommended (Class I, LOE: B-NR)
- In patients with short QT syndrome who have a cardiac arrest or sustained VA, an ICD is recommended (Class I, LOE: B-NR)

For adult congenital heart disease:

- In patients with adult congenital heart disease and hemodynamically unstable VT, an ICD is recommended after evaluation and appropriate treatment for residual lesions/ventricular dysfunction (Class I, LOE: B-NR)
- In patients with adult congenital heart disease with SCA due to VT or VF in the absence of reversible causes, an ICD is recommended (Class I, LOE: B-NR)
- In adults with repaired tetralogy of Fallot physiology and inducible VT/VF or spontaneous sustained VT, implantation of an ICD is reasonable (Class IIa, LOE: B-NR)
- In patients with repaired moderate or severe complexity adult congenital heart disease with unexplained syncope and at least moderate ventricular dysfunction or marked hypertrophy, either ICD implantation or an electrophysiological study with ICD implantation for inducible sustained VA is reasonable (Class IIa, LOE: B-NR)

For other indications:

- In patients resuscitated from SCA due to coronary artery spasm in whom medical therapy is ineffective or not tolerated, an ICD is reasonable (Class IIa, LOE: B-NR)
- In patients with arrhythmogenic right ventricular cardiomyopathy and an additional marker of increased risk of SCD (resuscitated SCA, sustained VT, significant ventricular dysfunction with RVEF or LVEF  $\leq 35\%$ ), an ICD is recommended (Class I, LOE: B-NR)
- In patients with arrhythmogenic right ventricular cardiomyopathy and syncope presumed due to VA, an ICD can be useful (Class IIa, LOE: B-NR)
- In patients with HFrEF who are awaiting heart transplant and who otherwise would not qualify for an ICD (e.g., NYHA class IV and/or use of inotropes) with a plan to discharge home, an ICD is reasonable (Class IIa, LOE: B-NR)
- In patients with an LVAD and sustained VA, an ICD can be beneficial (Class IIa, LOE: C-LD)
- In patients resuscitated from SCA due to idiopathic polymorphic VT or VF, an ICD is recommended (Class I, LOE: B-NR)

Subcutaneous ICD recommendations:

- In patients who meet criteria for an ICD who have inadequate vascular access or are at high risk for infection, and in whom pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated, a subcutaneous implantable cardioverter-defibrillator is recommended (Class I, LOE: B-NR)
- In patients who meet indication for an ICD, implantation of a subcutaneous implantable cardioverter-defibrillator is reasonable if pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated (Class IIa, LOE: B-NR)

## **PEDIATRIC AND CONGENITAL ELECTROPHYSIOLOGY SOCIETY (PACES)/ HEART RHYTHM SOCIETY (HRS)**

In 2014, PACES and HRS issued an expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease (CHD) which made the following recommendations on the use of ICD therapy in adults with CHD:<sup>[105]</sup>

- **Class I Recommendations:**
  - ICD therapy is indicated in adults with CHD who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable ventricular tachycardia after evaluation to define the cause of the event and exclude any completely reversible etiology (LOE: B).
  - ICD therapy is indicated in adults with CHD and spontaneous sustained ventricular tachycardia who have undergone hemodynamic and electrophysiologic evaluation (LOE: B).
  - ICD therapy is indicated in adults with CHD and a systemic left ventricular ejection fraction <35%, biventricular physiology, and New York Heart Association (NYHA) class II or III symptoms (LOE: B).
- **Class IIa Recommendations:**
  - ICD therapy is reasonable in selected adults with tetralogy of Fallot and multiple risk factors for sudden cardiac death, such as left ventricular systolic or diastolic dysfunction, nonsustained ventricular tachycardia, QRS duration >180 ms, extensive right ventricular scarring, or inducible sustained ventricular tachycardia at electrophysiologic study (LOE: B).
- **Class IIb Recommendations:**
  - ICD therapy may be reasonable in adults with a single or systemic right ventricular ejection fraction <35%, particularly in the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II or III symptoms, QRS duration >140 ms, or severe systemic AV valve regurgitation (LOE: C)
  - ICD therapy may be considered in adults with CHD and a systemic ventricular ejection fraction <35% in the absence of overt symptoms (NYHA class I) or other known risk factors (LOE of: C).
  - ICD therapy may be considered in adults with CHD and syncope of unknown origin with hemodynamically significant sustained ventricular tachycardia or fibrillation inducible at electrophysiologic study (LOE: B).
  - ICD therapy may be considered for nonhospitalized adults with CHD awaiting heart transplantation (LOE: C).
  - ICD therapy may be considered for adults with syncope and moderate or complex CHD in whom there is a high clinical suspicion of ventricular arrhythmia and in whom thorough invasive and noninvasive investigations have failed to define a cause (LOE: C).
- **Class III Recommendations:**
  - All Class III recommendations listed in current ACC/AHA/HRS guidelines apply to adults with CHD (LOE: C).

- Adults with CHD and advanced pulmonary vascular disease (Eisenmenger syndrome) are generally not considered candidates for ICD therapy (LOE: B).
- Endocardial leads are generally avoided in adults with CHD and intracardiac shunts. Risk assessment regarding hemodynamic circumstances, concomitant anticoagulation, shunt closure prior to endocardial lead placement, or alternative approaches for lead access should be individualized (LOE: B).

## SUMMARY

### TRANSVENOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICDS)

#### Pediatric Patients

There is enough research to show that implantable cardioverter defibrillators (ICDs) can improve survival for pediatric patients that are at increased risk of cardiac events. Therefore, the use of ICDs may be considered medically necessary for pediatric patients.

#### Patients with Prior Arrhythmogenic Events and Ischemic Cardiomyopathy

There is enough research to show that transvenous implantable cardioverter defibrillators (ICDs) can improve survival for certain patients that have had arrhythmogenic events and ischemic cardiomyopathy. A number of clinical guidelines based on research recommend these ICDs for patients meeting specific criteria. Therefore, the use of ICDs may be considered medically necessary for patients that meet the policy criteria.

There is not enough research to show that transvenous implantable cardioverter defibrillators (ICDs) can improve health outcomes for patients with ischemic cardiomyopathy that do not meet the policy criteria. This includes people who have had a myocardial infarction (heart attack) in the past 40 days, people with a relatively high level of heart function. Therefore, the use of ICDs in ischemic cardiomyopathy patients that do not meet the policy criteria is considered investigational.

#### Heart Failure

There is enough research to show that transvenous implantable cardioverter defibrillators (ICDs) can improve survival for certain heart failure patients, including patients with a reduced ejection fraction who will be discharged home to await heart transplantation, and patients with NYHA *Class IV* symptoms that are candidates for a left ventricular assist device or heart transplantation. Clinical guidelines based on research recommend ICDs for patients meeting these criteria. Therefore, the use of ICDs may be considered medically necessary for heart failure patients that meet the policy criteria.

There is not enough research to show that implantable cardioverter defibrillators (ICDs) can improve health outcomes for patients with heart failure patients that do not meet the policy criteria. This includes people who have had a myocardial infarction (heart attack) in the past 40 days, people with a relatively high level of heart function, and people with NYHA *Class IV* symptoms that are not eligible to receive a combination cardiac resynchronization therapy ICD device, left ventricular assist device, or cardiac transplantation. Therefore, the use of ICDs in patients that do not meet the policy criteria is considered investigational.

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## **Nonischemic Cardiomyopathy (NICM)**

There is enough research to show that transvenous implantable cardioverter defibrillators (ICDs) can improve survival for certain patients with nonischemic cardiomyopathy (NICM) and certain neuromuscular disorders that affect heart function. Also, clinical guidelines based on research recommend ICD use for these patients. Therefore, ICD implantation among patients with NICM or neuromuscular disorders that meet the policy criteria may be considered medically necessary.

There is not enough research to show that transvenous implantable cardioverter defibrillators (ICDs) can improve survival for patients with nonischemic cardiomyopathy (NICM) or neuromuscular disorders that do not meet policy criteria, including patients that have a treatable cause for their NICM. Therefore, ICD use in these patients is considered investigational.

## **Hypertrophic Cardiomyopathy**

There is enough research to show that implantable cardioverter defibrillators (ICDs) can improve survival in some patients with hypertrophic cardiomyopathy (HCM). There are also clinical guidelines based on research that recommend ICDs for certain patients with HCM. Therefore, ICD implantation among patients with HCM that meet policy criteria may be considered medically necessary.

There is not enough research to show that implantable cardioverter defibrillators (ICDs) can improve health outcomes for people with hypertrophic cardiomyopathy (HCM) that do not have major risk factors for sudden cardiac death. Therefore, ICD use is considered investigational for patients with HCM that do not meet the policy criteria.

## **LMNA-related Cardiac Arrhythmia or Cardiomyopathy**

There is enough research to show that implantable cardioverter defibrillators (ICDs) can improve health outcomes compared with pacemakers or medical treatment in patients with *LMNA*-related cardiac arrhythmias or cardiomyopathy. Because of the high risk for sudden cardiac death, ICDs may be considered medically necessary in patients with *LMNA* gene mutations that have cardiomyopathy or symptomatic arrhythmias, or have certain risk factors.

There is not enough research to show that implantable cardioverter defibrillators (ICDs) can improve health outcomes in patients with *LMNA* gene mutations that do not have cardiomyopathy, symptomatic arrhythmias, or specific risk factors, and therefore, the use of ICDs among these patients is considered investigational.

## **Cardiac Ion Channelopathies**

There is enough research to show that implantable cardioverter defibrillators (ICDs) can reduce sudden cardiac death in certain patients with long QT syndrome, short QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia. Clinical guidelines based on research also recommend ICD therapy in patients with these conditions that have other cardiac risk factors. Therefore, ICDs may be considered medically necessary in select patients with cardiac ion channelopathies.

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There is not enough research to show that implantable cardioverter defibrillators (ICDs) can improve health outcomes in patients with cardiac ion channelopathies that do not have certain cardiac risk factors, and therefore, the use of ICDs among these patients is considered investigational.

### **Cardiac Sarcoidosis**

There is enough research to show that implantable cardioverter defibrillators (ICDs) can reduce sudden cardiac death in certain patients with cardiac sarcoidosis. Clinical guidelines based on research also recommend ICD therapy in patients with this condition that have other cardiac risk factors. Therefore, ICDs may be considered medically necessary in select patients with cardiac sarcoidosis.

There is not enough research to show that implantable cardioverter defibrillators (ICDs) can improve health outcomes in patients with cardiac sarcoidosis that do not have certain cardiac risk factors, and therefore, the use of ICDs among these patients is considered investigational.

### **ICDs for Secondary Prevention**

There is enough research to show that implantable cardioverter defibrillators (ICDs) can be effective for *secondary* prevention in certain patients, including those that have had life-threatening ventricular arrhythmia not caused by a reversible condition. Therefore, ICD use may be considered medically necessary for secondary prevention in these patients.

There is not enough research to show that implantable cardioverter defibrillators (ICDs) can improve health outcomes in patients that have had arrhythmia events caused by reversible conditions, and ICD use is therefore considered investigational for these patients.

### **SUBCUTANEOUS ICDS**

There is enough research to show that subcutaneous implantable cardioverter defibrillators (S-ICDs) can improve health outcomes in patients that may benefit from ICD use, and have no indications for antibradycardia or antitachycardia pacing. Therefore, the use of S-ICDs may be considered medically necessary for the same indications as transvenous ICDs.

There is not enough research to show that subcutaneous implantable cardioverter defibrillators (S-ICDs) use can improve health outcomes in people who do not meet policy criteria for transvenous ICD placement, and people with indications for antibradycardia or antitachycardia pacing. Therefore, S-ICD placement is considered investigational for patients that do not meet policy criteria for transvenous ICD placement and patients that may require antibradycardia or antitachycardia pacing.

### **ICDS WITH ST SEGMENT MONITORING CAPABILITY**

There is not enough research to show that implantable cardioverter defibrillators (ICDs) with ST segment monitoring capability can improve health outcomes compared to traditional transvenous ICDs. Also, there are no ICDS with segment monitoring capabilities that have received U.S. Food and Drug Administration (FDA) approval for marketing in the U.S. Therefore, the use of implantable cardioverter defibrillators with ST segment monitoring capability is considered investigational for all indications.

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## EXTRAVASCULAR (EV) ICDS

There is not enough research to show that extracardiac implantable cardioverter defibrillators (EV ICDs), also known as substernal ICDs, improve health outcomes compared to traditional transvenous or subcutaneous ICDs. Also, there are no EV ICDs that have received U.S. Food and Drug Administration (FDA) approval for marketing in the U.S. Therefore, the use of EV ICDs is considered investigational for all indications

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106. BlueCross BlueShield Association Medical Policy Reference Manual "Implantable Cardioverter Defibrillator (ICD)." Policy No. 7.01.44

## CODES

Codes	Number	Description
CPT	0571T	Insertion or replacement of permanent implantable cardioverter defibrillator system, with substernal electrode(s), including all imaging guidance defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters, when performed
	0572T	Insertion of substernal implantable defibrillator electrode
	0573T	Removal of substernal implantable defibrillator electrode
	0574T	Repositioning of previously implanted extravascular substernal implantable defibrillator-pacing electrode
	0575T	Programming device evaluation (in person) of implantable cardioverter defibrillator system with substernal electrode, with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional
	0576T	Interrogation device evaluation (in person) of implantable cardioverter defibrillator system with substernal electrode, with analysis, review and report

Codes	Number	Description
		by a physician or other qualified health care professional, includes connection, recording and disconnection per patient encounter
	0577T	Electrophysiologic evaluation of implantable cardioverter defibrillator system with substernal electrode (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters)
	0578T	Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter defibrillator system w/interim analysis, review(s) and report(s) by a physician or other qualified health care professional
	0579T	Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter defibrillator system, remote data acquisition(s), receipt of transmissions and technician review, technical support and distribution of results
	0580T	Removal of substernal implantable defibrillator pulse generator only
	0614T	Removal and replacement of substernal implantable defibrillator pulse generator
	33216	Insertion of a single transvenous electrode, permanent pacemaker or cardioverter-defibrillator
	33217	Insertion of 2 transvenous electrodes, permanent pacemaker or cardioverter-defibrillator
	33218	Repair of single transvenous electrode for a single chamber, permanent pacemaker or single chamber pacing cardioverter-defibrillator
	33220	Repair of 2 transvenous electrodes for a dual chamber permanent pacemaker or dual chamber pacing cardioverter-defibrillator
	33223	Relocation of skin pocket for cardioverter-defibrillator
	33230	Insertion of pacing cardioverter-defibrillator pulse generator only; with existing dual leads
	33231	Insertion of pacing cardioverter-defibrillator pulse generator only; with existing multiple leads
	33240	Insertion of single or dual chamber pacing cardioverter-defibrillator pulse generator
	33241	Removal of implantable defibrillator pulse generator only
	33243	Removal of single or dual chamber implantable defibrillator electrode(s); by thoracotomy
	33244	;by transvenous extraction
	33249	Insertion or replacement of permanent implantable defibrillator system, with transvenous lead(s), single or dual chamber
	33262	Removal of implantable defibrillator pulse generator with replacement of implantable defibrillator pulse generator; single lead system
	33263	;dual lead system
	33264	;multiple lead system
	33270	Insertion or replacement of permanent subcutaneous implantable defibrillator system, with subcutaneous electrode, including defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters, when performed
	33271	Insertion of subcutaneous implantable defibrillator electrode
	33272	Removal of subcutaneous implantable defibrillator electrode
	33273	Repositioning of previously implanted subcutaneous implantable defibrillator electrode
HCPCS	C1721	Cardioverter-defibrillator, dual chamber (implantable)
	C1722	Cardioverter-defibrillator, single chamber (implantable)

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<b>Codes</b>	<b>Number</b>	<b>Description</b>
	C1882	Cardioverter-defibrillator, other than single or dual chamber (implantable)

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*Date of Origin: April 2012*

## ***Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants***

**Effective:** January 1, 2020

**Next Review:** August 2020

**Last Review:** December 2019

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Policy provides breast reconstruction and implant management criteria based on Public Law 105-277, the Women's Health and Cancer Rights Act of 1998.

### **MEDICAL POLICY CRITERIA**

#### **Notes:**

- Contractual limitations and exclusions may apply to both reconstructive and cosmetic procedures, to illnesses and conditions initially occurring prior to coverage, and to complications of non-covered procedures.
- For the purposes of this policy, mastectomy is defined as complete or partial, including lumpectomy.
- Some codes listed may have specific criteria to be met in other medical policies (e.g., reduction mammoplasty), or may not be considered medically necessary for any indication. See Cross References to confirm the correct policy is applied.

- I. Reconstructive breast surgery of a diseased or injured breast may be considered **medically necessary** when either of the following criteria is met and the treating

physician recommends it:

- A. After prophylactic or therapeutic mastectomy
  - B. After accidental injury or trauma to the breast
- II. Reconstructive breast surgery of an unaffected breast to achieve symmetry with the contralateral breast may be considered **medically necessary** when reconstruction of the contralateral diseased or injured breast was medically necessary as defined in Criterion I above and it is recommended by the treating physician.
- III. Breast implant explantation is considered **medically necessary** when the implant(s) was/were placed during reconstructive breast surgery that was medically necessary as defined in Criterion I. Explantation of implant(s) requires documentation of the original indication for implantation.
- IV. Breast revision surgery following a cosmetic primary breast procedure, is considered **cosmetic** when medical necessity Criteria (I, II, or III) are not met.

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

## CROSS REFERENCES

1. [Gender Affirming Interventions for Gender Dysphoria](#), Medicine, Policy No. 153
2. [Endometrial Ablation](#), Surgery, Policy No. 01
3. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12
4. [Reduction Mammoplasty](#), Surgery, Policy No. 60
5. [Adipose-derived Stem Cell Enrichment in Autologous Fat Grafting to the Breast](#), Surgery, Policy No. 182

## BACKGROUND

Reconstructive breast surgery is defined as those surgical procedures which are intended to restore the normal appearance of the breast after surgery, accidental injury, or trauma. The most common indication for reconstructive breast surgery is mastectomy. In contrast, cosmetic breast surgery is defined as surgery intended to alter or enhance the appearance of a breast which does not have a significantly altered appearance due to surgery, accidental injury, or trauma. Reduction mammoplasty and surgery to alter the appearance of a congenital breast abnormality are examples of breast surgeries which may be cosmetic. (See Surgery Policy No. 60, Reduction Mammoplasty and Surgery Policy No. 12, Cosmetic and Reconstructive Surgery). The most common type of reconstructive breast surgery is insertion of a silicone gel-filled or saline-filled breast implant, either inserted immediately at the time of mastectomy -or sometime afterward in conjunction with the previous use of a tissue expander. Significant local complications of breast implants, such as contracture, may require removal of the implant. Other types of reconstruction include nipple/areola reconstruction, nipple tattooing, and/or the use of autologous tissue, such as a transverse rectus abdominis myocutaneous flap (TRAM procedure) or a latissimus dorsi flap. In addition, mastopexy, reduction mammoplasty, or implant on the contralateral breast may be performed in order to achieve symmetry with the reconstructed breast.

## POSITION STATEMENT

This policy is written to assist in interpreting Public Law 105-277, the Women's Health and Cancer Rights Act of 1998<sup>[1]</sup> which requires all health insurance carriers that cover mastectomies to also cover the following in a manner determined in consultation with the attending physician and patient:

- All stages of reconstruction of the breast on which the mastectomy was performed
- Surgery and reconstruction of the contralateral breast to produce a symmetrical appearance
- Prostheses
- Treatment of physical complications of mastectomy, including lymphedema

## REFERENCES

1. Your Rights After A Mastectomy...Women's Health & Cancer Rights Act of 1998. [cited 7/25/2018]; Available from: <https://www.dol.gov/sites/default/files/ebsa/about-ebsa/our-activities/resource-center/publications/your-rights-after-a-mastectomy.pdf>

## CODES

**NOTE:** CPT code 20926 is the recommended code when autologous fat grafting is used for reconstructive breast surgery. For autologous fat grafting **with additional** adipose-derived stem cells (aka, stem cell enrichment), see Cross References to confirm correct criteria is applied.

Codes	Number	Description
CPT	11920	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.0 sq. cm or less
	11921	Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation; 6.1 to 20.0 sq cm
	11950	Subcutaneous injection of filling material (eg, collagen); 1 cc or less
	11951	Subcutaneous injection of filling material (eg, collagen); 1.1 to 5.0 cc
	11952	Subcutaneous injection of filling material (eg, collagen); 5.1 to 10.0 cc
	11954	Subcutaneous injection of filling material (eg, collagen); over 10.0 cc
	11970	Replacement of tissue expander with permanent prosthesis
	11971	Removal of tissue expander(s) without insertion of prosthesis
	15769	Grafting of autologous soft tissue, other, harvested by direct excision (eg, fat, dermis, fascia)
	15771	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; 50 cc or less injectate
	15772	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; each additional 50 cc injectate, or part thereof (List separately in addition to code for primary procedure)
	19316	Mastopexy
	19318	Reduction mammoplasty
	19324	Mammoplasty, augmentation; without prosthetic implant
	19325	Mammoplasty, augmentation; with prosthetic implant
	19328	Removal of intact mammary implant
	19330	Removal of mammary implant material

<b>Codes</b>	<b>Number</b>	<b>Description</b>
	19340	Immediate insertion of breast prosthesis following mastopexy, mastectomy, or in reconstruction
		Delayed insertion of breast prosthesis following mastopexy, mastectomy, or in reconstruction
	19350	Nipple/areola reconstruction
	19357	Breast reconstruction, immediate or delayed, with tissue expander, including subsequent expansion
		Breast reconstruction with latissimus dorsi flap, without prosthetic implant
	19364	Breast reconstruction with free flap
	19366	Breast reconstruction with other technique
	19367	Breast reconstruction with transverse rectus abdominis myocutaneous flap (TRAM) single pedicle, including closure of donor site
	19368	;with microvascular anastomosis (supercharging)
	19369	Breast reconstruction with transverse rectus abdominis myocutaneous flap (TRAM) double pedicle, including closure of donor site
	19370	Open periprosthetic capsulotomy, breast
	19371	Periprosthetic capsulotomy, breast
	19380	Revision of reconstructed breast
	19396	Preparation of moulage for custom breast implant
	19499	Unlisted procedure, breast
	20926	<del>Tissue grafts, other (e.g., paratenon, fat, dermis)</del> (Deleted 1/1/2020)
HCPCS	L8039	Breast prosthesis, not otherwise specified
	L8600	Implantable breast prosthesis, silicone or equal
	S2066	Breast reconstruction with gluteal artery perforator (GAP) flap, including harvesting of the flap, microvascular transfer, closure of donor site and shaping the flap into a breast, unilateral
	S2067	Breast reconstruction of a single breast with "stacked" deep inferior epigastric perforator (DIEP) flap(s) and/or gluteal artery perforator (GAP) flap(s), including harvesting of the flap(s), microvascular transfer, closure of donor site(s) and shaping the flap into a breast, unilateral
	S2068	Breast reconstruction with deep inferior epigastric perforator (DIEP) flap or superficial inferior epigastric artery (SIEA) flap, including harvesting of the flap, microvascular transfer, closure of donor site and shaping the flap into a breast, unilateral

**Date of Origin:** January 1996

**NOTE: This policy has been revised. The revised policy will be effective January 1, 2021. To view the revised policy, [click here](#).**

Medical Policy Manual

Surgery, Policy No. 45

## ***Spinal Cord and Dorsal Root Ganglion Stimulation***

**Effective:** July 1, 2019

**Next Review:** April 2020

**Last Review:** May 2019

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Standard and high-frequency spinal cord stimulation, as well as dorsal root ganglion stimulation, delivers electrical stimulation to the spinal cord using implanted electrodes to block pain sensation. Dorsal root ganglion stimulation is different from spinal cord stimulation in terms of the placement of the electrodes.

### **MEDICAL POLICY CRITERIA**

**Notes:**

- Spinal cord stimulation should be initiated with a *trial period* of spinal cord stimulation with a *temporarily implanted* lead and may be followed by *permanent implantation*. This policy addresses these services as one combined episode beginning with the temporary placement.
- Please see the Regulatory Status section for a list of standard (non-high frequency), high-frequency, and dorsal root ganglion devices.

- I. Spinal cord stimulation (standard or high frequency) may be considered **medically necessary** when all of the following criteria (A – C) are met:

- A. Presence of severe and chronic refractory pain of the trunk or limbs, *other than* critical limb ischemia; and
  - B. The treatment is used only as a last resort; other treatment modalities (pharmacological, surgical, psychological, or physical, if applicable) have been tried and failed or are judged to be unsuitable or contraindicated; and
  - C. Trunk and limb pain is neuropathic in nature (i.e. resulting from actual damage to the peripheral nerves). Common indications include, but are not limited to the following: failed back surgery syndrome, complex regional pain syndrome (i.e., reflex sympathetic dystrophy), arachnoiditis, radiculopathies, phantom limb/stump pain, and peripheral neuropathy.
- II. Spinal cord stimulation device revision(s) or replacement(s) may be considered **medically necessary** after the device has been placed.
- III. Spinal cord stimulation is considered **investigational** for all other indications, including but not limited to treatment of the following: cancer-related pain, central deafferentation pain (related to CNS damage from a stroke or spinal cord injury), headache including chronic cluster headaches, nociceptive pain (resulting from irritation, not damage to the nerves), postherpetic neuralgia, and visceral pain.
- IV. Dorsal root ganglion stimulation may be considered **medically necessary** when all of the following criteria (A – B) are met:
- A. Presence of severe and chronic refractory pain of the trunk or limbs due to type I or type II complex regional pain syndrome, including reflex sympathetic dystrophy or causalgia; and
  - B. The treatment is used only as a last resort; other treatment modalities (pharmacological, surgical, psychological, or physical, if applicable) have been tried and failed or are judged to be unsuitable or contraindicated.
- V. Dorsal root ganglion stimulation device revision(s) or replacement(s) may be considered **medically necessary** after the device has been placed.
- VI. Dorsal root ganglion stimulation is considered **investigational** for all other indications, including but not limited to treatment of the following: critical limb ischemia, cancer-related pain, central deafferentation pain (related to CNS damage from a stroke or spinal cord injury), headache including chronic cluster headaches, nociceptive pain (resulting from irritation, not damage to the nerves), postherpetic neuralgia, and visceral pain.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and Physical/Chart Notes
- Current Symptomology

- Documentation of other treatment modalities (pharmacological, psychological, surgical, or physical if applicable) tried and failed or judged to be unsuitable or contraindicated

## CROSS REFERENCES

1. [Deep Brain Stimulation](#), Surgery, Policy No. 84
2. [Occipital Nerve Stimulation](#), Surgery, Policy No. 174
3. [Implantable Peripheral Nerve Stimulation for Chronic Pain of Peripheral Nerve Origin](#), Surgery, Policy No. 205

## BACKGROUND

Spinal cord stimulation (SCS; also called dorsal column stimulation) involves the use of low-level epidural electrical stimulation of the spinal cord dorsal columns. The neurophysiology of pain relief after SCS is uncertain but may be related to either activation of an inhibitory system or to blockage of facilitative circuits. SCS has been used in a wide variety of chronic refractory pain conditions, including pain associated with cancer, failed back pain syndromes, arachnoiditis, and complex regional pain syndrome (i.e., chronic reflex sympathetic dystrophy). There has also been interest in SCS as a treatment of critical limb ischemia, primarily in patients who are poor candidates for revascularization and in patients with refractory chest pain.

SCS devices consist of several components: (1) the lead that delivers the electrical stimulation to the spinal cord; (2) an extension wire that conducts the electrical stimulation from the power source to the lead; and (3) a power source that generates the electrical stimulation. The lead may incorporate from 4 to 8 electrodes, with 8 electrodes more commonly used for complex pain patterns. There are two basic types of power source. One type, the power source (battery), can be surgically implanted. The other, a radiofrequency receiver, is implanted, and the power source is worn externally with an antenna over the receiver. Totally implantable systems are most commonly used.

The patient's pain distribution pattern dictates at what level in the spinal cord the stimulation lead is placed. The pain pattern may influence the type of device used; for example, a lead with 8 electrodes may be selected for those with complex pain patterns or bilateral pain. Implantation of the spinal cord stimulator is typically a 2-step process. Initially, the electrode is temporarily implanted in the epidural space, allowing a trial period of stimulation. Once treatment effectiveness is confirmed (defined as at least 50% reduction in pain), the electrodes and radio-receiver/transducer are permanently implanted. Successful SCS may require extensive programming of the neurostimulators to identify the optimal electrode combinations and stimulation channels.

Traditional SCS devices use electrical stimulation with a frequency on the order of 100 to 1000 Hz. In 2015, an SCS device, using a higher frequency of electrical stimulation (10,000 Hz) than predicate devices was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The high-frequency stimulation is proposed to be associated with fewer paresthesias, which are a recognized effect of SCS. In addition, in 2016, FDA approved a clinician programmer "app" that allows an SCS device to provide stimulation in "bursts" rather than at a constant rate. Burst stimulation is proposed to provide pain relief with fewer paresthesias. The burst stimulation device works in conjunction with standard SCS devices. With the newly approved app, stimulation is provided in five 500-Hz burst spikes at a rate of 40 Hz, with a pulse width of 1 ms.

Another variation on SCS stimulation is the wireless injectable stimulator. These miniaturized neurostimulators are transforaminally placed at the dorsal root ganglion (DRG) and are used to treat pain. DRG are located between spinal nerves and the spinal cord on the posterior root and are believed to play an important role in neuropathic pain perception. Two systems have received approval or clearance from FDA.

## REGULATORY STATUS

A large number of neurostimulator devices, some used for spinal cord stimulation (SCS), have been approved by the U.S. Food and Drug Administration (FDA) through the premarket approval (PMA) process. Examples of fully implantable SCS devices approved through the PMA process include the Cordis programmable neurostimulator (Cordis Corp., Downers Grove, IL), approved in 1981, the Itrel<sup>□</sup> (Medtronic, Minneapolis, MN), approved in 1984, the Genesis and Eon devices (St Jude Medical) in 2001 and the Precision Spinal Cord Stimulator (Advanced Bionics, Switzerland), approved in 2004. FDA product code: LGW.

In May 2015, the Nevro Senza<sup>™</sup> Spinal Cord Stimulator (Nevro Corp., Menlo Park, CA), a totally implantable neurostimulator device, was approved by FDA for the following indications: chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome (FBSS), intractable low back pain, and leg pain. This device uses a higher frequency of electrical stimulation (10 kHz) than standard devices.

Two wireless injectable neurostimulators have been approved or cleared by FDA. In February 2016, FDA approved the Axiom Neurostimulator System (Spinal Modulation, Menlo Park, CA) through the PMA process. The device is indicated as an aid the management of moderate-to-severe intractable pain of the lower limbs in adults with complex regional pain syndrome types 1 and II. In August 2016, the Freedom Spinal Cord Stimulator (Stimwave Technologies, Fort Lauderdale, FL) was cleared by FDA through the 510(k) process for treating chronic, intractable pain of the trunk and/or lower limbs.

In October 2016, FDA approved BurstDR stimulation (St Jude Medical, Plano, TX), a clinician programmer application that provides intermittent “burst” stimulation for patients with certain St Jude SCS devices.

## EVIDENCE SUMMARY

The principal outcomes for treatment of pain are symptom relief and improved functional level. Relief of pain is a subjective outcome and can be influenced by nonspecific effects, placebo response, the natural history of the disease, and regression to the mean. Therefore, randomized controlled trials (RCTs) are important to control for nonspecific effects and to determine whether any treatment effect provides a significant advantage over the placebo/sham treatment or other treatments. Appropriate comparison groups depend on the condition being treated and may include placebo/sham stimulation, or medical or surgical management.

In the evaluation of the risks for implantable devices, observational studies can provide data on the likelihood of potential complications. The following complications for spinal cord stimulation (SCS) have been reported:<sup>[1]</sup>

- Lead migration, connection failure, generator failure, and/or lead breakage

- Superficial and deep infection with or without abscess
- Hematoma
- Nerve injury

The following evidence summary focuses on the investigational indications noted in criteria III, as listed above.

## **CANCER-RELATED PAIN**

In 2015, Peng published an update to their 2013 systematic review, to evaluate the effectiveness of SCS for cancer-related pain compared with standard care using conventional analgesic medication.<sup>[2,3]</sup> The literature search yielded 430 initial articles; however, just 18 were deemed relevant to include in the review. No RCTs were identified that evaluated the efficacy of SCS in adult patients with cancer-related pain. No new publications were identified, since the four case series<sup>[4-7]</sup> using a before-after design, with a total of 92 patients, included in the original review. In the absence of randomized controlled studies, the efficacy of SCS for treating cancer-related pain cannot be determined.

## **CHRONIC REFRACTORY ANGINA**

Two populations of patients have been studied: 1) patients who were not considered candidates for a revascularization procedure due to comorbidities or other factors, where SCS was compared to continued medical management; or 2) patients who would be considered candidates for a revascularization procedure for the purpose of symptom relief only, where SCS was compared to coronary artery bypass grafting. Aggregating results across these different patient populations may yield misleading conclusions about treatment effect or patient selection criteria as these patient populations may not be interchangeable (both sets of patients may not be eligible for both procedures). Therefore, the trials included in this review for each of these distinct patient populations are discussed separately below.<sup>[8-13]</sup>

### **Systematic Reviews**

In 2016, Pan identified 12 RCTs that evaluated SCS in patients with refractory angina pectoris.<sup>[14]</sup> Most studies had small sample sizes (ie <50 patients) and together there were a total of 476 patients. Reviewers did not report the control interventions reported in the RCTs. Pooled analyses favored the SCS group in most cases for exercise time after intervention, pain level (VAS score) and angina frequency, but there was not a significant difference between intervention and control groups on physical limitation and angina stability.

A 2015 systematic review by Tsigaridas included nine RCTs evaluating SCS for refractory angina, seven of which compared SCS to low or no stimulation and two of which compared SCS to alternative medical or surgical therapy for angina.<sup>[15]</sup> Similar to the Taylor et al. review described below, the authors found that most RCTs were small and variable in quality based on assessment with the modified Jadad score. The authors reported: “two of the RCTs were of high quality; two were of low quality and the remaining ones were of intermediate quality.” Most trials which compared SCS to low or no stimulation, found improvements in outcomes with SCS; however, given limitations in the evidence base, the authors concluded that larger multicenter RCTs are needed to assess the efficacy of SCS for angina.

In 2009 Taylor published a systematic review of five randomized controlled trials comparing active SCS with placebo (four studies) or no treatment (one study).<sup>[16]</sup> The studies included for

analysis were judged to be of moderate or poor quality (based on a lack of reported treatment randomization and/or treatment blinding among cited limitations). Follow-up ranged from 48 hours to two-months and study size ranged from 22 to 30 patients. Primary outcomes identified by the review included impact on health-related quality of life, functional class and exercise capacity. Of these outcomes, active treatment was significantly associated with improvement in exercise capacity and health-related quality of life. No other differences between groups were identified. However, these results are limited by the moderate to poor quality of the reviewed studies which, because of their small sample sizes and limited follow-up duration, do not answer questions about the long-term durability of this type of treatment. In addition, the lack of distinction between placebo- and natural history- controlled groups does not allow for isolation of any treatment benefit of SCS over and beyond that conferred by placebo alone.

In 2008, a systematic review of the literature based on the Swedish Council on Technology Assessment in Health Care report on SCS in severe angina pectoris was published.<sup>[17]</sup> Seven controlled studies (five randomized), two follow-up reports, and a preliminary report, as well as two nonrandomized studies determined to be of medium-to-high quality were included in the review.

- The largest RCT<sup>[11-13]</sup> included 104 subjects and compared SCS and coronary artery bypass graft (CABG) in patients accepted for CABG and who were considered to have only symptomatic indication (i.e., no prognostic benefit) for CABG, according to the American College of Cardiology/American Heart Association guidelines, to run an increased risk of surgical complications, and to be unsuitable for percutaneous transluminal coronary angioplasty. Between-group differences on nitrate consumption, anginal attack frequency, and self-estimated treatment effect were not statistically significant at the 6-month follow-up. At the 5-year follow-up, significantly fewer patients in the CABG group were taking long-acting nitrates, and between-group differences on quality of life and mortality were not significant.
- A 2006 report by McNab compared SCS and percutaneous myocardial laser revascularization (PMR) in a study with 68 subjects.<sup>[10]</sup> Thirty subjects in each group completed a 12-month follow-up, and differences on mean total exercise time and mean time to angina were not significant. Eleven participants in the SCS group and 10 in the PMR group had no angina during exercise.
- The remaining RCTs included in the systematic review included 25 or fewer subjects.

## Randomized Controlled Trials

In another small pilot RCT, conducted by Eldabe in 2016 to address uncertainties related to recruitment, outcome measures, and care standardization for a larger trial comparing SCS to usual care for refractory angina, enrollment was planned for 45 patients, but the trial failed to meet its enrollment target.<sup>[18]</sup> Among the 29 patients randomized to SCS (n=15) or usual care (n=14), there were no significant differences in primary or secondary outcomes between groups, but the trial was underpowered.

In 2012 Zipes and colleagues published the results from a multi-center, single-blind RCT (n=68) which compared high SCS (two-hours of stimulation four times per day) versus sham SCS (one-minute of stimulation once per day) among patients with angina who were not candidates for revascularization.<sup>[19]</sup> The study was terminated (at 6 months) due to slow enrollment and per the Data Safety Monitoring Board recommendation that the study be terminated for futility based on an interim data analysis. The 68 subjects who underwent SCS

implantation were randomized to either high stimulation (n=32) or low stimulation (control group; n=36). The low-stimulation control was designed so that patients would feel paresthesia, but the effect of stimulation would be subtherapeutic. Major adverse cardiac events (MACE) and rate of angina attacks were the primary outcomes of interest, along with total exercise time and exercise time to onset of angina. At 6 months an intention-to-treat analysis was conducted; data was available only for 58 of the 68 subjects (85%) No differences were found between groups in any of the outcomes, prompting the researchers to conclude the SCS was not more effective than placebo. However, long-term differences between groups are still not known as the study was terminated early. In addition, the small sample size may have been underpowered for assessing clinically meaningful differences.

In 2011 Lanza and colleagues reported on a small RCT in which 25 patients were randomly assigned to 1 of 3 treatment groups: SCS with standard levels of stimulation (n=10), SCS with low-level stimulation (75% to 80% of the sensory threshold) (n=7), or SCS with very low intensity stimulation (n=8).<sup>[20]</sup> Thus, patients in groups 2 and 3 were unable to feel sensation during stimulation. After a protocol adjustment at 1 month, patients in the very low intensity group were re-randomized to one of the other groups after which there were 13 patients in the standard stimulation group and 12 patients in the low-level stimulation group. At the 3-month follow-up (2 months after re-randomization), there were statistically significant between-group differences in 1 of 12 outcome variables. There were a median of 22 angina episodes in the standard stimulation group and 10 in the low-level stimulation group (p=0.002), indicating evidence for a significantly higher rate of angina episodes with standard SCS treatment. Non-significant variables included use of nitroglycerin, quality of life (VAS), Canadian Cardiovascular Society angina class, exercise-induced angina, and five sub-scales of the Seattle angina questionnaire. The small sample size and short-term follow-up does not permit conclusions about the long-term safety and effectiveness of SCS in these patients.

## Section Summary

Numerous small RCTs have evaluated SCS as a treatment for refractory angina. While some studies have reported benefit, most have not. In two of the larger, more recent RCTs that enrolled more than 100 patients reported no benefit on the primary outcomes. Overall, this evidence is mixed and is not sufficient to allow conclusions on whether health outcomes are improved.

## CRITICAL LIMB ISCHEMIA

Critical limb ischemia (CLI) is described as pain at rest or the presence of ischemic limb lesions. If the patient is not a suitable candidate for limb revascularization (typically due to insufficient distal run-off), it is estimated that amputation will be required in 60-80% of these patients within a year. Spinal cord stimulation has been investigated in this small subset of patients as a technique to relieve pain and decrease the incidence of amputation.

## Systematic Reviews

In 2015, Aub Dabrh conducted a systematic review of nonrevascularization-based treatments, including SCS, for patients with critical limb ischemia also included five RCTs.<sup>[21]</sup> In pooled analysis, the authors found that SCS was associated with reduced risk of amputation (odds ratio [OR], 0.53; 95% CI, 0.36 to 0.79). However, the reviewers concluded that there was “relatively low quality of the evidence mainly due to imprecision (ie, small sample size and wide CIs) and the risk of bias.”

A 2013 update of a systematic review from the Cochrane group on use of SCS in non-reconstructible chronic critical leg ischemia (NR-CCLI) included 10 articles of six studies with a total of 444 patients.<sup>[22]</sup> None of the studies were blinded due to the nature of the treatment. One of the studies was non-randomized and one included only patients with ischemic ulcers. Treatment groups received SCS along with the same standard nonsurgical treatment as the control groups. At 12, 18 and 24 months follow-up individual studies showed a trend toward a better limb salvage that did not reach statistical significance. However, when results were pooled, a small but significant decrease in amputations was found for the SCS group at 12 months follow-up (pooled risk difference (RD): -0.11, 95% confidence interval: -0.20 to -0.02). The 11% difference in the rate of limb salvage means that 9 patients would need to be treated to prevent one additional amputation (number needed to treat [NNT]: 9, 95% CI: 5 to 50). Upon excluding results from the non-randomized trial from the analysis, the treatment difference for the group treated with SCS was no longer significant (pooled RD: -0.09, 95% confidence interval: -0.19 to 0.01). When results from the study with patients in Fontaine stage IV (the most severe stage of critical limb ischemia) were excluded, the direction of treatment benefit switched (from negative to positive, RD: 0.13, 95% CI 0.02 to 0.23), indicating evidence for increased risk of amputation following treatment with SCS.

Outcomes for pain relief and ulcer healing could not be pooled and the researchers reported mixed findings. Quality of life was unchanged in both control and treatment groups. The overall risk of complications or additional SCS treatment was 17%. Nevertheless, the report concluded that “There is evidence that SCS is better than conservative treatment alone to achieve amputation risk reduction, pain relief and improvement of the clinical situation” in patients with chronic critical leg ischemia. This seemingly incongruous conclusion may be explained by the authors’ conclusion that, “The benefits of SCS against the possible harm of relatively mild complications and costs must be considered.” A potential conflict of interest was noted for the principal investigator, who was part of the non-randomized study included in the analysis. Published comments by Klomp and Steyerberg strongly criticized the inclusion of this non-randomized trial, along the exclusion of data from a randomized study from the pooled analysis, stating:<sup>[23]</sup>

The same meta-analysis, performed with a different amputation data input of five randomized studies [instead of 4 RCTs and a non-randomized study], generated a risk difference of -0.07 (95% CI: -0.17 to +0.03) instead of -0.13 (95% CI: -0.22 to -0.04). The main conclusion, that spinal cord stimulation is better than conservative treatment alone in achieving a reduction in amputation risk, is not justified. If SCS is beneficial, the magnitude of the effect is very small.

In 2009, Klomp and colleagues published a meta-analysis of the same five RCTs identified in the 2013 Cochrane review.<sup>[24]</sup> The authors did not find a statistically significant difference in the rate of amputation in the treatment and control groups. There was a relative risk of amputation of 0.79 and a risk difference of -0.07 (p=0.15). They found insufficient evidence that SCS is more efficacious than best medical treatment alone. They also conducted additional analyses of data from their 1999 RCT to identify factors associated with a better or worse prognosis. They found that patients with ischemic skin lesions had a higher risk of amputation compared to patients with other risk factors. There were no significant interactions between this or any other prognostic factor. The analyses did not identify any subgroup of patients who might benefit from SCS.

In 2009, Simpson systematic review described above also reviewed studies on SCS for treatment of inoperable critical limb ischemia.<sup>[25]</sup> Four RCTs met inclusion criteria; comparators

were conventional medical management (CMM)<sup>[26-29]</sup>, oral analgesics<sup>[30]</sup>, or prostaglandin E1 injection<sup>[31]</sup>. The authors concluded that evidence for a treatment difference was found in reduction of analgesics up to six months, but not at 18 months. However, no between-group differences were found in pain relief, limb survival, health-related quality of life, or any other outcomes.

## Randomized Controlled Trials

There have been no new randomized trials published since those included in the systematic reviews summarized above.

## Conclusion

A number of small RCTs of SCS versus usual care have been completed on patients with critical limb ischemia. In pooled analyses of these RCTs, SCS did not result in a significantly lower rate of amputation, although one systematic review and meta-analysis did report a significant difference. This evidence is not sufficient to conclude that SCS improves outcomes for patients with critical limb ischemia.

## HEART FAILURE

### Randomized Controlled Trials

In 2016, Zipes reported the results of the DEFEAT-HF trial, a prospective, multicenter, single-blind RCT trial comparing SCS with active stimulation to sham control in patients with New York Heart Association functional class III heart failure with a left ventricular ejection fraction of 35% or less.<sup>[32]</sup> Sixty-six patients were implanted with an SCS and randomized in a 3:2 manner to SCS ON (n=42) or SCS OFF (sham; n=24). For the study's primary end point (change in left ventricular end systolic volume index from baseline to six months), there was no significant difference between groups (p=0.30). Other end points related to heart failure hospitalization and heart failure-related QOL scores and symptoms did not differ significantly between groups. After completion of the six month randomization period, all subjects received active SCS stimulation. From baseline to 12 months of follow-up, there were no significant echocardiographic treatment effects in the overall patient population in echocardiographic parameters (p=0.36). The study was originally powered based on a planned enrollment of 195 implanted patients, but enrollment was stopped early due to enrollment futility. The nonsignificant difference between groups may have been the result of underpowering. However, the absence of any treatment effects or between-group differences are further suggestive of a lack of efficacy of SCS for heart failure.

Findings of a small pilot crossover RCT evaluating SCS for heart failure were published in 2014 by Torre-Amione.<sup>[33]</sup> Eligibility included symptomatic heart failure despite optimal medical therapy, left ventricular ejection fraction less than 30%, hospitalization or need for intravenous inotropic support in the past year, and inability to walk more than 450 meters on a six-minute walk test. All patients had an implanted heart device. Nine patients underwent SCS implantation. The efficacy of SCS therapy was assessed by changes in patient symptoms, LV function, and BNP level. In all cases, ICD sensing, detection, and therapy delivery were unaffected by SCS. Symptoms were improved in the majority of patients with SCS, while markers of cardiac structure and function were, in aggregate, unchanged. Two patients had minor implant-related events and no reported implant-related HF exacerbations or hospitalizations. These small, preliminary pilot studies were intended to report first-in-human

feasibility and safety to support further study. RCTs with large sample sizes and long-term follow-up are needed to draw conclusions on the safety and effectiveness of the therapy for this indication.

## **Nonrandomized Studies**

In 2015 Tse performed a small, nonrandomized, prospective, multicenter pilot trial in male patients with New York Heart Association (NYHA) class III HF, left ventricular ejection fraction (LVEF) 20%-35%, and implanted defibrillator device who were prescribed stable optimal medical therapy.<sup>[34]</sup> Seventeen patients underwent implantation of a SCS device (cases) and four patients who did not fulfill the study criteria served as nontreated controls. At six-month follow up, no deaths or device-device interactions were reported. Composite score improved by  $4.2 \pm 1.3$  in all cases, and 11 cases (73%) showed improvement in  $\geq 4$  of 6 efficacy parameters, including NYHA class ( $p = 0.002$ ); peak maximum oxygen consumption ( $p = 0.013$ ); LVEF ( $p < 0.001$ ); and LV end-systolic volume ( $p = 0.002$ ). No improvements were observed in the four controls.

## **DORSAL ROOT GANGLION STIMULATION**

### **Systematic review**

A systematic review, published in 2013 by Pope , evaluated therapeutics for chronic pain that target the dorsal root ganglion.<sup>[35]</sup> This review focused on ganglionectomy, and radiofrequency treatment of the dorsal root ganglion, with discussion of electrical stimulation of the DRG as an emerging therapy. Three studies of electrical DRG stimulation were included in the review, two case reports and one nonrandomized feasibility trial. The Deer feasibility trial (described below) prospectively followed 10 patients with chronic, intractable neuropathic pain, over four weeks.<sup>[36]</sup> Eight of the nine patients who completed the trial experienced a clinically meaningful ( $>30\%$ ) reduction in pain, as measured using a visual analog scale, with an average pain reduction of 70%. Seven of the nine reduced their utilization of pain medication. There were no adverse events reported. The two case studies included in the review described successful treatment of cervicogenic headache, post-herpetic neuralgia, and discogenic pain.

### **Randomized Controlled Trials**

One RCT, the ACCURATE study, compared wireless injectable neurostimulators and standard SCS.<sup>[37]</sup> The trial, published by Deer in 2016, was a multicenter unblinded noninferiority trial. Eligibility criteria included chronic ( $\geq 6$  months) intractable (failed  $\geq 2$  drugs from different classes) neuropathic pain of the lower limbs associated with a diagnosis of CRPS or causalgia and no previous neurostimulation. Patients were randomized to receive DRG stimulation with the Axiom device or standard SCS. They first underwent a temporary trial of stimulation lasting 3 to 30 days, depending on the protocol at each site. Patients who had 50% or greater reduction in lower limb pain after the temporary trial were eligible for permanent stimulation. Those who failed temporary stimulation exited the trial but were included in the analysis as treatment failures. Implanted patients were followed for 12 months, with assessments at 3, 6, 9, and 12 months postimplant.

A total of 152 patients were randomized and 115 ( $n=61$  DRG,  $n=54$  SCS) had a successful temporary trial and continued to permanent implantation. Twelve-month data were available for 105 patients (55 patients in the DRG group, 50 in the SCS group). The primary outcome was a composite measure of treatment success. Success was defined as: (1) 50% or greater

reduction in VAS score from baseline to the end of the trial phase; (2) VAS at 3 months that was 50% or greater lower than baseline; and (3) no stimulation-related neurologic deficits experienced during the study. The noninferiority margin was set at 10%; the trial was designed such that, if the noninferiority end point was met, a superiority analysis was also performed. Treatment success at 3 month was achieved by 55 (81.2%) of 69 patients in the DRG arm and 39 (55.7%) of 70 in the SCS arm. The noninferiority margin was met, and DRG was found to be statistically superior to SCS ( $p < 0.001$ ). At the 12-month follow-up, the primary end point was achieved by 49 (74.2%) of 66 in the DRG group and 35 (53%) of 66 in the SCS group and, again, DRG was considered noninferior to SCS and also superior ( $p < 0.001$ ). In terms of paresthesias, at 3 months and 12, SCS patients were significantly more likely to report paresthesias in nonpainful areas than DRG patients. At 3 months, 84.7% of DRG patients and 65% of SCS patients reported paresthesias only in their painful areas; at 12 months, these percentages were 94.5% and 61.2%, respectively. Twenty-one serious adverse events occurred in 19 patients (8 in the DRG group, 11 in the SCS group; difference between groups,  $p = \text{NS}$ ). A limitation of the study was that it was unblinded and industry-sponsored, which could potentially bias outcome assessment and reporting.

Mekhail (2019) conducted a sub-analysis on the patients receiving DRG neurostimulation in the ACCURATE study, to evaluate the occurrence and risk factors for paresthesia.<sup>[38]</sup> Among the 61 patients with DRG implants, the rates of paresthesia at 1 month, 3 months, 6 months, 9 months, and 12 months were 84%, 84%, 66%, 62%, and 62%, respectively. The patients who were paresthesia-free reported similar or better outcomes for pain and quality of life. Risk factors for paresthesia occurrence included higher stimulation amplitudes and frequencies, number of implanted leads, and younger age.

## Nonrandomized Studies

Several case series have been published.<sup>[39-41]</sup> The largest of them are summarized below. Liem (2015) reported on the outcomes of an industry-sponsored multicenter, prospective trial of DRG stimulation at six months<sup>[42]</sup> and one year.<sup>[39]</sup> The trial consisted of a run-in period in which 51 participants received DRG stimulation via leads connected to an external stimulator, followed by surgical placement of a fully-implanted neurostimulator in 32 of the 39 patients that achieved 50% or greater pain relief during the run-in period. More than half of the patients with fully implanted DRG stimulators reported at least 50% relief in pain, as measured by visual analog scale. Average pain ratings were 58% lower than baseline at six months and 56% lower at 12 months post-implantation. Patients also reported improved quality of life and mood by questionnaire (EQ-5D-3L and POMS). Over 12 months, there were 86 adverse events reported in 29 patients, including temporary motor stimulation (12 events), CSF leak (seven events) and infection (seven events). Approximately half of these events were judged by the investigators to be related to the device. Seven subjects had their devices removed and were withdrawn from the study.

A subgroup analysis of the Liem study examined positional effects on paresthesia during DRG stimulation in the 32 patients with implanted neurostimulators.<sup>[43]</sup> Paresthesia and pain relief achieved with spinal cord stimulation can change as patients change position from upright to prone or supine, causing uncomfortable sensations. This study found no statistically significant difference in paresthesia intensity by body position. In order to truly determine the efficacy and safety of DRG stimulation well designed comparative studies with long-term follow-up must be performed to compare it to standard spinal cord stimulation.

Schu reported on an industry-sponsored multicenter European case series of 29 patients treated with DRG stimulation for chronic neuropathic groin pain.<sup>[40]</sup> Of the 29 patients who underwent a 30-day trial period, 25 (86.2%) underwent implantation with the Axium DRG device. Final lead placement between T12 and L4 was determined based on patient feedback during paraesthesia mapping. Data analysis was based on the results of 23 patients with a mean follow-up of 27.8 weeks. The average pain reduction was  $71.4 \pm 5.6\%$ , and 82.6% (19/23) of patients experienced a > 50% reduction in their pain at the latest follow-up. Adverse events were not reported. The authors stated that paraesthesia was largely unaffected by positional changes. Limitations of this study include small sample size, lack of comparative data, and potential bias inherent in pain as a subjective outcome measure.

In 2013 Deer conducted an industry-sponsored case series to evaluate the efficacy and safety of the Axium DRG system in ten patients with chronic intractable pain of the trunk and/ or limbs.<sup>[36]</sup> The study was conducted across four centers for a period of four weeks. The study protocol and lead implantation procedures were similar to those reported by Liem above; however, only results of trial DRGS over a period of three to seven days were reported. On average, there was a 70% reduction in pain following stimulation ( $p = 0.0007$ ). Eight of the nine patients experienced a clinically meaningful (>30%) reduction in pain, and seven of the nine reduced their pain medication utilization. The study did not consider longer term effects with a permanently implanted device. Seventeen adverse events occurred of which 14 were considered to be device-related; none were thought to be serious.

## PRACTICE GUIDELINE SUMMARY

### **AMERICAN SOCIETY OF INTERVENTIONAL PAIN PHYSICIANS (ASIPP)<sup>[44]</sup>**

In 2013, the ASIPP updated their evidence-based guidelines for interventional techniques in the management of chronic spinal pain. The guidelines included the statement that there is fair evidence in support of SCS in managing patient with failed back surgery syndrome.

### **AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION AND THE AMERICAN HEART ASSOCIATION (ACCF/AHA)**

Guidelines from the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published in 2007 with focused updates in 2011<sup>[45]</sup> and 2012<sup>[46]</sup> for the management of patients with unstable angina/non ST-Elevation myocardial infarction state:

“Transcutaneous electrical nerve stimulation and spinal cord stimulation for continued pain despite the implementation of Class I measures may be considered for patients with syndrome X. (Level of Evidence: B).”<sup>[47]</sup> However, the level of evidence indicates that the “treatment usefulness/ efficacy [is] less well established” and that this recommendation may be based on a single randomized controlled trial or one or more non-randomized studies.

The 2012 updated joint ACCF/AHA guidelines recommend that SCS may be considered for relief of refractory angina in patients with stable ischemia heart disease (Level of evidence: C, defined as very limited populations evaluated and/or only consensus opinion of experts, cases studies, or standard of care).<sup>[48]</sup> The guidelines conclude:

“Studies of spinal cord stimulation suggest that this technique might have some use as a method to relieve angina in patients with symptoms that are refractory to standard medical therapy and revascularization. There is a paucity of data on the mechanisms and long-term

risks and benefits of this therapeutic approach, however.”

## **NEUROPATHIC PAIN SPECIAL INTEREST GROUP OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN<sup>[49]</sup>**

In 2013, the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG) published consensus recommendations on management of neuropathic pain. The recommendations supporting the use of SCS for failed back surgery syndrome and for complex regional pain syndrome were rated as weak (quality of evidence moderate to low; strength of recommendation weak to inconclusive). The recommendation for SCS for postherpetic neuralgia was also rated as weak (quality of evidence low; strength of recommendation inconclusive).

## **INTERNATIONAL NEUROMODULATION SOCIETY<sup>[50]</sup>**

The International Neuromodulation Society convened a Neuromodulation Appropriateness Consensus Committee (NACC) to develop best practices for the use of DRG stimulation for the treatment of chronic pain syndromes. The NACC was comprised of experts in anesthesiology, neurosurgery, and pain medicine. The NACC performed a systematic literature search through June 2017 and identified 29 publications providing evidence for the consensus recommendations. The evidence was graded using the modified Pain Physician criteria and the USPSTF criteria. The NACC report gave a strong recommendation that DRG stimulation is recommended for CRPS type I or type II.

## **SUMMARY**

### **SPINAL CORD STIMULATORS**

There is enough research to show that spinal cord stimulation (SCS) including high frequency SCS for the treatment of chronic trunk or limb pain, when all other treatment modalities have failed to adequately reduce symptoms may improve health outcomes. In addition, practice guidelines recommend SCS for select patients. Therefore, SCS including temporary and the potential permanent implantation may be considered medically necessary for treatment of chronic refractory pain of the trunk or limbs when policy criteria are met.

There is not enough research to show that spinal cord stimulation (SCS), including standard or high frequency, in the treatment of conditions not related to severe and chronic refractory pain of the trunk or limbs improves health outcomes or is more effective than standard of care. Therefore, the use of SCS, including standard or high frequency is investigational for the treatment of all other conditions not related to severe and chronic refractory pain of the trunk or limbs.

### **DORSAL ROOT GANGLION STIMULATORS**

There is enough research to show that dorsal root ganglion (DRG) stimulation for the treatment of chronic trunk or limb pain, when all other treatment modalities have failed to adequately reduce symptoms may improve health outcomes. In addition, practice guidelines recommend DRG stimulation for select patients. Therefore, DRG stimulation may be considered medically necessary for treatment of chronic refractory pain of the trunk or limbs when policy criteria are met.

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There is not enough research to show that dorsal root ganglion (DRG) stimulation is safer and/or more effective than standard of care when policy criteria are not met. Therefore, the use of dorsal root ganglion stimulation is considered investigational when policy criteria are not met.

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## CODES

**NOTE:** HCPCS code C1823 is NOT the correct code to use for reporting these services. Please refer to the codes listed below for guidance.

Codes	Number	Description
CPT	63650	Percutaneous implantation of neurostimulator electrode array; epidural
	63655	Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural
	63661	Removal of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed
	63662	Removal of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed
	63663	Revision including replacement, when performed, of spinal neurostimulator electrode percutaneous array(s), including fluoroscopy, when performed
	63664	Revision including replacement, when performed, of spinal neurostimulator electrode plate/paddle(s) placed via laminotomy or laminectomy, including fluoroscopy, when performed
	63685	Insertion or replacement of spinal neurostimulator pulse generator or receiver, direct or inductive coupling
	63688	Revision or removal of implanted spinal neurostimulator pulse generator or receiver
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter, programming by physician or other qualified health care professional
95972	;with complex spinal cord, or peripheral (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional	
HCPCS	C1767	Generator, neurostimulator (implantable), nonrechargeable
	C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
	C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension	

**Date of Origin:** January 1996

## ***Bariatric Surgery***

**Effective:** July 1, 2020

**Next Review:** December 2020

**Last Review:** May 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Bariatric surgery is a major surgical intervention which aims to reduce weight, eliminate or improve comorbid conditions, and maintain weight loss in morbidly obese patients who have failed to achieve weight loss through lifestyle modifications.

### **MEDICAL POLICY CRITERIA**

**Note:** Member contracts for covered services vary. Member contract language takes precedence over medical policy.

- I. Bariatric surgery may be considered **medically necessary** in the treatment of morbid obesity when all of the following criteria (A. and B.) are met:
  - A. All of the general Criteria (1.- 4.) must be met:
    1. At the start of the medically-supervised, nonsurgical weight reduction program, one of the following must be met:
      - a. BMI greater than or equal to 40 kg/(meter squared); or
      - b. BMI greater than or equal to 35 kg/(meter squared) with at least one of the following comorbid conditions:

- i. Diabetes mellitus; or
    - ii. Hypertension; or
    - iii. Coronary artery disease; or
    - iv. Obstructive sleep apnea; and
  2. The patient meets one of the following age requirements:
    - a. Greater than or equal to 18 years; or
    - b. Less than 18 years of age and has attained Tanner 4 or 5 pubertal development. Note: For patients meeting this Criterion, greater consideration should be given to psychosocial and informed consent issues.
  3. Documentation of active participation for a total of at least 3 consecutive months in a structured, medically supervised nonsurgical weight reduction program. A comprehensive commercial weight loss program is an acceptable program component, but it must be approved and monitored under the supervision of the healthcare practitioner providing medical oversight. Comprehensive weight loss programs generally address diet, exercise and behavior modification (e.g., Weight Watchers).

Documentation from the clinical medical records must indicate that the structured medical supervision meets all of the following criteria:

- a. Occur during a total of at least 3 consecutive months within the 12 months prior to the request for surgery; and
      - b. Include at least 2 visits for medical supervision, during the 3 consecutive months of program participation. One visit must occur at the initiation, and another at least 3 months later; and
      - c. Be provided by an MD, DO, NP, PA, or RD under the supervision of an MD, DO, NP, or PA; and
      - d. Include assessment and counseling concerning weight, diet, exercise, and behavior modification; and
    4. Preoperative evaluation to include both of the following:
      - a. A licensed psychologist, psychiatrist, LCSW/LICSW, licensed masters-level counselor, or NP in a behavioral health practice, documents the absence of significant psychopathology that can limit an individual's understanding of the procedure or ability to comply with medical/surgical recommendations (e.g., active substance abuse, eating disorders, schizophrenia, borderline personality disorder, uncontrolled depression); and
      - b. Clinical documentation, by either a psychological or surgical evaluation, of willingness to comply with preoperative and postoperative treatment plan.; and
- B. The request is for one of the following procedures:
1. Sleeve gastrectomy as a stand-alone procedure; or

2. Adjustable gastric banding (consisting of an adjustable external band placed around the stomach); or
  3. Gastric bypass using a Roux-en-Y anastomosis with an alimentary limb of 150 cm or less.
- II. Reoperation may be considered **medically necessary** when one or more of the following criteria (A. or B.) are met:
- A. Reoperation with revision of a bariatric procedure (i.e. sleeve gastrectomy, adjustable gastric band, or gastric bypass) or adjustable gastric band removal when one or more of the following documented significant complications is present:
    1. Bowel perforation, including band erosion; or
    2. Band migration (slippage), that cannot be corrected with manipulation or adjustment. Records must demonstrate that manipulation or adjustment to correct band slippage has been attempted; or
    3. Leak; or
    4. Obstruction exceeding the inherent obstruction of the original bariatric procedure, documented by imaging; or
    5. Staple-line failure (such as, Gastro-gastric fistula); or
    6. Weight loss to 90% or less of ideal body weight; or
    7. Band infection; or
    8. Severe, clinically objective esophagitis (including Barrett's esophagus), or Cameron lesion(s) unresponsive to optimal medical management. Medical management must have been documented for at least 4 months; or
  - B. Removal of adjustable gastric band and conversion to a gastric bypass using a Roux-en-Y anastomosis with an alimentary limb of 150 cm or less when Criterion I. A. is met. Note: Criterion I. A. must be met during the period after placement of the adjustable gastric band.
- III. Sleeve gastrectomy, adjustable gastric banding, gastric bypass using a Roux-en-Y anastomosis with an alimentary limb of 150 cm or less is considered **not medically necessary** when Criterion I. above is not met.
- IV. Reoperation is considered **not medically necessary** when Criterion II. is not met, including but not limited to reoperation for early satiety, nausea, patient dissatisfaction, gastroesophageal reflux disease (GERD), or conversion of a prior procedure to a different procedure.
- V. The vertical banded gastroplasty is no longer a standard of care and is therefore considered **not medically necessary**.
- VI. The following procedures are considered **investigational** for the treatment of:
- A. Morbid obesity including distal or partial gastrectomy (other than standard sleeve gastrectomy) performed with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction; hiatal hernia repair including repair of sliding or paraesophageal hernia; and gastric restrictive procedure without gastric bypass

for morbid obesity (other than vertical banded gastroplasty or sleeve gastrectomy)

- B. Any condition *other than morbid obesity* (e.g. gastroesophageal reflux disease or gastroparesis) including sleeve gastrectomy, adjustable gastric banding, or gastric bypass using a Roux-en-Y anastomosis.
- C. Any condition including but not limited to morbid obesity and gastroesophageal reflux disease:
  - 1. Mini-gastric bypass (gastric bypass using a Billroth II type of anastomosis)
  - 2. Distal gastric bypass (long limb gastric bypass, i.e., >150 cm)
  - 3. Biliopancreatic bypass (i.e., the Scopinaro procedure)
  - 4. Biliopancreatic bypass with duodenal switch
  - 5. Duodenal switch with single anastomosis, D-Loop surgery, or stomach intestinal pylorus sparing surgery (SIPS)
  - 6. Two-stage bariatric surgery procedures (e.g., sleeve gastrectomy followed by gastric bypass, sleeve gastrectomy followed by biliopancreatic diversion, removal of gastric band followed by sleeve gastrectomy or gastric bypass)
  - 7. Adjustable gastric banding with existing gastric bypass or sleeve gastrectomy or other bariatric surgical procedure.
  - 8. Parietal cell separating gastrojejunostomy
  - 9. Gastric plication

VII. Endoscopic procedures are considered **investigational** for the following:

- A. As the primary bariatric procedure
- B. Secondary bariatric procedures (See Policy Guidelines) to treat complications of primary bariatric surgery including but not limited to weight gain due to a large gastric stoma or large gastric pouch and dumping syndrome.
- C. Balloon dilatation of structures when Criterion II.A.4 is not met.

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

## POLICY GUIDELINES

Examples of endoscopic devices/procedures include but are not limited to the following:

1. StomaphyX (EndoGastric Solutions, Inc)
2. ROSE procedure (Restorative Obesity Surgery, Endoscopic)
3. EndoCinch (Bard)
4. EndoSurgical Operating System (EOS) (USGI Medical, Inc.)
5. Sclerotherapy of stoma
6. Endoscopic gastroplasty

7. Endoscopically placed duodenal-jejunal sleeve
8. Endoscopic stoma revision
9. Gastric balloon systems
10. AspireAssist
11. OverStitch Endoscopic Suturing System (Apollo Endosurgery, Inc.)

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION:

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

1. If patient is less than 18 years of age, documentation is provided of Tanner 4 or 5 pubertal development.
2. Clinical documentation of a medically supervised nonsurgical weight reduction program or comprehensive commercial weight loss program approved and monitored under the supervision of the healthcare practitioner providing medical oversight, that includes:
  - A. BMI at the start of the program
  - B. Comorbid conditions
  - C. The program occurred during at least 3 consecutive months within the 12 months prior to request for surgery
  - D. At least 2 visits for medical supervision during the 3 consecutive months of program participation. One visit must occur at the initiation, and another at least 3 months later.
  - E. Assessment and counseling concerning weight, diet, exercise and behavior modification
  - F. Documentation the program was provided by an MD, DO, NP, PA, or RD under the supervision of an MD, DO, NP, or PA
3. Preoperative evaluation by a licensed psychologist, psychiatrist, LCSW/LICSW, licensed masters-level counselor, or NP in behavioral health that includes:
  - A. Documentation of the absence of significant psychopathology that can limit an individual's understanding of the procedure or ability to comply with medical/surgical recommendations (e.g., active substance abuse, eating disorders, schizophrenia, borderline personality disorder, uncontrolled depression)
4. Preoperative evaluation by either a psychological or surgical evaluation, of willingness to comply with preoperative and postoperative treatment plan
5. History and Physical including current medications
6. For Reoperation, Revision or Removal requests:
  - A. Complication present

- B. Interventions attempted. NOTE: For band migration (slippage), that cannot be corrected with manipulation or adjustment. Records must demonstrate that manipulation or adjustment to correct band slippage has been attempted.
- C. Imaging. NOTE: For obstruction, records must demonstrate that imaging has been performed.
- D. For severe esophagitis, documentation must demonstrate medical management has been tried for at least 4 months.

## CROSS REFERENCES

1. [Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease \(GERD\)](#), Surgery, policy No. 110
2. [Gastric Electrical Stimulation](#), Surgery, Policy No. 111
3. [Gastroesophageal Reflux Surgery](#), Surgery, Policy No. 186
4. [Magnetic Esophageal Ring to Treat Gastroesophageal Reflux Disease](#), Surgery, Policy No. 190
5. [Vagus Nerve Blocking Therapy for Obesity](#), Surgery, Policy No. 200

## BACKGROUND

Morbid obesity is defined as a body mass index (BMI) >40 kg/m<sup>2</sup> (normal BMI range: 19-25 kg/m<sup>2</sup>)

**Note:** BMI may be calculated by using the [BMI calculator](#).

Individuals with morbid obesity are at high risk for developing weight-related complications such as diabetes, hypertension, obstructive sleep apnea, and various types of cancers (colon, prostate, breast, uterus, and ovaries). In addition, morbid obesity is associated with a shortened life span.<sup>[1]</sup>

The first-line treatment of morbid obesity involves dietary and lifestyle changes. Although this strategy may be effective in some patients, a majority of morbidly obese patients do not achieve significant weight loss through lifestyle modifications. In addition, the weight loss may not be durable, as only a small number of patients are able to comply with the changes on a long-term basis. When conservative measures fail, some patients may consider surgery for morbid obesity (bariatric surgery).

Several bariatric procedures have been developed, but based on the underlying mechanism of weight loss, all fall into one or both of the following categories:

Restrictive procedures

- Decrease the size of the stomach and limit food intake

Malabsorptive procedures

- Limit the absorption of calories and nutrients by altering the way food moves through the intestinal track

Multiple variants exist, differing in the reconfiguration of the small intestines and consequently the extent of malabsorption.

The following table briefly summarizes different bariatric procedures:

Procedure	CPT Code	Description
<b>Gastric Bypass with Roux-en-Y Anastomosis (RYGBP)</b> AKA: Proximal or Short Limb Gastric Bypass	43846 43644	<ul style="list-style-type: none"> <li>• Currently considered “gold-standard” for weight loss surgery</li> <li>• Involves both restrictive and malabsorptive components: <ul style="list-style-type: none"> <li>○ A small gastric pouch is created from the upper part of the stomach by segmentation or resection to restrict the amount of food that can be ingested</li> <li>○ The mid portion of the jejunum is divided and the cut end of the distal limb (<math>\leq 150</math> cm) is attached to the gastric pouch outlet (Roux limb). The cut end of the proximal limb (the limb consisting of the duodenum and proximal jejunum) is attached to the side of the Roux limb (the limb connected to the pouch). This creates the Y configuration of the small intestine, allowing food to bypass the duodenum and proximal jejunum, resulting in malabsorption.</li> </ul> </li> </ul>
<a href="#"><u>Distal (Long Limb) Gastric Bypass</u></a>	43847	<ul style="list-style-type: none"> <li>• The procedure involves both restrictive and malabsorptive components and is a variant of the standard gastric bypass with the longer (<math>&gt;150</math> cm) Roux limb. The longer the Roux limb, the greater the bypass of the small intestine and consequently the degree of malabsorption.</li> </ul>
<a href="#"><u>Biliopancreatic Diversion (Bypass) Procedure</u></a> AKA Scopinaro procedure	43847	<ul style="list-style-type: none"> <li>• Involves both restrictive and malabsorptive components: <ul style="list-style-type: none"> <li>○ Subtotal (distal) gastrectomy creates small gastric pouch at the top of the stomach to limit food intake</li> <li>○ A long limb Roux-en-Y anastomosis (<math>&gt;150</math> cm) results in the biliopancreatic juices being diverted into the distal ileum, significantly increasing malabsorption</li> </ul> </li> <li>• Designed to preferentially inhibit the absorption of fat</li> <li>• Only partially reversible</li> </ul>
<a href="#"><u>Biliopancreatic Diversion (Bypass) with Duodenal Switch (BPD-DS)</u></a>	43845	<ul style="list-style-type: none"> <li>• This procedure is an adaptation of the standard biliopancreatic bypass: <ul style="list-style-type: none"> <li>○ The restrictive component involves subtotal gastrectomy resulting in a tube or sleeve-like stomach remnant that leaves the pyloric valve and the initial segment of duodenum intact.</li> <li>○ The long limb Roux-en-Y anastomosis (<math>&gt;150</math> cm) provides malabsorption in this variant as well, but the distal ileum is connected to the duodenal segment leading from the stomach sleeve, instead of the stomach pouch itself.</li> </ul> </li> </ul>
<a href="#"><u>Laparoscopic duodenal switch with single anastomosis</u></a> AKA Single loop duodenal switch	No specific CPT code	<ul style="list-style-type: none"> <li>• Restrictive and malabsorptive procedure</li> <li>• Simplified version of the BPD-DS procedure</li> <li>• Surgery consists of: <ul style="list-style-type: none"> <li>○ Creation of a small gastric pouch by section the curvature of the stomach</li> <li>○ Duodenum is transected while keeping the pylorus intact</li> <li>○ A 1-loop duodenal switch is performed with creation of a 200-250 cm anastomosis</li> </ul> </li> </ul>
<a href="#"><u>Mini-Gastric Bypass</u></a>	no specific code	<ul style="list-style-type: none"> <li>• The procedure is a variant of the gastric bypass and involves both restrictive and malabsorptive components: <ul style="list-style-type: none"> <li>○ The stomach is segmented to create a small gastric pouch similar to traditional gastric bypass</li> <li>○ Instead of creating a Roux-en-Y anastomosis, the loop of jejunum is anastomosed directly to the stomach pouch (similar to a Billroth II procedure)</li> </ul> </li> </ul>
<a href="#"><u>Sleeve Gastrectomy</u></a>	43775	<ul style="list-style-type: none"> <li>• Greater curvature of the stomach is resected resulting in a gastric remnant shaped like a tube or sleeve.</li> <li>• The pyloric sphincter is preserved leaving stomach function unaltered.</li> <li>• Not reversible</li> <li>• Can be performed as: <ul style="list-style-type: none"> <li>○ A stand-alone procedure (restrictive)</li> </ul> </li> </ul>

Procedure	CPT Code	Description
		<ul style="list-style-type: none"> <li>○ The first part of a two-stage surgical procedure for the very high-risk patients (BMI <math>\geq 50</math> kg/m<sup>2</sup>) who need to lose some weight before they can proceed with a malabsorptive procedure (most commonly BPD-DS or RYGBP)</li> </ul>
<a href="#">Adjustable Gastric Banding</a>	43770- 43774 43886- 43888	<ul style="list-style-type: none"> <li>● Restrictive procedure</li> <li>● An adjustable, external, constrictive band is wrapped around the upper portion of the stomach to create a small stomach pouch</li> <li>● The band can be adjusted through a subcutaneous access port, foregoing the need to enter the gastric cavity when adjusting the band</li> <li>● The least invasive and least technically complex bariatric procedure</li> <li>● Lap-Band® (original applicant, Allergan, Inc.; sold to Apollo Endosurgery, Inc.) and the REALIZE™ (Ethicon Endo-Surgery, Inc.) have received approval from the U.S. Food and Drug Administration (FDA).</li> </ul>
<a href="#">Vertical Banded Gastroplasty</a> AKA Vertically banded gastric partition or Gastric stapling	43842	<ul style="list-style-type: none"> <li>● Restrictive procedure</li> <li>● Surgical stapling is used to create a small, vertical gastric pouch at the top of the stomach</li> <li>● The pouch outlet (stoma) is reinforced with an external mesh collar</li> </ul>
<a href="#">Endoscopic (Endoluminal) Bariatric Procedures</a>	No specific CPT code	<ul style="list-style-type: none"> <li>● The access to the stomach is gained through the mouth, so no incisions are necessary.</li> <li>● Endoluminal procedures being developed: <ul style="list-style-type: none"> <li>○ Primary bariatric procedure</li> <li>○ Revision (e.g. for treatment of enlarged gastric stoma and/or enlarged gastric pouches that may be associated with weight gain after bariatric surgery)</li> </ul> </li> <li>● Examples of the endoscopic revision bariatric procedures include: <ul style="list-style-type: none"> <li>○ Gastroplasty using an endoscopically guided stapler (reduces the size of the gastric pouch)</li> <li>○ Placement of gastric balloon (soft, silicone balloon inserted into the stomach and filled with sterile saline to induce feeling of satiety)</li> <li>○ Placement of duodenal-jejunal sleeve (sleeve placed inside duodenum and upper jejunum to prevent contact between food and the intestine).</li> </ul> </li> <li>● StomaphyX®, an endoscopically guided system intended for tissue plication and ligation, has received 510(k) FDA approval. The device is also being investigated for endoscopic treatment of gastroesophageal reflux.</li> <li>● OverStitch™ Endoscopic Suturing System is intended for endoscopic placement of sutures and approximation of soft tissue, and has received FDA approval. The system may be used as an incisionless revision surgery, with the intent to reduce the size of a stomach pouch that has stretched out following a previous bariatric procedure.</li> </ul>
<a href="#">Laparoscopic Gastric Plication</a>	No specific CPT code	<ul style="list-style-type: none"> <li>● Sutures are laparoscopically placed over the greater curvature (laparoscopic greater curvature plication) or anterior gastric region (laparoscopic anterior curvature plication) to create a tube-like stomach.</li> <li>● The procedure involves 2 main steps: <ul style="list-style-type: none"> <li>○ Mobilization of the greater curvature of the stomach, and</li> <li>○ Suture plication of the stomach to achieve gastric restriction</li> </ul> </li> </ul>

## EVIDENCE SUMMARY

- Roux-en-Y Gastric Bypass (RYGBP)

The Roux-en-Y gastric bypass is the most commonly performed procedure with the most accumulated evidence in the published literature.<sup>[2]</sup> Consequently, in order to determine the safety and efficacy of other bariatric surgical procedures, they need to be compared to RYGBP in well-designed, well-executed randomized controlled trials (RCTs).

- Laparoscopic Adjustable Gastric Banding (LAGB)

RCT data comparing LAGB and RYGBP are limited, however:

- LAGB is reversible and the least invasive of all bariatric procedures.
- Weight loss following LAGB is less than what is usually seen following RYGBP.
- LAGB has low perioperative complications; however inadequate weight loss or long term complications of band erosion, slippage, or malfunction may require additional surgery.

- Sleeve Gastrectomy (SG)

- Despite limited evidence, SG has been gaining increased acceptance in clinical practice.
- SG offers an alternative to adjustable gastric banding with potentially greater weight loss but without the complications associated with malabsorptive procedures, such as RYGBP.

- Other Bariatric Surgical Procedures

### *Randomized Controlled Trials*

Very few randomized controlled trials compared other bariatric procedures with RYGBP. Overall, the trials were of poor quality and the findings unreliable due to at least one of the following design flaws:

- The trials had very small study populations, limiting the ability to rule out the role of chance as an explanation of findings.
- The randomization scheme was either inadequate or not explained. Inadequate randomization of study participants may result in unequal distribution of potential confounders, such as clinical characteristics, which in turn may affect the outcome.
- The studies have short follow-up times so there is no long-term (5-10 years or longer) evidence regarding:
  - durability of weight loss
  - complications (e.g. metabolic side effects, nutritional deficiencies, anastomotic ulcers, esophagitis, procedure-specific complications such as band erosion)
  - resolution of comorbidities (e.g. diabetes, hypertension, obstructive sleep apnea, increased cholesterol)
  - need for reoperations

- Short-term complications, adverse events, morbidity, resolution of comorbidities, and reoperation rates are inconsistently reported, limiting conclusions and comparisons across studies.
- There is limited understanding of appropriate patient selection criteria for each of the non-RYGBP bariatric procedures (e.g. superobese patients vs. morbidly obese patients).

### *Nonrandomized Studies*

Although the published, peer-reviewed literature on non-RYGBP bariatric procedures is voluminous, it consists mostly of case series and retrospective, nonrandomized comparisons. Evidence from these studies is unreliable due to design flaws, such as non-random allocation of treatment, lack of adequate comparison groups, and short-term follow-up. In addition, the inconsistent reporting of weight loss, resolution of comorbidities, adverse events, morbidity, and reoperation rates further limit meaningful comparisons across these studies.

- **Bariatric Surgery in the Pediatric Population**

Overall, there is very little evidence on the role of bariatric surgery in treating morbidly obese pediatric patients. Moreover, the evidence mostly comes from small, nonrandomized and therefore unreliable studies. Specifically:

- There is limited evidence that bariatric surgery leads to clinically significant, long-term sustained weight loss and resolution of obesity-related comorbidities in the pediatric population.
- The evidence does not permit conclusions regarding morbidity associated with and safety of any bariatric procedure in the pediatric population.
- There is no evidence regarding the long-term potential impact of bariatric procedures on growth and development in the pediatric population.

- **Bariatric Surgery as a Treatment for Gastroesophageal Reflux Disease (GERD)**

In order to determine the safety and efficacy of bariatric surgical procedures as treatments for GERD, they need to be compared to standard medical or surgical treatments of this condition in well-designed, well-executed randomized controlled trials.

- **Endoscopic Bariatric Procedures**

There is insufficient evidence to determine the safety and efficacy of any endoluminal procedure as either a primary bariatric procedure or a revision procedure. The published evidence is very limited and consists of only a few case series and one unreliable randomized trial.

- **Multidisciplinary Approach to the Clinical Management of Bariatric Surgery Patients**

The National Institutes of Health/National Heart, Lung, and Blood Institute (NIH/NHLBI) clinical practice guidelines state the importance of a multidisciplinary approach to the clinical management of bariatric surgery patients. Comprehensive programs should address nursing, nutrition, exercise, behavior modification, and psychological support, and they should provide lifelong follow-up for treated patients.<sup>[1]</sup>

- **Bariatric Surgery Centers of Excellence**

The published evidence indicates that high volume bariatric centers are more likely to be successful in achieving optimal outcomes and lower complication and mortality rates than low volume bariatric centers.<sup>[3-5]</sup> These data have led to national efforts to establish bariatric surgery centers of excellence by the American Society for Metabolic and Bariatric Surgery, the American College of Surgeons, and the BlueCross BlueShield Association.

The following literature appraisal is based on randomized controlled trials (RCT), Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) Assessments, Cochrane reviews, Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness reviews, Washington State Health Technology Assessment and evidence-based guidelines.

## **DISTAL (LONG LIMB) GASTRIC BYPASS**

### **SYSTEMATIC REVIEWS**

The 2005 Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) Assessment identified six comparative trials of long limb gastric bypass with Roux-en-Y anastomosis (LL-RYGBP) vs. standard RYGBP.<sup>[2]</sup> However, only two were randomized controlled trials (RCT). The assessment determined that there was not sufficient evidence to reach conclusions on the efficacy and safety of LL-RYGBP compared to standard RYGBP:

- In both RCTs, there was no significant difference in weight loss between the two groups at 1 year.
- The evidence for the super obese (BMI  $\geq 50$  kg/m<sup>2</sup>) population was weak and did not allow conclusions concerning whether LL-RGYBP is superior in this subgroup of patients
- The adverse events were poorly reported in all comparative studies. Some of the reports contradicted one another.
- There was no definite cut-off for “long” vs. “standard” limb, making comparisons even more challenging.

### **RANDOMIZED CONTROLLED TRIALS**

One RCT evaluated the effectiveness of the distal gastric bypass for weight loss and control of comorbidities.<sup>[6]</sup> The study included only super obese patients (BMI  $\geq 50$  kg/m<sup>2</sup>). There was no significant difference in the control or improvement of hypertension, sleep apnea, or gastroesophageal reflux disorder between the patients who underwent long-limb (Roux limb = 250 cm) and short-limb gastric bypass (Roux limb = 150 cm). In addition, there was no difference in excess weight loss between the groups. Although the study reports better control of lipid disorders and diabetes in patients who underwent the long-limb gastric bypass, several design flaws undermine the reliability of the study findings:

- The small study population (n=105) limits the ability to rule out the role of chance as an explanation of findings.
- The randomization scheme was not explained. Inadequate randomization of study participants may result in unequal distribution of potential confounders, such as clinical characteristics.
- The short-term follow-up limits conclusions regarding the long-term complications and the effectiveness of the distal gastric bypass in controlling weight loss and comorbidities.

- The study included only super obese patients limiting the generalizability of the study findings to other patient populations (i.e. morbidly obese).
- The need for nutritional supplementation after the surgery was reported for the two treatment groups, but there was a failure to include statistical testing for this outcome.

## NONRANDOMIZED STUDIES

A number of nonrandomized studies (retrospective comparisons, case series) describe the experiences of patients undergoing distal gastric bypass.<sup>[2,7-9]</sup> As noted at the beginning of the evidence section, conclusions cannot be reached from these studies as the evidence is considered unreliable.

## SECTION SUMMARY

Evidence regarding long limb gastric bypass with Roux-en-Y anastomosis (LL-RYGBP) vs. standard RYGBP is limited to three RCTs which showed either no benefit to the LL approach compared to the RYGBP and/or had numerous methodological limitations. In addition, without a standardized cut-off for long vs. standard limb length, comprehensive assessment of the long limb procedure is unlikely. Therefore, current evidence is insufficient to recommend LL-RYGBP over standard RYGBP, including in the super obese.

## BILIOPANCREATIC BYPASS AND BILIOPANCREATIC BYPASS WITH DUODENAL SWITCH

### SYSTEMATIC REVIEWS

In 2013, Colquitt updated a 2009 Cochrane review<sup>[10]</sup> which compared outcomes for a variety of surgical weight loss procedures.<sup>[11]</sup> Two RCTs were identified which assessed outcomes of biliopancreatic diversion with duodenal switch (BPD-DS) compared to RYGBP. At a mean three year follow-up, data from the two trials were pooled (n= 107) and the following conclusions were reached:

- BPD-DS resulted in significantly greater weight loss than RYGBP.
- Quality of life measures were similar between the two groups.
- Reoperation rates were higher in the BPD-DS group (16.1%-27.6%) compared to the RYGBP group (4.3%-8.3%), with one death reported in the BPD-DS group.

The 2005 BCBSA TEC Assessment identified only one comparative trial that compared RYGBP with BPD-DS.<sup>[2]</sup> Although the trial included 237 RYGBP and 113 BPD-DS patients, it was not a randomized clinical study (the choice of the surgery was determined by surgeon and/or patient) and it followed participants for only one year. The TEC Assessment did not find this data sufficient to determine the risk/benefit ratio for this procedure or that it results in greater weight loss than RYGBP:

- The % estimated weight loss (EWL) at one year was the same for both the RYGBP and BPD-DS groups.
- Data on short-term adverse events was limited, except for the mortality and wound infection rates which were equivalent in both groups.
- More anastomotic leaks were reported in BPD-DS group.
- Long-term complications were not reported.

- Nutritional concerns were not adequately addressed. This is of concern because BPD-DS further reduces fat absorption, affecting the absorption of fat soluble vitamins.

## **RANDOMIZED CONTROLLED TRIALS**

Two prospective randomized trials compared the experiences of obese patients undergoing RYGBP vs. BPD.

The first trial compared weight loss, metabolic deficiencies, and resolution of comorbidities in morbidly obese patients undergoing RYGBP vs. a variant of BPD (BPD with RYGBP).<sup>[12]</sup> The study reports comparable nutritional deficiencies between the two procedures. Although better weight loss and resolution of diabetes and hypercholesterolemia was reported in the BPD group, several design flaws undermine the reliability of the study findings:

- The study employed an inadequate randomization scheme: the report states that patients were chosen to undergo RYGBP or BPD, but fails to provide any further explanation of how the treatment was assigned. Inadequate randomization of study participants may result in unequal distribution of potential confounders, such as clinical characteristics.
- The RYGBP group had a significantly higher level of preexisting comorbidities ( $p = 0.01$ ), suggesting a difference between the treatment groups that may have affected the outcome.
- The small study population (65 patients/surgery group) limits the ability to rule out the role of chance as an explanation of findings.
- The short-term follow-up (2 years) limits conclusions regarding the long-term metabolic complications and the long-term effectiveness of the BPD in controlling weight loss and comorbidities.

Another small randomized trial ( $n=60$ ) compared laparoscopic RYGBP and BPD-DS for superobese patients ( $BMI\ 50-60\ kg/m^2$ ).<sup>[13]</sup> The study found comparable 30-day perioperative safety and greater weight loss following BPD-DS in the first year. However, several design flaws undermine the reliability of the study findings:

- It is not certain from the data presented whether the study was adequately powered to reliably observe the treatment differences, especially in the stratified sub-analyses.
- The effectiveness of the procedures in controlling comorbidities was not compared in this study.

In 2015, long-term 5-year follow-up results were published on data from 55 patients (92%).<sup>[14]</sup> Results indicated a mean reduction of body mass index was greater with duodenal switch compared to bypass (mean between-group difference was 8.5 [95% CI, 4.9-12.2;  $P < .001$ ]); however, duodenal switch was associated with more surgical, nutritional and gastrointestinal adverse effects.

## **NONRANDOMIZED STUDIES**

A number of non-randomized studies (retrospective comparisons, case series) describe the experiences of patients undergoing biliopancreatic diversion with or without duodenal switch.<sup>[15-33]</sup> As noted at the beginning of the evidence section, conclusions cannot be reached from these studies as the evidence is considered unreliable.

## **SECTION SUMMARY**

Studies that compared RYGBP with BPD-DS are limited by methodological limitations, including inadequate power analysis, unequal distribution of preexisting comorbidities between groups, small sample size and short-term follow-up. In addition, a recent Cochrane review reported higher reoperation rates with BPD-DS compared to RYGBP. Given these limitations and high reoperation rates, the efficacy of BPD-DS versus RYGBP as a treatment for obesity cannot be determined.

## SLEEVE GASTRECTOMY

There are various types of gastrectomy, which include distal, partial (including sleeve gastrectomy) or complete gastrectomy which may be performed with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction. There is insufficient evidence regarding the use of gastrectomy, other than sleeve gastrectomy, as a treatment of obesity. Numerous studies were identified which evaluated outcomes of these alternative gastrectomy methods as a treatment of other conditions, including gastric cancer; however, no studies or clinical practice guidelines were identified which evaluated the efficacy of these alternative types of gastrectomy as a treatment of obesity. Therefore, the following evidence review will focus on the use of sleeve gastrectomy as a treatment of obesity, in the context of systematic reviews and well-designed randomized controlled trials:

### SYSTEMATIC REVIEWS

In 2017, Juodeikis evaluated five-year results following sleeve gastrectomy in a systematic review of the literature through May 2016.<sup>[34]</sup> The review was conducted according to PRISMA guidelines. Twenty studies were included for evaluation, however, only one study was a randomized controlled trial. Of the 2,713 patients included amongst all the studies combined, 1,626 reached at least five years follow-up (duration ranged from 5-11 years follow-up). Although mean percentage excess weight loss of greater than 56% was achieved at each time point from 5 to 11 years time, the review was substantially limited by the lack of RCT data.

In 2016, Osland compared the efficacy of Roux-En-Y gastric bypass versus vertical sleeve gastrectomy in randomized controlled trials.<sup>[35]</sup> Six RCTs performed between 2005 and 2015 were included (N = 695; 347 for SG and 348 for RYGB). The authors summarized recent publications, without pooled analysis. Although the results stated comparable efficacy and improvement or resolution in comorbidities, the authors also noted the significant limitation of short follow-up time (one year, with significant loss of follow-up), and lack of blinding in five of the six studies included. In 2017, Osland published an additional meta-analysis, again comparing vertical sleeve gastrectomy in RCT's to LRYGB (N=865 patients; 437 for SG and 428 for LRYGB).<sup>[36]</sup> The authors concluded once again that a significant gap exists in the literature with respect to well-designed studies using intent-to-treat analysis.

In 2015, Zhang published a separate review comparing LSG to laparoscopic RYGBP (LRYGBP) which included 21 studies involving 18,766 morbidly obese patients.<sup>[37]</sup> Data regarding percentage of excess weight loss (%EWL), resolution or improvement of comorbidities, and adverse events were pooled. Although no difference in %EWL was observed between the two groups in the first 6 months-1.5 year follow-up, LRYGBP achieved higher %EWL compared to LSG (p<0.05). Except for improvements in type 2 diabetes, comorbidities did not differ significantly between the two groups. Adverse events were more frequent following Roux-en-Y bypass (OR for major complication: 1.29; 95% CI 1.22 to 3.22; P<0.01). Results of this review must be interpreted with caution as 13 of the 21 included studies were nonrandomized, limiting the ability to control for confounding factors.

A 2014 review by Zellmer compared complication rates of laparoscopic RYGBP to LSG in 61 publications which included 10,906 laparoscopic RYGBP patients and 4,816 LSG patients.<sup>[38]</sup> Authors reported similar leak and mortality rates in both groups; laparoscopic RYGBP (leak: 1.9%, mortality: 0.4%) vs. LSG (leak: 2.3%, mortality: 0.2%).

The 2013 Cochrane review of bariatric surgery identified only one randomized controlled trial that compared sleeve gastrectomy to gastric bypass with Roux-en-Y anastomosis (RYGBP).<sup>[10,11,39]</sup> This very small (n=32) and short trial that followed participants for only 1 year reported that:

- Weight loss and BMI were similar between the two procedures, but % excess weight loss was greater with sleeve gastrectomy.
- Two patients had diabetes at baseline, both in the RYGBP group. The condition was resolved at 1 year in both patients. The outcome of other comorbidities reported at baseline was not reported for the RYGBP or SG groups.
- Although the study reported no conversions to open surgery and no intraoperative and postoperative complications, the other complications and additional operative procedures were not reported.
- The study did not assess a two-stage approach using sleeve gastrectomy prior to another bariatric procedure and consequently no conclusions about the two-stage approach could be made.
- The short duration of the follow-up results in underestimation of the impact of late complications and the need for revision surgery.

In 2013, Trastulli published a systematic review of randomized trials that compared sleeve gastrectomy to other bariatric procedures.<sup>[40]</sup> A total of 15 RCTs with 1191 patients were included. In six trials laparoscopic sleeve gastrectomy (LSG) was compared to laparoscopic RYGBP. The authors reported mean complication rates with sleeve gastrectomy of 12.1% (range 10%-13.2) compared with 20.9% with laparoscopic gastric bypass (range 10%-26.4%). Percentage of excess weight loss ranged from 49%-81% with sleeve gastrectomy compared with 62.1%-94.4% with laparoscopic gastric bypass. Included studies which compared LSG to laparoscopic RYGBP were small<sup>[41-43]</sup> (n<60) and several contained a risk for bias which included unclear blinding, randomization methods and outcome data.

A 2013 meta-analysis by Li pooled data from five trials, four of which were included in the Trastulli review, to compare the impact of these procedures on type 2 diabetes rates.<sup>[44]</sup> Laparoscopic Roux-en-Y gastric bypass was associated with higher rates of type 2 diabetes remission and greater estimated weight loss, but higher rates of complications.

## **RANDOMIZED CONTROLLED TRIALS**

Hofsø (2019) published the results of a single-center, triple-blind RCT comparing the efficacy of Roux-en-Y gastric bypass (RYGB) (n=54) vs sleeve gastrectomy (SG)(n=55) on diabetes remission and  $\beta$ -cell function in patients with obesity and T2D. Inclusion criteria included previously verified BMI  $\geq 35$  kg/m<sup>2</sup> and current BMI  $\geq 33.0$  kg/m<sup>2</sup>, hemoglobin A1c (HbA1c)  $\geq 6.5\%$  or use of antidiabetic medications with HbA1c  $\geq 6.1\%$ , and age  $\geq 18$  years. One-year follow-up was completed by 107 (98%) of 109 patients, with 1 patient in each group withdrawing after surgery. In the intention-to-treat population, diabetes remission rates were superior in the gastric bypass group than in the sleeve gastrectomy group (risk difference 27%;

relative risk [RR] 1.57). Results were similar in the per-protocol population (risk difference 27%; RR 1.57). The two procedures had a similar beneficial effect on  $\beta$ -cell function.

Peterli (2018) published a randomized study of adults with morbid obesity treated with either laparoscopic sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB).<sup>[45]</sup> Two hundred five patients treated at four bariatric centers were randomly assigned to receive SG (n=101) or RYGB (n=104) with 5-year follow-up. Excess BMI loss was 61.6% for SG and 68.3% for RYGB. Gastric reflux remission was seen in 25.0% of SG and 60.4% of RYGB patients. Reoperations or interventions were necessary for 15.8% in the SG group and 22.1% of the RYGB group. The study was limited by the lack of analysis of diabetes remission information and the results may not be generalizable.

Salminen (2018) published a randomized trial (SLEEVEPASS) comparing 5-year outcomes of morbidly obese patients who underwent either laparoscopic sleeve gastrectomy (SG; n=121) or Roux-en-Y gastric bypass (RYGB; n=119).<sup>[33]</sup> Five-year estimated mean percentage excess weight loss was 49% for sleeve gastrectomy and 57% for gastric bypass. For SG and RYGB, respectively, rates of remission of type 2 diabetes were 37% and 45%. Medication for hypertension was discontinued in 20/68 (29%) SG patients and 37/73 (51%) RYGB patients. Overall 5-yr morbidity rate was 19% for SG and 26% for RYGB, and there was no significant difference in QOL between groups. The study was limited by the following: the study having a higher reoperation rate for sleeve gastrectomy than other trials reported, approximately 20% of patients were lost to follow-up, and there was a lack of reliable information for diabetes duration at baseline.

## CLINICAL PRACTICE GUIDELINES

In 2012, the American Society for Metabolic & Bariatric Surgery (ASMBS) updated their position statement on *Sleeve Gastrectomy as a Bariatric Procedure*.<sup>[46]</sup> The ASMBS recognizes sleeve gastrectomy as an acceptable option as a primary bariatric procedure and as a first stage procedure in high risk patients as part of a planned staged approach. In addition, the group noted that substantial comparative and long-term data have now been published which demonstrate durable weight loss, improved medical comorbidities, long-term patient satisfaction, and improved quality of life after SG. However, the ASMBS Statement does not include a critical appraisal of the reviewed evidence.

## SECTION SUMMARY

Recent systematic reviews of existing trials indicate sleeve gastrectomy (SG) is a comparable procedure to RYGBP. Although the evidence regarding SG with RYGBP compared to standard RYGBP is limited by short-term follow-up, SG has become a recognized surgical option in clinical practice for the treatment of morbid obesity.

## ADJUSTABLE GASTRIC BANDING

### SYSTEMATIC REVIEWS

Park (2019) conducted a systematic review with a network meta-analysis evaluating the comparative efficacy of various bariatric surgery techniques against standard-of-care in the treatment of morbid obesity and diabetes.<sup>[47]</sup> The literature search was conducted through February 2018, identifying 45 RCTs for inclusion on Roux-en-Y gastric bypass (RYGB; 2 studies), sleeve gastrectomy (SG; 3 studies), laparoscopic adjustable gastric band (LAGB; 5

studies), and biliopancreatic diversion with duodenal switch (BPD-DS; 3 studies vs RYGB). Based on 33 trials, superior efficacy for % excess weight loss compared to standard-of-care was seen for BPD-DS (mean difference [MD] 38.2%), RYGB (MD 32.1%), and SG (MD 32.5%) at 6 months post procedure. LAGB was not superior to standard-of-care (MD -0.2%). At 3 years post-procedure, superior efficacy for %EWL compared to standard-of-care was seen for RYGB (MD 45%) and SG (MD 39.2%). BPD-DS (RR 7.51), RYGB (RR 7.51), and SG (RR 6.69) were all superior to standard-of-care with respect to remission rates at 3-5 years post-procedure and remission rates were not significantly different among procedures. SG was found to have a relatively lower risk of adverse events compared to RYGB.

A 2017 systematic review by Kang reported results from a network meta-analysis of RCTs evaluating the three most commonly performed bariatric procedures – Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), and laparoscopic adjustable gastric band (LAGB).<sup>[48]</sup> The review was conducted with literature through July 2016, and in accordance with PRISMA guidelines. Evidence was synthesized from 11 trials (8 RYGB vs SG; 2 RYGB vs LAGB; 1 SG vs LAGB) in order to evaluate the primary outcome of changes in weight loss, expressed as the mean difference in BMI reduction and in percentage excess weight loss (%EWL) following 1 year after the surgery. The smallest treatment effect was observed in LAGB (8 trials, totalling 656 patients). The mean %EWL for RYGB, SG, and LAGB were 67.3% (n=294), 71.2% (n=209), and 40.6% (n=153), respectively. Heterogeneity between studies was low (as evaluated by calculating the  $I^2$  statistic), and the studies were consistent between direct and indirect comparisons – both demonstrated strengths of the analysis. The study was limited by fewer trials evaluating LAGB, and inclusions of RCTs with a lack of blinding.

The 2013 Cochrane review of bariatric surgery identified three randomized controlled trial that compared laparoscopic adjustable gastric banding (LAGB) to laparoscopic gastric bypass with Roux-en-Y anastomosis (RYGBP).<sup>[10,11,49]</sup> At five-year follow-up, the review reported the following conclusions:

- RYGBP was superior to LAGB on more than one measure of weight loss (% excess weight loss, mean BMI).
- Quality of life measures and comorbidities were not assessed due to the low quality of the evidence.
- RYGBP resulted in a greater duration of hospitalization and a greater number of late major complications.
- One study reported high rates of reoperation for removal of LAGB (9 patients, 40.9%).

In 2012, TEC conducted an updated Assessment, focusing on LAGB in patients with BMIs less than 35 kg/m<sup>2</sup>.<sup>[50]</sup> TEC made the following observations and conclusions:

- The evidence on LAGB for patients with lower BMIs is limited both in quantity and quality. There was only one small randomized, controlled trial, which had methodologic limitations, one nonrandomized comparative study based on registry data, and several case series. Using the GRADE evaluation, the quality of evidence on the comorbidity outcomes was judged to be low and the quality of the evidence on the weight loss outcomes was judged to be moderate.
- The evidence was sufficient to determine that weight loss following LAGB was greater than with nonsurgical therapy.

- Direct data on improvement in weight-related comorbidities was lacking. The limited evidence was not sufficient to conclude that the amount of weight loss was large enough that improvements in weight-related comorbidities could be assumed.
- There was very little data on quality of life in this population of patients.
- The frequency and impact of long-term complications following LAGB was uncertain, thus it was not possible to determine whether the benefit of LAGB outweighed the risk for this population. TEC concluded that while the short-term safety of LAGB was well-established, the long-term adverse effects occur at a higher rate and are less well-defined.

## **RANDOMIZED CONTROLLED TRIALS**

An updated literature search failed to identify any additional randomized controlled trials that compare LAGB with RYGBP.

## **NONRANDOMIZED STUDIES**

A number of non-randomized studies (retrospective comparisons, case series) describe the experiences of patients undergoing LAGB.<sup>[32,51-58]</sup> As noted at the beginning of the evidence section, conclusions cannot be reached as the evidence from these studies is considered unreliable.

## **SECTION SUMMARY**

Although the evidence regarding the laparoscopic adjustable gastric banding (LAGB) compared to standard RYGBP is limited, there appear to be benefits associated with LAGB in terms of the procedure's reversibility and laparoscopic approach. Despite limited evidence, the LAGB has been gaining increased acceptance in clinical practice.

## **LAPAROSCOPIC DUODENAL SWITCH WITH SINGLE ANASTOMOSIS**

Several nonrandomized studies were identified which describe the experiences of patients undergoing laparoscopic duodenal switch with single anastomosis (LSDSA).<sup>[59-63]</sup> As noted at the beginning of the evidence section, conclusions cannot be reached from these studies as the evidence is considered unreliable. Well-designed RCTs which compare LSDSA with RYGBP are needed in order to evaluate the safety and efficacy of this procedure compared to accepted surgical treatments of morbid obesity.

## **MINI-GASTRIC BYPASS**

### **SYSTEMATIC REVIEWS**

In 2014, Georgiadou published a systematic review regarding the safety and efficacy of laparoscopic mini gastric bypass.<sup>[64]</sup> The review included a search of the literature through July 2013, and was conducted according to PRISMA guidelines. Ten articles with a total of 4,899 patients were included for review, of which three were comparative studies (two versus LRYGB and one versus LAGB). Excess weight loss at two years ranged from 64.4% ± 8.8% to 80%. Minor postoperative complication rates ranged from 3.6%-7.5%, and major early postoperative complication rates ranged from 0-7%. Authors noted a major concern for postoperative esophagitis and gastritis caused by bile reflux, and the risk for gastric cancer. Overall, the study was limited by the limitations of the included studies (e.g., short term follow-up and noncomparative design).

## RANDOMIZED CONTROLLED TRIALS

One small RCT compared the safety and effectiveness of laparoscopic RYGBP and mini-gastric bypass (MGBP).<sup>[65]</sup> The study found a comparable rate of late complications (>30 days post-op), weight loss, and comorbidity resolution. MGBP was associated with fewer early complications (<30 days post-op). However, the following design flaws undermine reliability of the study findings:

- The small study population (n=80) limits the ability to rule out the role of chance as an explanation of findings.
- Short-term follow-up (2 years) limits comparisons regarding the longer-term complications rates and the effectiveness of the two procedures in controlling weight loss and comorbidities

## NONRANDOMIZED STUDIES

In 2017, Plamper reported a comparison of mini gastric bypass and sleeve gastrectomy in super-obese patients (i.e., BMI > 50 kg/m<sup>2</sup>) at a single institution.<sup>[66]</sup> At one-year follow-up, 90.8% (99 of 109) and 78.7% (74 of 94) of the MGB and SG patients were available for follow-up, respectively. Reasons for loss of follow-up were not discussed. One patient in the SG group died within 30 days of the operation due to multi-organ failure after staple line leakage. Percent excess weight loss was statistically significantly greater in the MGB group at 12 months. The authors cited limitations of their review to include the retrospective design, and short-term results.

Several other nonrandomized studies (retrospective comparisons, case series), describe experiences of patients undergoing MGBP.<sup>[67-71]</sup> As noted at the beginning of the evidence section, conclusions cannot be reached as this evidence is considered unreliable.

## SECTION SUMMARY

Data regarding the mini-gastric bypass (MGBP) is limited to a small RCT, prohibiting conclusions regarding the efficacy of this procedure compared to RYGBP.

## VERTICAL BANDED GASTROPLASTY (VBG)

VBG has largely been abandoned in the United States due to insufficient weight loss and high reoperation rates (approximately 30%).<sup>[10,72]</sup>

## HIATAL HERNIA REPAIR

Numerous studies<sup>[73-76]</sup> were identified which evaluated outcomes of hiatal hernia repair performed in conjunction with other bariatric surgical procedures; however, no studies or clinical practice guidelines were identified which evaluated the efficacy of hiatal hernia repair and an independent treatment of obesity.

## TWO-STAGE BARIATRIC SURGERY PROCEDURES

Bariatric surgeries that are performed in two stages have been proposed as a treatment option, particularly for patients with “super-obesity” defined as a BMI greater than 50. The rationale for a two-stage procedure is that the risk of an extensive surgery is prohibitive in patients with extreme levels of obesity. Therefore, an initial procedure with low risk, usually a

sleeve gastrectomy, is performed first. After a period of time in which the patient loses some weight, thus lowering the surgical risk, a second procedure that is more extensive, such as a biliopancreatic diversion (BD), is performed.

## **RANDOMIZED CONTROLLED TRIALS**

Coffin (2017) published results on the use of intragastric balloon (IGB) prior to a laparoscopic gastric bypass in patients with super-obesity.<sup>[45]</sup> Patients with BMI greater than 45 kg/m<sup>2</sup> were randomized to an IGB (n=55) or standard medical care (n=60) during the 6 months prior to a planned laparoscopic gastric bypass procedure. Five patients had the IGB removed earlier than 6 months due to complications (n=3) or patient request (n=2). Patients receiving IGBs during the first 6 months of the study experienced significantly more BMI reduction (2.8 kg/m<sup>2</sup>; range 1.7-6.2 kg/m<sup>2</sup>) than patients receiving standard care (0.4 kg/m<sup>2</sup>; range 0.3-2.2 kg/m<sup>2</sup>). Weight loss during months 6 through 12, after the laparoscopic gastric bypass procedure, was greater in the patients who received standard of care before the procedure. Duration of hospitalization after laparoscopic gastric bypass and quality of life did not differ between groups.

## **NONRANDOMIZED STUDIES**

Case series on two-stage procedures for patients undergoing sleeve gastrectomy (SG) as the initial procedure generally did not report on the second-stage operation, and in those that did, only a minority of patients undergoing the first stage actually proceeded to the second-stage surgery. For example, Cottam<sup>[77]</sup> reported on 126 patients with a mean BMI of 65 who underwent laparoscopic SG as the first portion of a planned two-stage procedure. A total of 36 patients (29%) proceeded to the second-stage procedure, which was laparoscopic gastric bypass. In a similar study, Alexandrou<sup>[78]</sup> reported on 41 patients who underwent SG as the first stage of a planned 2-stage procedure. After 1-year follow-up, 12 patients (29%) achieved a BMI less than 35 and were not eligible for the second-stage procedure. Of the remaining 28 patients, 10 (24% of total) underwent the second-stage procedure. The remaining 18 patients (44% of total) were eligible for, but had not undergone, the second-stage procedure at the last follow-up.

Patients who undergo two-stage procedures are at risk for complications from both procedures. Silecchia<sup>[79]</sup> described the complication rates in 87 patients undergoing a stage I SG followed by a BPD in 27 patients. For the first stage of the operation, 16.5% of patients had complications of bleeding, fistula, pulmonary embolism, acute renal failure, and abdominal abscess. For the 27 patients who underwent the second-stage BPD, major complications occurred in 29.6% including bleeding, duodenoileal stenosis, and rhabdomyolysis.

## **SECTION SUMMARY**

The current evidence does not indicate that a two-stage bariatric surgery procedure improves outcomes for patients with extreme levels of obesity. There is no evidence to suggest that weight loss is improved or that complications are reduced by this approach. A majority of patients who received SG as the initial procedure lost sufficient weight during the first year such that a second procedure was no longer indicated. In addition, patients undergoing a two-stage procedure are at risk for complications from both procedures; therefore, it is possible that overall complications are increased by this approach.

## **ENDOSCOPIC (ENDOLUMINAL) BARIATRIC PROCEDURES**

## SYSTEMATIC REVIEWS

Several systematic reviews of RCTs evaluating intragastric balloon (IGB) devices for the treatment of obesity have been published; none was limited to FDA-approved devices.<sup>[80-82]</sup>

The systematic review by Tate (2017) focused on recent RCTs, published between 2006 and 2016.<sup>[83]</sup> Additional inclusion criteria were: sham, lifestyle modification, or pharmacologic agent as a comparator; at least 1 outcome of body weight change; and study duration of 3 or more months. Eight RCTs were included in the review, with four contributing to the meta-analysis. The meta-analysis included 777 patients and showed a significant improvement in percent TBWL with IGB compared with control (5.5%; 95% CI, 4.3% to 6.8%). However, there was significant heterogeneity among the trials ( $I^2=62\%$ ), so interpretation of results is limited. The percent TBWL with IGB is lower than expected with RYGB (reported 27%) or with the most efficacious pharmacologic agent (reported 9%).

Saber (2017) identified 20 RCTs reporting weight loss outcomes after IGB implantation or a non-IGB control intervention.<sup>[82]</sup> IGB was compared with sham in 15 trials, behavioral modification in 4 trials, and pharmacotherapy in 1 trial. In 17 trials, patients received lifestyle therapy in addition to other interventions. Studies were published between 1987 and 2015 and sample sizes varied from 21 to 326 participants. Outcomes were reported between 3 and 6 months. In a meta-analysis of 7 RCTs reporting BMI loss as an outcome, there was a significantly greater BMI loss in the IGB group than in the control group (mean effect size [ES], 1.59 kg/m<sup>2</sup>; 95% CI, -0.84 to 4.03 kg/m<sup>2</sup>;  $p<0.001$ ). Findings on other outcomes were similar. A meta-analysis of 4 studies reporting percent EWL favored the IGB group (ES=14.25%; 95% CI, 2.09% to 26.4%;  $p=0.02$ ). Also, a meta-analysis of 6 studies reporting absolute weight loss favored the IGB group (ES=4.6 kg; 95% CI, 1.6 to 7.6 kg;  $p=0.003$ ).

Although the review was not limited to FDA-approved devices, older devices were air-filled and newer devices, including the two approved by FDA in 2015, are fluid-filled. Sufficient data were available to conduct a sensitivity analysis of 3-month efficacy data. A meta-analysis of 4 studies did not find a significant difference in weight loss with air-filled IGB devices or a control intervention at 3 months (ES= 0.26; 95% CI, -0.12 to 0.64;  $p=0.19$ ). In contrast, a meta-analysis of 8 studies of fluid-filled devices found significantly better outcomes with the IGB than with control (ES=0.25; 95% CI, 0.05 to 0.45;  $p=0.02$ ).

In 2017, Vargas performed a systematic review of two observational studies with no comparator group combined with results from a multi-center study of 130 consecutive patients.<sup>[84]</sup> Between the three studies, 330 endoscopic transoral outlet reduction (TORe) cases were performed with the Apollo OverStitch system. TORe was performed in patients experiencing weight regain following RYGB. Study quality was evaluated using the Newcastle-Ottawa Quality Assessment Scale for cohort studies; all were rated to be of moderate overall quality. Using a random effects model, the pooled absolute weight loss at 6, 12, and 18–24 months was 9.5 kg (95% CI 7.9–11.1), 8.4 kg (95% CI 6.5–10.3), 8.4 kg (95% CI 5.9–10.9), respectively. Given the fluctuation of absolute weight loss reported between timelines by each of the three studies, longer term follow-up would aid in evaluating the overall efficacy of TORe.

A systematic review of the effect of EndoBarrier® on weight loss and diabetic outcomes was published in 2015.<sup>[85]</sup> There were five small RCTs included with a total of 235 individuals (range, 18-77) and follow-up ranging from 12 to 24 weeks. The comparators were diet and/or other lifestyle modifications, and 2 studies had sham controls. All studies were judged to be at high risk of bias using the Cochrane risk of bias tool. Combined results demonstrated that the

EndoBarrier® group had 12.6% greater EWL (95% CI, 9.0 to 16.2) compared to medical therapy. For diabetic outcomes, there were trends toward greater improvement in the EndoBarrier® group that did not reach statistical significance. The mean difference in HgA1c was -0.8% (95% CI, -1.8 to 0.3) and the relative risk of reducing or discontinuing diabetic medications was 3.28 (95% CI, 0.54 to 10.73).

## **RANDOMIZED CONTROLLED TRIALS**

In June 2016 the AspireAssist (Aspire Bariatrics, King of Prussia, PA) weight loss therapy system was approved by the FDA to assist in weight reduction in adults aged 22 and older with a BMI of 35.0-55.0 kg/m<sup>2</sup> who have failed to achieve and maintain weight loss with non-surgical weight loss therapy. Feasibility data for the AspireAssist was reported by Sullivan and colleagues in 2013.<sup>[86]</sup> Preliminary results from the ongoing PATHWAY Pivotal Trial (sponsored by Aspire Bariatrics) are included in the FDA Summary of Safety and Effectiveness Data, though results have not been published in peer-reviewed literature at this point in time.<sup>[87]</sup>

In 2014, Eid reported results from a single-center RCT of the StomaphX device compared with a sham procedure for revision procedures in patients with prior weight loss after Roux-en-Y gastric bypass at least two years earlier.<sup>[88]</sup> Enrollment was initially planned for 120 patients, but the trial was stopped prematurely after 1-year follow up was completed by 45 patients in the StomaphyX group and 29 patients in the sham control group after preliminary analysis failed to achieve the primary efficacy endpoint in at least 50% of StomaphyX patients. The primary efficacy end point (reduction in pre-Roux-en-Y gastric bypass excess weight by 15% or more, excess BMI loss, and BMI less than 35, at 12 months post-procedure) was achieved by 10/45 (22.2%) of the StomaphyX group and 1/29 (3.4%) of the sham control group (P<0.01). Conclusions regarding the use of the StomaphX device as a primary procedure for the treatment of obesity may not be drawn due to the discontinuation of the trial and the limited use of the device as a revision procedure in patients who had failed a prior bariatric surgery.

In 2014, Koehestanie published results from an RCT of duodenal-jejunal bypass liner (DJBL) treatment in comparison with dietary intervention for obesity and type 2 diabetes mellitus (T2DM).<sup>[89]</sup> A total of 77 patients were included in the trial with 38 patients randomized to 6 months DJBL in combination with dietary intervention and 39 patients were randomized to dietary interventions only. The total study duration for both groups was 12 months, including 6 months of post-DJBL removal follow-up. At 6 months follow-up, prior to DJBL removal, the DJBL group lost a higher percentage of excess weight compared to the dietary only group, 32% (22%-46.7%) vs. 16.4% (4.1%-34.6%) respectively. However, better HbA1c levels improvement was observed in the dietary only group compared to the DJBL at both 6 and 12 month follow-ups. Conclusions are limited in this study as both groups underwent dietary interventions limiting the isolation of the effects of DJBL upon obesity and type 2 diabetes.

In 2013, Sullivan reported results from a small feasibility pilot RCT (n=18) comparing the AspireAssist siphon assembly (Aspire Bariatrics, King of Prussia, PA) combined with lifestyle therapy (AT) versus lifestyle therapy (LT) alone.<sup>[86]</sup> Only fourteen subjects completed the 12-month trial (10 in the AT group and four in the LT group). Although weight loss in the AT group was greater at 52 weeks than the LT group (18.6% ± 2.3% of body weight vs 5.9% ± 5.0%) the study was limited by the very small sample size, and unblinded design. The study was partially funded by the manufacturer. The authors all disclosed having previously performed contracted research for the manufacturer of the device and one author also disclosed having consulted on a pivotal trial for the company.

In 2013, Fuller published a small RCT (n=66) which evaluated intragastric balloons (IGB) compared to behavioral modification as a treatment of obesity.<sup>[90]</sup> Subjects were either randomized to IGB and 12 months behavior modification (BH) and or 12 months BH alone. At six months the IGB treatment group demonstrated superior weight loss compared to the BH group (-14.2 vs. -4.8; P < 0.0001). However, at 12 months the difference in weight loss between groups, although still statistically significant, diminished (-9.2 vs. -5.2; P = 0.007). There were numerous adverse events related to IGB placement which typically resolved in two weeks. Limitations of this study include a relatively small population size and short-term follow-up with which to evaluate the lasting effects of weight reduction with IGB. In addition, RCTs which evaluate IGB to other standard surgical treatments of obesity are needed.

Additional, small RCTs assessing IGB were identified<sup>[91-93]</sup>; however, large, long-term data remain lacking with which to evaluate the safety and sustained benefit of IGB in weight reduction compared to conservative measures and accepted bariatric procedures.

## **NONRANDOMIZED STUDIES**

A small number of non-randomized studies, primarily case series, describe experiences of patients undergoing different endoluminal procedures, such as endoscopic gastroplasty and endoscopically placed sleeves, gastric balloons or tissue anchors.<sup>[84,94-111]</sup> As noted at the beginning of the evidence section, conclusions cannot be reached as this evidence is considered unreliable.

## **LAPAROSCOPIC GASTRIC PPLICATION**

Similar to the data for endoscopic bariatric procedures, the data for laparoscopic gastric plication (also known as laparoscopic gastric imbrication) is limited to case series and case reports and few, small RCT's.

## **RANDOMIZED CONTROLLED TRIALS**

Sullivan (2017) published results from the ESSENTIAL trial, a randomized sham-controlled trial evaluating the efficacy and safety of endoscopic gastric plication.<sup>[112]</sup> Patients (N=332) were randomized 2:1 to the active or sham procedure. All patients were provided low-intensity lifestyle therapy. The primary end point was total body weight loss (TBWL) at 12-month follow-up. The mean difference in TBWL for patients receiving the procedure compared with patients receiving the sham procedure was 3.6% (95% CI, 2.1% to 5.1%). Significant differences between the active and sham groups were also reported in a change in weight from baseline, percent excess weight loss, BMI, and improvement in diabetes. No significant differences were detected in improvements in hyperlipidemia or hypertension between the treatment groups.

Talebpour (2017) randomized patients to laparoscopic gastric plication (n=35) or laparoscopic SG (n=35).<sup>[113]</sup> Patients were followed for 2 years. Both procedures were equally effective based on weight reduction outcomes. Adverse events (eg, nausea, hair loss, vitamin D deficiency, iron deficiency) were similar between groups. One death due to pulmonary thromboembolism occurred in the gastric plication group.

## **NONRANDOMIZED STUDIES**

Additional studies describe patient outcomes after different laparoscopic plication procedures.<sup>[114-118]</sup> As noted at the beginning of the evidence section, conclusions cannot be reached as this evidence is considered unreliable.

## REVISION BARIATRIC SURGICAL PROCEDURES

There are a number of reasons why patients who are treated with accepted forms of bariatric surgery may not lose weight or may regain weight that is initially lost. These reasons include issues of adherence (compliance), as well as technical (structural) issues. A number of studies<sup>[119-121]</sup> have evaluated the efficacy of revision procedures after failed bariatric surgery and reported satisfactory weight loss and resolution of co-morbidities with somewhat higher complication rates than for primary surgery. However, criteria for classifying what constitutes a failed, primary bariatric procedure, has not been clearly established.<sup>[122]</sup>

In 2018, Almalki published a retrospective analysis of patients diagnosed with failed restrictive procedure who underwent revision bariatric surgery.<sup>[36]</sup> One hundred sixteen patients between 2001 and 2015 had revision RY gastric bypass (R-RYGB) or revision single-anastomosis (mini-) gastric bypass (R-RSAGB); the primary indications for revisional procedures were weight regain (50.9%), inadequate weight loss (31%), and intolerance (18.1%). Major complications occurred in 12 patients without significant difference between groups. At one year after revision surgery, the R-SAGB group (76.8% EWL) showed better weight loss than R-RYGB (32.9% EWL). In the 37.1% of patients available for follow-up at five years, R-SAGB had significantly lower hemoglobin levels than R-RYGB ( $8.2 \pm 3.2$  g/dl vs  $12.8 \pm 0.5$  g/dl). The study was limited by its retrospective nature, relatively short follow-up time, and lack of consideration of data related to patient compliance.

In 2016, Dang reported results from a systematic review and meta-analysis comparing revisional single-step versus two-step bariatric surgery from laparoscopic adjustable gastric banding (LAGB) to Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG).<sup>[123]</sup> Single-step procedures involved revisional surgery wherein the LAGB was removed and replaced by RYGB or SG in the same operation; two-step procedures allowed a delay before the second bariatric procedure was performed. Although the authors found comparable rates of complications, morbidity and mortality between the one- and two-step procedures, the study was not designed to evaluate differences in patient outcomes between the second bariatric procedure (i.e., RYGB vs SG).

In 2014, Sudan reported safety and efficacy outcomes for reoperative bariatric surgeries using data from a national registry, the Bariatric Outcomes Longitudinal Database.<sup>[124]</sup> The Bariatric Outcomes Longitudinal Database is a large multi-institutional bariatric surgery-specific database to which data was submitted from June 2007 through March 2012 by 1,029 surgeons and 709 hospitals participating in the Bariatric Surgery Centers of Excellence (BSCOE) program. Surgeries were classified as primary or reoperative bariatric surgery. Reoperations were further divided into corrective operations (when complications or incomplete treatment effect of a previous bariatric operation was addressed but the initial operation was not changed) or conversions (when an index bariatric operation was changed to a different type of bariatric operation or a reversal restored original anatomy.) There were a total of 449,473 bariatric operations in the database of which 420,753 (93.6%) operations had no further reoperations (primary operations) while 28,270 (6.3 %) underwent reoperations. Of the reoperations, 19,970 (69.5%) were corrective operations and 8,750 (30.5%) were conversions. The primary bariatric operations were Roux-en-Y gastric bypass (N=204,705, 49.1 %), adjustable gastric banding (N=153,142, 36.5 %), sleeve gastrectomy (N=42,178, 10 %), and BPD±DS (N=4,260, 1 %), with the rest classified as miscellaneous. Adjustable gastric banding was the most common primary surgery among conversions (57.5% of conversions; most often [63.5%] to Roux-en-Y gastric bypass). Compared with primary operations, mean length of stay

was longer for corrections (2.04±6.44 vs 1.8±4.9, P<0.001) and for conversions (2.86±4.58 vs 1.8±4.9, P<0.001). The mean % excess weight loss at one year was 43.5 % after primary operation, 39.3 % after conversions, and 35.9 % after corrective operations (statistical comparison not reported). One-year mortality was higher for conversions compared with primary operations (0.31% vs 0.17%, P<0.001), but not for corrections compared with primary operations (0.24% vs 0.17%, P=NS). One-year serious adverse event rates were higher for conversions compared with primary operations (3.61% vs 1.87%, P<0.001), but not for corrections compared with primary operations (1.9% vs 1.87%, P=NS). The authors conclude that reoperation after primary bariatric surgery is relatively uncommon, but generally safe and efficacious when it occurs.

As part of the American Society for Metabolic and Bariatric Surgery Revision Task Force, Brethauer conducted a systematic review of reoperations after primary bariatric surgery that included 175 studies, most of which were single-center retrospective reviews.<sup>[125]</sup> The review was primarily descriptive, but the authors made the following conclusions:

“The current evidence regarding reoperative bariatric surgery includes a diverse group of patient populations and procedures. The majority of the studies are single institution case series reporting short- and medium-term outcomes after reoperative procedures. The reported outcomes after reoperative bariatric surgery are generally favorable and demonstrate that additional weight loss and co-morbidity reduction is achieved with additional therapy. The risks of reoperative bariatric surgery are higher than with primary bariatric surgery and the evidence highlights the need for careful patient selection and surgeon expertise.”

## REVISION OR REMOVAL OF ADJUSTABLE GASTRIC BAND

Evidence regarding the indications for band removal or revision procedure is primarily limited to small cohort<sup>[126]</sup> and case series studies; however, reoperation or removal rates are estimated to range from 4.1%- 53%, depending on the time of reported follow-up.<sup>[127-130]</sup> Several of the largest cohort studies have reported the following complications which resulted in reoperation or band removal:

Arapis reported the following complications in 87 patients who underwent reoperation:<sup>[131]</sup> chronic dilatation of the proximal gastric pouch (27 patients - 14.5%), acute dilatation (21 patients - 11.3%), intragastric migration of the prosthesis (6 patients - 3.2%), reflux esophagitis (6 patients - 3.2%), infection of the gastric band (1 patient - 0.5%), and Barrett's esophagus (1 patient - 0.5%).

Perathoner reported on 108 patients who underwent laparoscopic conversion of gastric banding to gastric bypass due to the following complications: band migration, inadequate weight loss, pouch dilation, band leakage, band intolerance, band infection and esophageal dilation.<sup>[132]</sup>

Other reported complications included: band erosion,<sup>[129,133,134]</sup> gastric obstruction,<sup>[11]</sup> and gastric slippage.<sup>[129,134]</sup>

Avriel reported major respiratory complications and chronic disease development in 30 patients who underwent LAGB.<sup>[135]</sup> Reported complications included aspiration pneumonia (19 patients) including pulmonary abscess (4 patients) and empyema (2 patients), exacerbation of asthma (3 patients), hemoptysis (1 patient), interstitial lung disease (5

patients) and bronchiectasis (3 patients). However, the impact of LAGB upon the development of these conditions is unclear given that 83% of the patients smoked or had a smoking history (mean pack years 34).

Studies which evaluated band conversion to a second bariatric surgery primarily indicated that bypass was the preferred revision surgery due to better long-term outcomes compared to sleeve gastrectomy.<sup>[136-139]</sup> In one large retrospective study published in 2014, bypass was compared to sleeve gastrectomy after band removal and conversion.<sup>[140]</sup> National Surgical Quality Improvement Project data from 2005-2011 were analyzed and included 495 patients who converted from LAGB to bypass and 130 patients who converted to sleeve gastrectomy. Conversion to bypass was not associated with higher morbidity or mortality compared to primary RYGB; however, conversion to sleeve gastrectomy was independently associated with a higher rate of major complications and mortality compared to primary sleeve gastrectomy (OR 8.02, 95 % CI 1.08-59.34, p = 0.04).

## SECTION SUMMARY

For surgical revision of bariatric surgery after failed treatment, evidence from nonrandomized studies suggests that revisions are associated with improvements in weight similar to those seen in primary surgery. However, evidence from large long-term studies is required to determine the appropriate clinical indications for band removal or reoperation.

## BARIATRIC SURGERY IN PATIENTS WITH DIABETES WITH BMI < 35KG/M<sup>2</sup>

### SYSTEMATIC REVIEWS

In 2015 Muller-Stich published a systematic review comparing surgical versus medical treatment of type II diabetes in patients with a BMI less than 35 kg/m<sup>2</sup>.<sup>[141]</sup> The analysis included data from five RCTs and six observational studies for a total of 702 patients. The follow-up of included studies ranged from 12-36 months. Authors concluded that surgery was associated with higher diabetes remission rate (OR: 14.1, 95% CI: 6.7–29.9, P < 0.001), higher rate of glycemic control (OR: 8.0, 95% CI: 4.2–15.2, P < 0.001) and lower HbA1c level (MD: -1.4%, 95% CI -1.9% to -0.9%, P < 0.001) compared to medical treatment. However, results are limited by inclusion of studies in which the BMI of some patients was greater than 35 kg/m<sup>2</sup> and short-term follow-up, limiting conclusion regarding the long-term benefits of bariatric surgery upon glycemic control.

In 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of bariatric surgery and nonsurgical therapy in adults with metabolic conditions, including diabetes, and a BMI of 30.0-34.9 kg/m<sup>2</sup>.<sup>[142]</sup> The report evaluated key issues which included the effectiveness of bariatric surgery compared to nonsurgical therapies, short and long-term effects in symptom control and racial and demographic disparities regarding benefits and harms of surgery in patients with metabolic conditions and a BMI of 30.0-34.9 kg/m<sup>2</sup>. Evidence was gathered from global literature searches, reference mining and titles identified from external sources. A total of 24 studies reported bariatric surgery results, with a majority of studies evaluating RYGBP or LAGB procedures in diabetic patients with a BMI of 30-35 kg/m<sup>2</sup>. The AHRQ report concluded that there was moderate strength evidence of efficacy for certain bariatric procedures as a treatment for diabetes in the short term. However, the report noted that the evidence contained many limitations, “(m)ost importantly, very few studies of this target population have long-term follow-up. Only two studies followed patients for more than 2 years; one has a followup rate of only 13.8 percent and the other

includes only seven patients. Thus, we have almost no data on long-term efficacy and safety.” In addition, the AHRQ report noted the lack of evidence on major clinical outcomes such as all-cause mortality, cardiovascular risks, or peripheral arterial disease. Although short-term studies suggest an improvement in glucose control, the AHRQ report pointed out that, “...the available evidence from the diabetes literature indicates it may be premature to assume that controlling glucose to normal or near normal levels completely mitigates the risk of microvascular and macrovascular events. Thus, claims of a “cure” for diabetes based on glucose control within 1 or 2 years require longer term data before they can be substantiated.”

## **RANDOMIZED CONTROLLED TRIALS**

Since the publication of the AHRQ report, two RCTs have been reported on bariatric surgery compared to medical therapy in diabetic patients with a BMI between 30-40 kg/m<sup>2</sup>.

Ikramuddin performed an unblinded RCT of gastric bypass versus intensive medical therapy on 120 patients with type II diabetes for at least 6 months and an HgbA1C of at least 8.0%.<sup>[143]</sup> Patients were followed for 12 months with the primary endpoint being a composite of HgA1C less than 7.0%, low-density lipoprotein (LDL) cholesterol less than 100 mg/dl and systolic blood pressure less than 130 mm Hg. A total of 28 patients in the surgery group achieved the primary outcome compared to 11 patients in the medical therapy group (odds ratio [OR]: 4.8, 95% CI: 1.9-11.7). The percent of patients achieving HgbA1C of less than 7.0% was 75% in the surgery group compared to 32% of patients in the medical therapy group (OR: 6.0, 95% CI: 2.6-13.9). There were 22 serious complications in the surgery group, including 4 perioperative complications, compared to 15 serious complications in the medical group. A limitation of this study was that results were not provided separately for patients who were above and below a BMI of 35 kg/m<sup>2</sup>, thus restricting conclusions regarding the benefits of bariatric surgery compared to medical management in diabetic patients with a BMI < 35 kg/m<sup>2</sup>.

In 2014, Prikh published a small (n=57), short-term (6-month follow-up) RCT which compared intensive medical weight management to bariatric surgery in patients with a BMI of 30-35 kg/m<sup>2</sup> and type 2 diabetes.<sup>[144]</sup> Significant improvements in primary outcome measures of homeostatic model of insulin resistance and higher diabetes remission rates were observed in the surgical group compared to the MWM group. Additional small RCTs have been identified;<sup>[145]</sup> however, larger, long-term RCTs are needed to confirm these findings.

In 2015, Mingrone published results of a small (n=60) RCT comparing long-term outcomes of either medical treatment or surgery by Roux-en-Y gastric bypass or biliopancreatic diversion in patients with type II diabetes.<sup>[146]</sup> A total of 53 patients were included in the 5-year follow-up assessment. Primary outcome measures included the rate of diabetes remission at 2 years which was defined as glycated HbA1c concentration of 6.5% or less ( $\leq 47.5$  mmol/mol) and a fasting glucose concentration of 5.6 mmol/L or less without active pharmacological treatment for 1 year. At 5-year follow-up 19 (50%) of the 38 surgical patients (7 of 19 [37%] in the gastric bypass group and 12 of 19 in the [63%] biliopancreatic diversion group) maintained diabetes remission at 5 years, compared with none of the 15 medically treated patients (p=0.0007). Fifteen incidents of hyperglycemic relapse occurred in 34 surgical of the patients who achieved 2-year remission, suggesting continued monitoring of glycemic control may be necessary. Authors also reported that both surgical procedures were associated with significantly lower plasma lipids, cardiovascular risk, and medication use and no late complications or deaths.

## **CLINICAL PRACTICE GUIDELINES**

## **American College of Cardiology, American Heart Association, and the Obesity Society**

In 2013, the American College of Cardiology (ACC), American Heart Association (AHA), and the Obesity Society published guidelines on the management of obesity and overweight in adults.<sup>[147]</sup> The guidelines were based upon a high-quality systematic review of the evidence which included transparent methods for grading the strength of the evidence and subsequent recommendations. The guidelines make the following recommendations related to bariatric surgery:

“For adults with a BMI >40kg/m<sup>2</sup> or BMI >35 kg/m<sup>2</sup> with obesity-related comorbid conditions who are motivated to lose weight and who have not responded to behavioral treatment (with or without pharmacotherapy) with sufficient weight loss to achieve targeted health outcome goals, advise that bariatric surgery may be an appropriate option to improve health and offer referral to an experienced bariatric surgeon for consultation and evaluation.” (Grade A: Indicating a strong recommendation, indicating there is a high certainty based on the evidence that the net benefit is substantial).

“For individuals with a BMI <35 kg/m<sup>2</sup>, there is insufficient evidence to recommend for or against undergoing bariatric surgical procedures.” (No recommendation given, indicating there is insufficient evidence or evidence is unclear or conflicting)

## **American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery**

In 2013, joint guidelines were published by the American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery (AAACE/ASM/Obesity Society) regarding the perioperative nutritional, metabolic and nonsurgical support of the bariatric surgery patient.<sup>[148]</sup> Recommendations regarding which patients should be offered bariatric surgery indicated the following:

“Patients with BMI of 30–34.9kg/m<sup>2</sup> with diabetes or metabolic syndrome may also be offered a bariatric procedure although current evidence is limited by the number of subjects studied and lack of long-term data demonstrating net benefit.

There is insufficient evidence for recommending a bariatric surgical procedure specifically for glycemic control alone, lipid lowering alone, or cardiovascular disease risk reduction alone, independent of BMI criteria.”

## **Institute for Clinical Systems Improvement**

In 2014, the Institute for Clinical Systems Improvement (ICSI) published revised guidelines regarding the diagnosis and management of type 2 diabetes mellitus in adults and indicated:<sup>[149]</sup>

A clinician may recommend a patient diagnosed with T2DM and a BMI >35 kg/m<sup>2</sup> consider bariatric surgery if diabetes or comorbidities are difficult to control with lifestyle and pharmacologic therapy. [Quality of Evidence: Moderate, Strength of Recommendation: Weak]

## **SECTION SUMMARY**

Evidence regarding the efficacy of bariatric surgery as a treatment for diabetes in patients with a BMI < 35 kg/m<sup>2</sup> primarily consists of small cases series with short-term follow-up as noted in

the AHRQ report. Since the publication of these reports a single RCT was identified which was limited by the inclusion of obese (BMI 35-40 kg/m<sup>2</sup>) and non-obese (BMI 30-34.9 kg/m<sup>2</sup>) patients, precluding conclusions regarding the clinically non-obese population. Only one clinical practice guideline was identified which recommended bariatric surgery in diabetic patients who do not meet the clinical definition of obesity; however, a lack of long-term data was noted. Overall, the current evidence does not demonstrate the safety and efficacy of bariatric surgery as a treatment for diabetes in patients with a BMI < 35 kg/m<sup>2</sup>.

## ADOLESCENT AND PEDIATRIC BARIATRIC SURGERY

### SYSTEMATIC REVIEWS

Qi (2017) published a systematic review and meta-analysis on the use of bariatric surgery for the treatment of adolescents with obesity. 49 studies were identified for inclusion and study quality was assessed using the Newcastle-Ottawa Scale. Age of patients ranged from 14 to 20 years. BMI ranged from 34 to 63 kg/m<sup>2</sup>. Overall results showed significant improvements in BMI as well as glycemic and lipid control with various bariatric surgery techniques. RYGB showed the largest improvements compared with other procedures, with LAGB and sleeve gastrectomy also showing improvements in this population.

The 2007 Washington State Health Technology Assessment evaluated the published, peer reviewed scientific literature describing bariatric surgery in the pediatric population.<sup>[150]</sup> Data from 17 studies that enrolled a total of 553 pediatric patients were included. Only one study was clearly prospective. Eight studies reported outcomes after LAGB, six after RYGBP, two after VBG, and one after banded bypass. The report concluded that:

- The evidence that LAGB for morbidly obese pediatric patients leads to sustained and clinically significant weight loss compared to non-operative approaches was weak at the longest follow-up after surgery (1.7 to 3.3 years).
- The evidence that RYGBP for morbidly obese pediatric patients leads to sustained and clinically significant weight loss compared to non-operative approaches was weak at the longest follow-up after surgery (1 to 6.3 years).
- The evidence was insufficient to permit quantitative estimates of the precise amount of weight loss after any bariatric surgical procedure for pediatric patients.
- The evidence was insufficient to permit any conclusions about weight loss after other bariatric surgical procedures for pediatric patients.
- The evidence was insufficient to permit any conclusions about weight loss in specific age subgroups (18-21, 13-17, 12 or less) within the pediatric population.
- The evidence that LAGB for morbidly obese pediatric patients does resolve comorbid conditions linked to obesity (diabetes, hypertension) compared to non-operative approaches was weak.
- The evidence that RYGBP for morbidly obese pediatric patients does resolve comorbid conditions linked to obesity (diabetes, hypertension) compared to non-operative approaches was weak.
- The evidence was insufficient to permit quantitative estimates of the likelihood of comorbidity resolution, quality of life improvement, or survival after any bariatric surgical procedure for pediatric patients.
- The evidence was insufficient to permit any conclusions about comorbidity resolution in specific age subgroups (18-21, 13-17, 12 or less) within the pediatric population.

- The LAGB studies reported no in-hospital or postoperative death. However, the most commonly reported complication was band slippage. Reoperations were performed on 7.9% of the LAGB patients to correct various complications (band slippage, intragastric migration, port/tubing problems).
- The RYGBP studies reported one postoperative death. The most frequently reported complication was related to malnutrition and micronutrient deficiency. In addition, potentially life-threatening complications (shock, pulmonary embolism, severe malnutrition, bleeding, gastrointestinal obstructions) were reported.
- The evidence was insufficient to permit any conclusions on potential impacts of bariatric surgery on growth and development of pediatric patients.
- The evidence was insufficient to permit any conclusions on potential harms in specific age groups (18-21, 13-17, 12 or less).

In summary, the assessment found that longer term, prospective collection of data on physical growth, quality of life, weight loss, persistence or resolution of comorbid conditions, and long-term survival are needed in order to fully understand the role of bariatric surgical procedures in treating morbidly obese pediatric patients.

In 2013, Black published a systematic review and meta-analysis of 23 studies (22 nonrandomized) that included 637 young patients (age 6-18 years) who underwent bariatric surgery.<sup>[151]</sup> Although significant weight loss was reported at the 1-year follow-up, limitations of the evidence were similar to those reported in the Washington State Health Technology Assessment. Included studies were limited by small sample size with a median number of 24 patients per study (range: 10-108) and short term follow-up (range: 6-12 months). Authors reported that complications were inconsistently reported and indicated that, “long-term, prospectively designed studies, with clear reporting of complications and comorbidity resolution, alongside measures of [health-related quality of life], are needed to firmly establish the harms and benefits of bariatric surgery in children and adolescents.”

In 2015, the Washington State Health Technology Assessment compared various bariatric procedures and also re-examined the role of bariatric surgery in children and adolescents upon obesity related comorbidities.<sup>[152]</sup> The group concluded that there was, “a lack of both short- and long-term data demonstrating effectiveness for any bariatric surgery procedure in both children and adolescents.” Only two studies were identified which were deemed to be of sufficient quality and only one of those was a RCT. In addition, no comparative studies were identified which evaluated any bariatric procedure exclusively in children (under 13 years).

Additional reviews were identified; however, conclusions were limited due to a lack of long-term follow-up.<sup>[153-157]</sup>

## **RANDOMIZED CONTROLLED TRIALS**

One small randomized trial compared the outcomes of gastric banding with an optimal lifestyle program in adolescents 14-18 years of age with a BMI >35.<sup>[158]</sup> Although the study reports that gastric banding resulted in greater percentage achieving a loss of 50% of excess weight, several flaws undermine the reliability of the study findings:

- The small study population (n=50) limits the ability to rule out the role of chance as an explanation of findings.
- The study had significant loss to follow-up suggesting a difference that may affect the outcome.

- Short-term follow-up (2 years) limits comparisons regarding the longer-term complications rates and the effectiveness of the procedure in controlling weight loss and comorbidities.

## NONRANDOMIZED STUDIES

### Studies with short follow-up time

A small number of nonrandomized comparative studies reported significant weight loss and resolution of some of the comorbidities in pediatric patients undergoing bariatric surgery.<sup>[159-161]</sup> However, the studies were small and had a very short follow up time. In 2014, Inge reported results from Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study, a prospective, multicenter observational study of bariatric surgery in patients aged 19 or under.<sup>[162]</sup> The study enrolled 242 participants, with mean age 17.1 and median BMI 50.5 (IQR 45.2-58.2) at the time of operation. All patients had at least 1 obesity-related comorbidity, most commonly dyslipidemia (74%), followed by sleep apnea (57%), back and joint pain (46%), hypertension (45%), and fatty liver disease (37%). Roux-en-Y gastric bypass, adjustable gastric banding, and vertical sleeve gastrectomy were performed in 66.5%, 5.8%, and 27.7%, respectively. Within 30 days of surgery, 20 major complications occurred in 19 patients (7.9%), most of which were perioperative complications. The cohort will be followed to assess longer-term outcomes.

### Studies with mid-term follow-up time

Dumont (2018) published a retrospective study of obese adolescents who underwent LAGB. Between 2006 and 2015, 97 consecutive teenagers (average age at surgery 17.2 ± 0.7 years; mean BMI of 44.9 ± 6.1 kg/m<sup>2</sup>) who had achieved full growth and sexual maturity and had previously failed a medical nutritional and dietary management program for at least 1 year were enrolled in the study. After a mean follow-up time of 56.0 ± 22.0 months, mean total weight loss was 20.0 ± 16.6% and mean excess weight loss was 46.6 ± 39.5%. Nineteen patients underwent band removal (mean 43.0 ± 28.0 months). No limitations to the study were reported.

Two observational studies with mid-term follow-up times (≤10 and ≤8 years) reported experiences of pediatric patients undergoing LAGB (sample size 41 and 107 respectively).<sup>[163,164]</sup> The first study found that weight loss was initially successful and resulted in resolution of some comorbidities, but it slowly increased over the time and ultimately was unsatisfactory in many patients. The second study reported 65.5% excess weight loss at eight years. Both studies reported high complication and reoperation rates (Lanthaler: 46% patients had complications that required reoperation; Mittermaier: 46% patients had complications and 29% required reoperation).

## CLINICAL PRACTICE GUIDELINES FOR PEDIATRIC BARIATRIC SURGERY

### American College of Physicians

The 2005 American College of Physicians (ACP) evidence-based guideline on use of bariatric surgery in adolescents and children states that the current evidence on surgical treatment of pediatric populations is limited to a few case series which do not permit quantitative analysis.<sup>[165]</sup> Further, the guideline states that it is unclear whether extrapolation of adult data for bariatric surgery to the pediatric population is appropriate and that RCTs are needed (and feasible) to establish the role of bariatric surgery in this population.

## American Academy of Pediatrics

In 2007, the American Academy of Pediatrics (AAP) published, “Recommendations for Treatment of Child and Adolescent Overweight and Obesity,” which stated that although there is increased use of bariatric surgery in adults:<sup>[166]</sup>

“There is limited research on the safety, efficacy, and long-term outcomes of bariatric surgery for adolescents; therefore, data from adult studies must be considered as surrogate evidence.”

Ultimately, the AAP noted that additional trials are needed to determine whether bariatric surgery is acceptable in adolescents.

## American Heart Association

In 2013, the American Heart Association (AHA) published a statement regarding severe obesity in children and adolescents which concluded:<sup>[167]</sup>

“Current treatment approaches using lifestyle modification and medications to reduce BMI and improve chronic disease risk factors are insufficient for most patients and significant residual risk (unacceptably high BMI and risk factor levels) remains. Although experts recommend stepped intensification of interventions, the “step” after behavior-based and pharmaceutical interventions to the next established alternative, bariatric surgery, is unacceptably large because of its limited applicability and availability.”

The AHA indicated that the following evidence was needed before bariatric surgery could be widely recommended in children and adolescents:

“Generation of additional safety and efficacy data (especially long-term) on bariatric surgery, including studies describing improvements in vascular structure and function, insulin resistance, and  $\beta$ -cell function.”

## Society of American Gastrointestinal and Endoscopic Surgeons

The 2008 the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) evidence-based guidelines state:<sup>[168]</sup>

“RGB is well tolerated and produces excellent weight loss in patients younger than 18 years with 10-year follow-up... Well-designed prospective studies are just emerging to better define the place for adolescent bariatric surgery.”

This statement is based on eight publications of which six are retrospective studies, each with less than 35 participants and most with limited follow-up. Two of the supporting articles are opinion papers.

## Endocrine Society

In 2017, the Endocrine Society published an updated clinical practice regarding the assessment, treatment, and prevention of pediatric obesity.<sup>[169]</sup> The guideline was developed according to the GRADE system. The following statements were given a rating of “we suggest”, i.e., weak recommendations, and were based on “very low quality” to “low quality” evidence. Given the evidence quality, and the suggestion as opposed to a *recommendation*, the following statements are ultimately, expert opinion.

For pre-adolescent children, pregnant or breast-feeding adolescents (and those planning on becoming pregnant within two years of surgery), and in any patient who has not mastered the principles of healthy dietary and activity habits and/or has unresolved substance abuse, eating disorder or untreated psychiatric disorder, the Society suggests against bariatric surgery.

The Endocrine Society suggests that bariatric surgery be considered for adolescents only under the following conditions:

- The patient has attained Tanner 4 or 5 pubertal development and final or near-final adult height, the patient has a BMI of  $>40$  kg/m<sup>2</sup> or has a BMI of  $>35$  kg/m<sup>2</sup> and significant, extreme comorbidities
- extreme obesity and comorbidities persist despite compliance with a formal program of lifestyle modification, with or without pharmacotherapy
- psychological evaluation confirms the stability and competence of the family unit [psychological distress due to impaired quality of live (QOL) from obesity may be present, but the patient does not have an underlying untreated psychiatric illness]
- the patient demonstrates the ability to adhere to the principles of healthy dietary and activity habits
- there is access to an experienced surgeon in a pediatric bariatric surgery center of excellence that provides the necessary infrastructure for patient care, including a team capable of long-term follow-up of the metabolic and psychosocial needs of the patient and family.

### **Institute for Clinical Systems Improvement**

In 2013, ICSI published updated guidelines regarding the prevention and management of obesity for children and adolescents.<sup>[170]</sup> The group noted that, “there is limited information on the long-term efficacy and safety of bariatric surgery in children and adolescents.” However, ICSI concluded that bariatric surgery may be considered at centers of excellence when specific criteria were met and should not be considered in preadolescent children.

### **National Heart, Lung and Blood Institute**

In 2011, National Heart, Lung and Blood Institute (NHLBI) published guidelines regarding cardiovascular health and risk reduction in overweight and obese children and adolescents which indicated bariatric surgery may be considered:<sup>[171]</sup>

“For adolescents with BMI far above 35 kg/m<sup>2</sup> and associated comorbidities, bariatric surgery on a research protocol, in conjunction with a comprehensive lifestyle weight loss program, improved weight loss, BMI, and other outcomes—such as IR, glucose tolerance, and cardiovascular (CV) measures—in a small case series.”

This guideline is based on a Grade D recommendation which is defined as, “Expert opinion, case reports, or reasoning from first principles (bench research or animal studies).”

### **SECTION SUMMARY**

There is evidence to suggest bariatric surgery may provide the benefits of weight reduction and improved comorbidities compared to non-surgical treatments in the obese children and adolescents.

## **GASTROESOPHAGEAL REFLUX DISEASE**

This section focuses on evidence related to gastroesophageal reflux disease (GERD) as it relates to bariatric procedures as a treatment for obesity. See Cross References section, above, for policies focused on treatment of GERD.

## SYSTEMATIC REVIEWS

In 2016, Osland compared the efficacy of Roux-En-Y gastric bypass versus vertical sleeve gastrectomy in randomized controlled trials.<sup>[35]</sup> Six RCTs performed between 2005 and 2015 were included (N = 695; 347 for SG and 348 for RYGB). The authors summarized recent publications, citing worsened GERD symptoms following sleeve gastrectomy in patients with preoperative symptoms, and new symptoms in 9% of patients with no previous symptoms. Preexisting GERD in those who undergo sleeve gastrectomy is noted as being the cause of frequent revisional surgeries, and high rates of surgical complications. In addition those with preexisting GERD were found to have failure to achieve weight loss, and failure to resolve weight related comorbidities such as diabetes, obstructive sleep apnea, and hypertension.

In 2016, Oor reported results from a systematic review and meta-analysis of studies reporting prevalence of GERD symptoms, the use of anti-reflux medication, and/or outcome of esophageal function tests before and after laparoscopic sleeve gastrectomy (LSG) in patients with a BMI of more than 35.<sup>[172]</sup> Pooled data from seven studies using validated symptom questionnaires for new-onset of GERD symptoms resulted in a 20% incidence following LSG (follow-up time ranging from one- to 60-months). There was heterogeneity amongst these studies ( $I^2=68%$ ). For difference in prevalence of GERD before and after LSG, the pooled risk difference was found to be 4.3%; with heterogeneity present ( $I^2=89%$ ). Of the 24 studies reviewed, the authors found new-onset GERD symptom incidence to range from zero to 34.9%. The authors therefore concluded that LSG could induce serious GERD symptoms in patients with no preoperative GERD complaints. The heterogeneity found in analyses may be due to a lack of a standardized approach to LSG, as well as the variability in follow-up length. The authors also noted that range in prevalence of GERD symptoms may be in part due to the variability in reported preoperative BMI, as the LSG will be a more technically challenging procedure in those with a BMI of 60 kg/m<sup>2</sup> versus those with a BMI of 40 kg/m<sup>2</sup>.

Li and colleagues (2016) conducted a systematic review and meta-analysis comparing Roux-en-Y gastric bypass (LRYGB) with LSG for treating morbid obesity.<sup>[173]</sup> Randomized controlled trials and nonrandomized studies were included. Amongst five studies that reported GERD resolution post-operation (147 in the LRYGB group and 93 in the LSG group), symptoms resolved significantly more after LRYGB as compared to LSG (OR = 8.99, 95% CI 4.77-16.95). Heterogeneity was not detected between these groups ( $I^2 = 48%$   $P=0.12$ ).

## NONRANDOMIZED STUDIES

Several nonrandomized studies have retrospectively reviewed weight reduction and GERD symptoms following Roux-en-Y gastric bypass surgery for treatment of morbid obesity.<sup>[174-179]</sup> Authors have reported reduction in self-reported GERD symptoms, prescribed medications, and weight loss. As demonstrated in small case series, in combination with takedown of fundoplication, Roux-en-Y gastric bypass for morbid obesity has been effective in weight reduction as well as self-reported GERD symptom improvement.<sup>[177,178]</sup> Evidence regarding high incidence of GERD following laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy makes Roux-en-Y gastric bypass the ideal procedure in the presence of already existing reflux symptoms.<sup>[34,180-184]</sup>

## CLINICAL PRACTICE GUIDELINES

### Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)

The SAGES clinical practice guidelines for the surgical treatment of GERD (2010) state the following:<sup>[185]</sup>

Due to concerns for higher failure rates after fundoplication in the morbidly obese patient (BMI >35 kg/m<sup>2</sup>) and the inability of fundoplication to address the underlying problem (obesity) and its associated comorbidities, gastric bypass should be the procedure of choice when treating GERD in this patient group (Grade B). The benefits in patients with BMI > 30 is less clear and needs further study.

### SECTION SUMMARY

Systematic review of GERD symptoms following laparoscopic sleeve gastrectomy (LSG) as a treatment for morbid obesity is limited by heterogeneity in the technical approach to the procedure, therefore presenting statistical challenges to analyzing pooled results. In comparing LSG with Roux-en-Y gastric bypass (RYGB) directly, GERD symptoms resolve significantly more post-RYGB as compared to LSG. In the presence of GERD, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) clinical practice guidelines state that gastric bypass is the procedure of choice in patients who are morbidly obese. In those who are not morbidly obese, evidence does not indicate that bariatric surgery is an appropriate treatment for GERD, and SAGES states this is an area in need of further study.

## SAFETY OF BARIATRIC SURGERY

### GENERAL SURGICAL RISKS

Bariatric procedures are associated with all the potential risks of any major abdominal surgical procedure including but not limited to:

- Bleeding
- Death
- Infection
- Injury to internal organs or gastrointestinal tract
- Thromboembolic complications

### PROCEDURE-SPECIFIC SURGICAL RISKS

The following table summarizes the most common procedure-specific risks. However, other adverse events are also possible.

<b>RYGBP</b> <sup>[2,186,187]</sup>	<b>LL-RYGBP</b> <sup>[2]</sup>	<b>BPD/BPD-DS</b> <sup>[2,10,186]</sup>	<b>SG</b> <sup>[10,186,188-191]</sup>	<b>LAGB</b> <sup>[52,186]</sup>	<b>MGB</b> <sup>[65]</sup>	<b>Endoluminal Procedures</b>
<ul style="list-style-type: none"> <li>• Cholecystitis</li> <li>• Depression</li> <li>• Dilated stomach pouch</li> <li>• Dumping syndrome<sup>†</sup></li> <li>• Gastritis</li> <li>• Leaks or obstructions at the anastomotic site</li> <li>• Marginal ulcer</li> <li>• Reoperations<sup>†††</sup></li> <li>• Staple line failure</li> <li>• Vitamin/mineral deficiencies (iron, folate, B<sub>12</sub>)</li> <li>• Kidney stones</li> </ul>	<ul style="list-style-type: none"> <li>• All RYGBP risks</li> <li>• Additional unknown risks associated with the greater bypass of the small intestine and consequent increase in malabsorption<sup>††</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Dilated stomach pouch</li> <li>• Gastric obstruction</li> <li>• GERD</li> <li>• Leaks or stenoses at anastomotic sites</li> <li>• Malnutrition and/or vitamin deficiencies</li> <li>• Nausea/vomiting</li> <li>• Wound dehiscence</li> </ul>	<ul style="list-style-type: none"> <li>• Abscesses</li> <li>• Frequent vomiting</li> <li>• Gastric fistulas</li> <li>• GERD</li> <li>• Leaking from the stomach pouch</li> <li>• Reoperations<sup>†</sup> ††</li> </ul>	<ul style="list-style-type: none"> <li>• Band slippage</li> <li>• Dilated stomach pouch</li> <li>• Erosion of the device through gastric wall</li> <li>• GERD</li> <li>• Malnutrition and vitamin deficiencies</li> <li>• Nausea and vomiting</li> </ul>	<ul style="list-style-type: none"> <li>• Bile reflux</li> <li>• Gastrojejunostomy leak</li> <li>• Marginal ulcer</li> <li>• Reoperations<sup>†††</sup></li> <li>• Vitamin/mineral deficiency</li> </ul>	<p>The safety concerns are specific to the endoluminal procedure performed:</p> <p><u>Transoral circular stapler (SurgASSIST®)</u>:<sup>[192]</sup></p> <ul style="list-style-type: none"> <li>• Bowel obstruction</li> <li>• Intra-abdominal adhesions</li> </ul> <p><u>Dduodenal-jejunal bypass sleeve (DJBS)</u>:<sup>[97]</sup></p> <ul style="list-style-type: none"> <li>• Abdominal pain</li> <li>• Implant site inflammation</li> <li>• Nausea and vomiting</li> </ul> <p><u>TOGa system endoscopic stapling</u>:<sup>[98]</sup></p> <ul style="list-style-type: none"> <li>• Nausea</li> <li>• Vomiting</li> <li>• Pain</li> <li>• Transient dysphagia</li> </ul>

<sup>†</sup> Abdominal pain, diarrhea, and/or vomiting shortly after eating due to reduced transit time in the intestine;

<sup>††</sup>The evidence, especially from the studies with long-term follow-up, is limited and not much is known about the long-term complications of LL-RYGBP;

<sup>†††</sup>Due to insufficient weight loss or technical issues;

## SUMMARY

### **ROUX-EN-Y GASTRIC BYPASS, ADJUSTABLE GASTRIC BANDING, AND SLEEVE GASTRECTOMY**

Roux-en-Y gastric bypass is well established in clinical practice, is the most studied bariatric procedure in the published literature, and is used as the gold standard against which other procedures are measured. Adjustable gastric banding is reversible, the least invasive of all bariatric procedures, and has minimal complications. Sleeve gastrectomy as a stand-alone procedure gained acceptance in clinical practice. Sleeve gastrectomy offers an alternative to adjustable gastric banding with potentially greater weight loss and fewer complications. Therefore, Roux-en-Y gastric bypass, adjustable gastric banding, and sleeve gastrectomy may be considered medically necessary in the treatment of morbid obesity when policy criteria are met.

There is not enough research to show that any of the following procedures improves health outcomes. Therefore, Roux-en-Y gastric bypass, adjustable gastric banding, and sleeve gastrectomy are considered investigational for the treatment of any condition other than morbid obesity, including, but not limited to gastroesophageal reflux disease.

There is not enough research to show that any of the following procedures improves health outcomes. Therefore, the use of distal, partial (not including sleeve gastrectomy) or complete gastrectomy with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction, are considered investigational as a treatment of obesity.

### **MINI-GASTRIC BYPASS, DISTAL GASTRIC BYPASS, BILIOPANCREATIC BYPASS, BILIOPANCREATIC BYPASS WITH DUODENAL SWITCH, AND LAPAROSCOPIC DUODENAL SWITCH WITH SINGLE ANASTOMOSIS**

There is not enough research for these procedures on health outcomes. Therefore, mini-gastric bypass, distal gastric bypass, biliopancreatic bypass, biliopancreatic bypass with duodenal switch, and laparoscopic duodenal switch with single anastomosis are considered investigational for the treatment of morbid obesity, gastroesophageal reflux disease or any other condition.

### **HIATAL HERNIA REPAIR**

There is not enough research regarding the use of hiatal hernia repair as an independent treatment of obesity. In addition, no evidence-based clinical practice guidelines were identified which addressed the use of hiatal hernia repair as a treatment of obesity. Therefore, hiatal hernia repair is considered investigational as an independent treatment of obesity.

### **VERTICAL BANDED GASTROPLASTY**

Due to insufficient weight loss and high reoperation rates, vertical banded gastroplasty is no longer considered a standard of care and is therefore considered not medically necessary.

### **ENDOSCOPIC BARIATRIC PROCEDURES**

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There is not enough evidence to establish the safety and efficacy of any endoscopic bariatric procedure. Therefore, endoscopic bariatric procedures are considered investigational for all indications.

### **LAPAROSCOPIC GASTRIC PPLICATION**

There is not enough evidence to establish the safety and efficacy of any laparoscopic gastric plication bariatric procedure. Therefore, laparoscopic gastric plication procedures are considered investigational for all indications.

### **REVISION BARIATRIC SURGICAL PROCEDURES**

Research regarding reoperation of a primary bariatric surgery is limited to noncomparative studies without long-term outcome data. In addition, current research shows that the complication and mortality rate is slightly higher in cases of reoperation. However, reoperation appears to be beneficial for patients with serious complications related to the primary bariatric surgery and may be considered medically necessary when Criteria are met.

Research regarding the revision or removal of an adjustable gastric band is limited to noncomparative studies with short-term follow-up. These studies suggest band removal or revision is associated with improvement in band related complications. In addition, studies indicate gastric bypass is the preferred secondary procedure in cases of adjustable band conversion as bypass is associated with fewer complications and lower mortality rates compared to sleeve gastrectomy. Therefore, adjustable gastric band removal and/or conversion to gastric bypass may be considered medically necessary when Criteria are met.

The research is insufficient to determine the safety or efficacy of all other bariatric surgery reoperations or revisions; therefore, reoperations or revisions are considered not medically necessary when Criteria are not met.

### **TWO-STAGED BARIATRIC PROCEDURES**

There is not enough research to establish the safety and efficacy of any two-stage bariatric procedure. Therefore, two-stage bariatric procedures are considered investigational for all indications.

### **ADOLESCENT AND PEDIATRIC BARIATRIC SURGERY**

There is evidence to suggest that bariatric surgery may provide the benefits of weight reduction and improvement in comorbidities compared to non-surgical treatments in obese children and adolescents under the age of 18 years. Clinical practice guidelines suggest that bariatric surgery may be beneficial for patients under the age of 18 when they have achieved Tanner pubertal development of 4 or 5 and additional consideration is given to the psychosocial and informed consent issues. Therefore, bariatric procedures in patients younger than 18 years of age may be considered medically necessary when Criteria are met.

### **BARIATRIC SURGERY IN PATIENTS WITH DIABETES WITH BMI < 35KG/M<sup>2</sup>**

Research for the safety and effectiveness of bariatric procedures as a treatment for diabetes in patients with a BMI < 35 kg/m<sup>2</sup> is limited by small study sizes and short-term follow-up. High-quality studies that include long-term follow-up are needed in order to evaluate the

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impact of bariatric surgery on health outcomes in this population. In addition, the majority of evidence-based clinical practice guidelines do not recommend bariatric surgery in diabetic patients with a BMI < 35 kg/m<sup>2</sup>. Therefore, bariatric procedures in diabetic patients with a BMI < 35 kg/m<sup>2</sup> are considered not medically necessary.

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## CODES

**NOTE:** Code 43843 should not be reported if there is a more specific bariatric surgery code within code range listed below.

Codes	Number	Description
CPT	43631	Gastrectomy, partial, distal; with gastroduodenostomy
	43632	;with gastrojejunostomy
	43633	;with roux-en-Y reconstruction
	43634	;with formation of intestinal pouch

Codes	Number	Description
	43644	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and Roux-en-Y gastroenterostomy (roux limb 150 cm or less)
	43645	Laparoscopy, surgical, gastric restrictive procedure; with gastric bypass and small intestine reconstruction to limit absorption
	43659	Unlisted laparoscopy procedure, stomach
	43770	Laparoscopy, surgical, gastric restrictive procedure; placement of adjustable gastric restrictive device (gastric band and subcutaneous port components)
	43771	Laparoscopy, surgical, gastric restrictive procedure; revision of adjustable gastric restrictive device component only
	43772	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device component only
	43773	Laparoscopy, surgical, gastric restrictive procedure; removal and replacement of adjustable gastric restrictive device component only
	43774	Laparoscopy, surgical, gastric restrictive procedure; removal of adjustable gastric restrictive device and subcutaneous port components
	43775	Laparoscopy, surgical, gastric restrictive procedure; longitudinal gastrectomy (ie, sleeve gastrectomy)
	43820	Gastrojejunostomy; without vagotomy
	43842	Gastric restrictive procedure, without gastric bypass, for morbid obesity; vertical banded gastroplasty
	43843	Gastric restrictive procedure, without gastric bypass, for morbid obesity; other than vertical banded gastroplasty
	43845	Gastric restrictive procedure with partial gastrectomy, pylorus-preserving duodenoileostomy and ileoileostomy (50 to 100 cm common channel) to limit absorption (biliopancreatic diversion with duodenal switch)
	43846	Gastric restrictive procedure, with gastric bypass for morbid obesity; with short limb (150 cm or less) Roux-en-Y gastroenterostomy
	43847	Gastric restrictive procedure, with gastric bypass for morbid obesity; with small intestine reconstruction to limit absorption
	43848	Revision, open, of gastric restrictive procedure for morbid obesity, other than adjustable gastric restrictive device (separate procedure)
	43860	Revision of gastrojejunal anastomosis (gastrojejunostomy) with reconstruction, with or without partial gastrectomy or intestine resection; without vagotomy
	43865	;with vagotomy
	43886	Gastric restrictive procedure, open; revision of subcutaneous port component only
	43887	Gastric restrictive procedure, open; removal of subcutaneous port component only
	43888	Gastric restrictive procedure, open; removal and replacement of subcutaneous port component only
HCPCS	S2083	Adjustment of gastric band diameter via subcutaneous port by injection or aspiration of saline

**Date of Origin:** January 1996

## ***Reduction Mammoplasty***

**Effective:** October 1, 2020

**Next Review:** July 2021

**Last Review:** August 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Reduction mammoplasty is the surgical excision of a substantial portion of the breast, including the skin and underlying glandular tissue, until a clinically normal size is obtained.

### **MEDICAL POLICY CRITERIA**

#### **Notes:**

- This policy is not applicable when there has been a prior mastectomy for which the Women's Health & Cancer Rights Act applies. The Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants policy (Surgery, Policy No. 40 – see Cross References) may be applicable. Please refer to the Surgery, Policy No. 40 for reconstruction after partial or complete mastectomy.
- This policy is not intended to address treatment of gender dysphoria which is addressed in the Transgender Services medical policy (Medicine, Policy No. 153 – see cross references), which may be applicable.

- I. Reduction mammoplasty may be considered **medically necessary** when one or more of the following are met:

- A. As a preparatory first stage procedure preceding a nipple-sparing mastectomy, when the amount of breast tissue removed from each breast is at least the minimum in grams per breast for the patient's body surface area (in meters squared using the Mosteller formula) according to the Schnur Sliding Scale (see Policy Guidelines for body surface area/breast weight table); or
- B. When all of the following criteria (1. - 3.) are met:
1. The patient is aged 18 years or older; and
  2. The amount of breast tissue removed from each breast, not including fat removed by liposuction, must be at least the minimum in grams per breast for the patient's body surface area\* according to the Schnur Sliding Scale (see Policy Guidelines), or, in cases of asymmetry where one breast meets criterion but the other breast does not, the combined weight of the tissue removed from both breasts must total at least twice the Schnur Sliding Scale minimum for the patient's body surface area (the health plan may review medical records to confirm the amount of breast tissue removed during the procedure); and
  3. Two or more of the following clinical indications have been present for at least 12 months and have failed to respond to appropriate conservative therapy:
    - a. Pain in the upper back, neck, shoulders, and/or arms, with all of the following documented in the medical records by the referring physician or provider:
      - i. The pain is of long-standing duration and increasing intensity; and
      - ii. The pain has been evaluated to determine that it is not associated with another diagnosis such as arthritis, if applicable; and
      - iii. The pain is not relieved by at least three months of conservative therapy such as an appropriate support bra with wide straps, exercises, heat/cold treatments and appropriate non-steroidal anti-inflammatory agents/muscle relaxants.
    - b. Dermatitis of the shoulder or shoulder grooving not responding to at least three months of conservative treatment including a support bra or appropriate dermatologic treatments, (e.g. taking steps to eliminate friction, heat, and maceration by keeping skin cool and dry and where appropriate, topical agents).
    - c. Intertrigo between the pendulous breasts and the chest wall persisting despite at least three months of conservative dermatologic treatments (e.g. taking steps to eliminate friction, heat, and maceration by keeping skin cool and dry and where appropriate, antimycotic agents).
    - d. Kyphosis documented by x-ray.
    - e. Ulnar paresthesia not relieved by at least three months of conservative therapy such as an appropriate support bra with wide straps, range of motion exercises, physical therapy, and appropriate non-steroidal anti-inflammatory agents/muscle relaxants.

- II. Reduction mammoplasty is considered **not medically necessary** when Criteria I. is not met.
- III. Reduction mammoplasty for gynecomastia is considered **not medically necessary**.
- IV. The use of liposuction as an additional procedure with breast reduction surgery is considered **not medically necessary**.
- V. The use of liposuction as the sole procedure for breast reduction is considered **investigational**.

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

## POLICY GUIDELINES

Mosteller formula: body surface area (m<sup>2</sup>) = ( [height (cm) x weight (kg) ] / 3600 )<sup>½</sup> [1]

[Click here for link to Body Surface Area Calculator](#)

### Schnur Sliding Scale

<u>Body Surface Area (m<sup>2</sup>) and Minimum Requirement for Breast Tissue Removal</u>	
Body Surface Area m <sup>2</sup>	Grams per Breast of Minimum Breast Tissue to be Removed
<i>NOTE: When BSA is &lt; 1.350 minimum is 199 grams</i>	
1.350-1.374	199
1.375-1.399	208
1.400-1.424	218
1.425-1.449	227
1.450-1.474	238
1.475-1.499	249
1.500-1.524	260
1.525-1.549	272
1.550-1.574	284
1.575-1.599	297
1.600-1.624	310
1.625-1.649	324

1.650-1.674	338
1.675-1.699	354
1.700-1.724	370
1.725-1.749	386
1.750-1.774	404
1.775-1.799	422
1.800-1.824	441
1.825-1.849	461
1.850-1.874	482
1.875-1.899	504
1.900-1.924	527
1.925-1.949	550
1.950-1.974	575
1.975-1.999	601
2.000-2.024	628
2.025-2.049	657
2.050-2.074	687
2.075-2.099	717
2.100-2.124	750
2.125-2.149	784
2.150-2.174	819
2.175-2.199	856
2.200-2.224	895
2.225-2.249	935
2.250-2.274	978

2.275-2.299	1022
2.300-2.324	1068
2.325-2.349	1117
2.350-2.374	1167
2.375-2.399	1219
2.400-2.424	1275
2.425-2.449	1333
2.450-2.474	1393
2.475-2.499	1455
2.500-2.524	1522
2.525-2.549	1590
2.550 or greater	1662

## LIST OF INFORMATION NEEDED FOR REVIEW

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

1. Total amount of breast tissue to be removed, include if L/R or bilateral
2. Height and weight
3. Any two of the following detailed in chart notes, history and physical, physical therapy notes, radiologic exams, dermatology treatments notes, and/or any other clinical notes:
  - A. Medical records by the referring physician, which include pain in the upper back, neck, shoulders and/or arms with documentation of long standing pain, and detailed notes regarding treatment with at least three months of conservative therapy, and that the pain is not associated with another diagnosis such as arthritis;
  - B. Documentation of shoulder grooving or dermatitis of the shoulder with description of at least three months of conservative treatment with dermatology notes and outcome;
  - C. Intertrigo despite three months detailed documentation of conservative therapy;
  - D. X-ray showing kyphosis;
  - E. Ulnar paresthesia despite three months documentation of conservative therapy and outcome with chart notes detailing specific treatment.

## CROSS REFERENCES

1. [Gender Affirming Interventions for Gender Dysphoria](#), Medicine, Policy No. 153

2. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12
3. [Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants](#), Surgery, Policy No. 40
4. [Autologous Fat Grafting to the Breast and Adipose-derived Stem Cells](#), Surgery, Policy No. 182

## BACKGROUND

Female breast hypertrophy, or macromastia, is the development of abnormally large breasts in the female. This condition can cause significant clinical manifestations when the excessive breast weight adversely affects the supporting structures of the shoulders, neck and trunk. Macromastia is distinguished from large, normal breasts by the presence of persistent symptoms such as shoulder, neck, or back pain, shoulder grooving, or intertrigo. This condition can be improved and the associated signs and symptoms can be alleviated by reduction mammoplasty surgery.

## EVIDENCE SUMMARY

The following literature appraisal is focused on the investigational technique of reduction mammoplasty by liposuction alone. In order to understand the impact on health outcomes of reduction mammoplasty by liposuction alone, prospective clinical trials are needed, comparing liposuction with standard reduction mammoplasty. These comparisons are necessary in order to understand the safety and efficacy of liposuction and to determine whether liposuction offers advantages over conventional surgical procedures with respect to patient satisfaction, complications, durability, and cosmesis.

While there are some published articles concerning the use of liposuction as the sole procedure for breast reduction, none compare the outcomes of liposuction alone to standard excisional reduction mammoplasty.<sup>[2-9]</sup> Examples of these articles are detailed below:

Moskovitz (2007) conducted a study of liposuction alone for treatment of macromastia in twenty-four African-American women due to their high risk for complex scar formation following standard excision mammoplasty.<sup>[8]</sup> The mean aspirate was 1075 cc of fat per breast; however, the before and after liposuction pictures indicate that the participants continued to support large breasts. Outcome measures included the SF-36, EuroQol, Multidimensional Body-Self Relations Questionnaire, McGill Pain Questionnaire and Breast-Related Symptoms Questionnaire. Statistical analysis demonstrated a significant improvement in breast-related symptoms and pain. This was a relatively small, non-randomized trial and patients were not blinded to the intervention. Conclusions concerning the effect of liposuction alone on breast-related symptoms in patients with macromastia cannot be made.

Jakubietz (2011) reported the indications and limitations of this procedure compared to conventional surgical excision.<sup>[9]</sup> Advantages included selective removal of fat, ease of procedure, and the advantages of less invasive procedures such as faster recovery time and reduced scarring. One disadvantage of liposuction alone included the inability to correct shape and ptosis, making aesthetic results optimal only for young patients. In addition, there are concerns about the extent to which subsequent breast imaging may be impaired, and the possible spread of cancer cells. The authors recommended caution when considering use of this technique.

In summary, high quality evidence on the use of liposuction for reduction mammoplasty has not been identified; comparative trials of sufficient size and duration are needed before any conclusions can be made about the use of this technique for breast reduction.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN SOCIETY OF PLASTIC SURGEONS

In 2011, the American Society of Plastic Surgeons (ASPS) released an evidence-based clinical practice guideline on the use of reduction mammoplasty.<sup>[10]</sup> Several clinical questions were addressed, including whether women who did not meet standard health insurance criteria for volume of breast resection experience postoperative relief. On the basis of a single study which compared satisfaction outcomes of women who met standard insurance criteria with women who did not meet such criteria, the society concluded that, “resection volume is not correlated to the degree of postoperative symptom relief.” The society recommended extending the option of reduction mammoplasty to this category of patient. However, among women not meeting standard criteria for resection volume, no comparisons were made between surgical and standard conservative treatment, limiting interpretation of the above findings. Additionally, these recommendations did not specifically address the safety and effectiveness of reduction mammoplasty by liposuction.

### SUMMARY

Female breast hypertrophy, or macromastia, is the development of abnormally large breasts in the female, which can cause medical problems. There is enough research to show that reduction mammoplasty can improve health outcomes for certain patients with this condition. Therefore, reduction mammoplasty may be considered medically necessary when policy criteria are met. Reduction mammoplasty as treatment for macromastia is considered not medically necessary when policy criteria are not met.

There is not enough research to show that liposuction mammoplasty can improve health outcomes more than traditional mammoplasty techniques. Therefore, reduction mammoplasty by liposuction alone is considered investigational.

Gynecomastia refers to the benign enlargement of the male breast, mainly due to excessive growth of glandular tissue. Reduction mammoplasty (partial removal) for the treatment of gynecomastia is considered not medically necessary as the current standard of care is for the removal of most or all glandular tissue.

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14. BlueCross BlueShield Association Medical Policy Reference Manual "Reduction Mammoplasty for Breast-Related Symptoms." Policy No. 7.01.21

## CODES

Codes	Number	Description
CPT	15877	Suction assisted lipectomy; trunk
	19318	Reduction mammoplasty
HCPCS	None	

**Date of Origin:** January 1996

**NOTE: This policy has been revised. The revised policy will be effective January 1, 2021. To view the revised policy, [click here](#).**

Medical Policy Manual

Surgery, Policy No. 74

## ***Vagus Nerve Stimulation***

**Effective:** June 1, 2019

**Next Review:** April 2020

**Last Review:** April 2019

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Vagus nerve stimulation (VNS) involves implantation of an infraclavicular pulse generator that sends weak electric impulses to the left vagus nerve within the carotid sheath in the neck.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy does not apply to vagus nerve **blocking** therapy. See Cross References.

- I. Implantable vagus nerve stimulation (VNS) may be considered **medically necessary** as a treatment of medically refractory seizures. Patients must have tried and been unresponsive to or intolerant of at least two antiepileptic drugs.
- II. Implantable vagus nerve stimulation revision(s) or replacement(s) may be considered **medically necessary** after the device has been placed.
- III. Implantable VNS is considered **investigational** for all other indications, including but not limited to essential tremors.
- IV. Transcutaneous and non-implantable vagus nerve stimulation devices are considered **investigational** for all indications.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and Physical/Chart Notes
- Current Symptomology
- Antiepileptic medications given and response

## CROSS REFERENCES

1. [Gastric Electrical Stimulation](#); Surgery, Policy No. 111
2. [Vagus Nerve Blocking Therapy for Obesity](#); Surgery, Policy No. 200
3. [Responsive Neurostimulation](#), Surgery, Policy No. 216

## BACKGROUND

An implanted VNS device delivers mild electronic impulses via two electrodes connected to the generator and wrapped around the vagus nerve. The stimulator may be programmed in advance or may be activated on demand by placing a magnet against the generator implantation site.

While the mechanisms for the therapeutic effects of VNS are not fully understood, the basic premise of VNS in the treatment of various conditions is that vagal visceral afferents have a diffuse central nervous system projection, and activation of these pathways has a widespread effect on neuronal excitability. An electrical stimulus is applied to axons of the vagus nerve, which have their cell bodies in the nodose and junctional ganglia and synapse on the nucleus of the solitary tract in the brainstem. From the solitary tract nucleus, vagal afferent pathways project to multiple areas of the brain. VNS may also stimulate vagal efferent pathways that innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and provide parasympathetic innervation to the gastrointestinal tract.

Other types of implantable vagus nerve stimulators that are placed in contact with the trunks of the vagus nerve at the gastroesophageal junction are not addressed in this evidence review.

## REGULATORY STATUS

### Implantable VNS Devices

Several VNS therapy systems by Cyberonics Inc. have pre-market approval (PMA) from the U.S. Food and Drug Administration (FDA) for treatment of refractory partial-onset seizures and chronic or recurrent depression, when certain criteria are met. For example, in 1997, the NeuroCybernetic Prosthesis (NCP®) system was approved for use in conjunction with drugs or surgery “as an adjunctive treatment of adults and adolescents over 12 years of age with medically refractory partial onset seizures.” The VNS Therapy™ System was approved in 2005 “for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.” FDA product code: LYJ

### Non-implantable VNS Devices

Cerbomed has developed a transcutaneous VNS (t-VNS®) system, NEMOS®, that uses a combined stimulation unit and ear electrode to stimulate the auricular branch of the vagus nerve, which supplies the skin over the concha of the ear. Patients self-administer electric stimulation for several hours a day; no surgical procedure is required. The device has not been FDA approved for use in the US.

electroCore, LLC has developed a non-invasive VNS (gammaCore®) released for use by the FDA in April of 2017. The device intended for non-invasive vagus nerve stimulation on the side of the neck to treat cluster headache and to reduce the frequency of cluster headache attacks. Product code: PKR

## EVIDENCE SUMMARY

### VAGUS NERVE STIMULATORS

In order to assess the safety and effectiveness of vagus nerve stimulation (VNS), particularly for indications in which the primary outcomes are subjective (e.g., pain reduction, improved mood, improved functioning), well-designed, randomized controlled trials (RCTs) are necessary. Such trials include double-blinding, appropriate randomization, an appropriate control group (i.e., sham VNS or standard medical treatment), large study populations, adequate follow-up time, and adverse events reporting.

#### MEDICALLY REFRACTORY SEIZURES

The criteria for VNS for seizures are based on a 1998 BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC) assessment<sup>[1]</sup>, a 2015 Cochrane review<sup>[2]</sup> which included the three published double-blind randomized controlled trials (RCTs)<sup>[3-5]</sup>, and numerous case series, retrospective reviews, and other non-randomized studies on adult<sup>[6-11]</sup>, pediatric,<sup>[12-19]</sup> or mixed<sup>[20-25]</sup> patient populations. Both reviews concluded that VNS reduced seizure frequency in patients with drug resistant partial-onset seizures.

The two RCTs were large, well-designed multicenter trials that reported an approximate 25% reduction in partial-onset seizure frequency following three months of VNS. Adverse effects were mild and consisted primarily of hoarseness or voice change during “on” periods of stimulation. The remaining literature is limited to numerous non-randomized trials. Although evidence from non-randomized studies are generally considered unreliable for assessing the safety and effectiveness of VNS, the findings from these numerous studies have consistently shown significantly reduced seizure activity in patients with drug-resistant epilepsy. In addition, clinical practice guidelines from the American Academy of Neurology stated that “...sufficient evidence exists to rank VNS for epilepsy as effective and safe...”<sup>[26]</sup> Thus, despite the lack of RCTs in the published clinical evidence, VNS has become a recognized standard of care for treatment in selected patients with medically refractory seizures.

More recently, a 2014 RCT reported long-term quality of life outcomes for 112 patients with pharmacoresistant focal seizures, which supported the beneficial effects of VNS for this group.<sup>[27]</sup>

#### REFRACTORY DEPRESSION

##### Technology Assessments

A 2006 BCBSA TEC Assessment<sup>[28]</sup>, evaluated the effectiveness of VNS in the treatment of refractory depression compared with continued medical management. The evidence consisted of one case series, one observational study, and one randomized controlled trial. The assessment found that “overall, the evidence supporting efficacy of VNS is not strong.”

The randomized controlled trial (RCT) of 221 patients that compared VNS with a sham control (implanted but inactivated VNS) did not show a statistically significant difference between VNS and continued medical therapy in relieving depression symptoms.<sup>[29-31]</sup> The trial was short and possibly underpowered to detect a smaller amount of VNS benefit. In addition, the adequacy of blinding was questionable. The observational study included a subset of 205 VNS treated patients from the RCT described above who were followed long-term. A separately recruited control group of 124 patients received ongoing treatment for depression.<sup>[29,32]</sup> Although the study findings favored the VNS therapy group, this evidence is considered unreliable due to significant methodological limitations including but not limited to the following: 1) Non-randomized allocation of treatment does not control for possible between-group differences in individual patient characteristics; thus, it cannot be ruled out that these differences, rather than the treatments received, were responsible for the observed outcomes; 2) The lack of a sham study group does not control for the expected placebo effects; 3) The inadequate, non-concurrent comparison group does not permit conclusions on the efficacy of VNS compared with placebo or other treatment options, 4) The differences in sites of care between VNS treated patients and controls may introduce response bias. (Analysis performed on subsets of patients cared for in the same sites, and censoring observations after treatment changes, generally showed diminished differences in apparent treatment effectiveness.); and 5) Differences in concomitant therapy changes cannot be ruled out as an explanation of the observed outcomes.

The case series (Study D-01) was a feasibility study of 60 patients receiving VNS; improvement was reported in depression scores.<sup>[33]</sup> It is uncertain whether loss to follow-up was addressed adequately in the analysis. In addition, the case series is limited by the lack of an appropriate comparison group.

## **Systematic Reviews**

In a meta-analysis that included 14 studies, Martin (2012) reported that among the uncontrolled studies in their analysis, 31.8% of subjects responded to VNS treatment.<sup>[34]</sup> However, results from a meta-regression to predict each study’s effect size suggested that 84% of the observed variation across studies was explained by baseline depression severity ( $p < 0.0001$ ). The authors concluded that current data was insufficient to determine whether VNS is an effective treatment for depression and noted that positive results from uncontrolled studies may be due to placebo effect.

A 2008 systematic review and meta-analysis for VNS of treatment-resistant depression identified no new RCTs since the pivotal RCT described above, which the authors determined to be inconclusive.<sup>[35]</sup> As noted above, RCTs are considered the appropriate design for studying VNS for any indication. However, this review also included 17 nonrandomized, open studies which found VNS to be associated with a reduction in depressive symptoms. The authors concluded that, while open studies have reported promising results, further clinical trials are needed to study the mechanism of action and cost-effectiveness, and to confirm the efficacy of VNS in treatment-resistant depression.

## **Randomized Controlled Trials**

Since the BCBSA TEC Assessment and the 2008 systematic review, a single randomized controlled trial was identified that evaluated the effectiveness of VNS for treatment of refractory depression. Aaronson randomized 331 patients with treatment-resistant depression (TRD) into one of three VNS dose groups: LOW (0.25 mA current, 130  $\mu$ s pulse width), MEDIUM (0.5-1.0 mA, 250  $\mu$ s), or HIGH (1.25-1.5 mA, 250  $\mu$ s).<sup>[34]</sup> Patients were included that had a history of failure to respond to at least 4 adequate dose/duration of antidepressant treatment trials from at least 2 different treatment categories. After 22 weeks, the current dose could be adjusted in any of the groups. At follow up visits at weeks 10, 14, 18, and 22 after enrollment, there was no statistically significant difference between the dose groups for the study's primary outcome, defined as a change in the Inventory of Depressive Symptomatology (IDS) score from baseline. However, the mean IDS score improved significantly for each of the groups from baseline to the 22 week follow up. At 50 weeks of follow up, there were no significant differences between the treatment dose groups for any of the depression scores used. Most patients completed the study; however, there was a high rate of reported adverse events, including voice alteration in 72.2%, dyspnea in 32.3%, and pain in 31.7%. Interpretation of the IDS improvement over time is limited by the lack of a no treatment control group. Approximately 20% of the patients included had a history of bipolar disorder; and therefore, the results may not be representative of most patients with treatment resistant unipolar depression. The lack of a placebo comparison group within this study limits conclusions regarding the isolated treatment effect of VNS in this patient population.

## **Nonrandomized Studies**

Numerous non-randomized studies evaluated the effectiveness of VNS for the treatment of refractory depression.<sup>[33,35-41]</sup> It is not possible to reach reliable conclusions from these studies as they fail to control for the biases discussed above.

## **TREATMENT OF CHRONIC HEART FAILURE**

### **Randomized Controlled Trials**

In 2015, Zannad reported results from the NECTAR-HF trial, a randomized, sham-controlled trial to outcomes from VNS in patients with severe left ventricular (LV) dysfunction despite optimal medical therapy.<sup>[42]</sup> Ninety-six patients were implanted with VNS and randomized in a 2:1 manner to VNS ON or VNS OFF for 6 months. Programming of the generator was performed by a physician un-blinded to treatment assignment, while all other investigators and site study staff involved in endpoint data collection were blinded to randomization. Sixty-three patients were randomized to the intervention, of whom 59 had paired pre-post data available, while 32 were randomized to control, of whom 28 had paired data available. The analysis was a modified intention-to-treat. For the primary endpoint of change in left ventricular end systolic diameter (LVESD) from baseline to 6 months, there were no significant differences between groups ( $P=0.60$  between-group difference in LVESD change). Other secondary efficacy endpoints related to LV remodeling parameters, LV function, and circulating biomarkers of heart failure, did not differ between groups, with the exception of SF-60 physical component score, which showed greater improvement in the VNS ON group than in the control group (from 36.3 to 41.2 in the VNS ON group vs from 37.7 to 38.4 in the control group;  $P=0.02$ ). Subject blinding was found to be imperfect, which may have biased the subjective outcome data reporting.

In the ANTHEM-HF study (2014), 60 patients with heart failure with reduced ejection fraction were implanted with VNS, randomly assigned to right- or left-sided implantation ( $n=29$  and  $31$ ,

respectively), and followed for 6 months.<sup>[43]</sup> Overall, from baseline to 6 month follow-up, LV ejection fraction improved by 4.5% (95% CI 2.4 to 6.6), left ventricular end systolic volume (LVESV) improved by -4.1 mL (95% CI -9.0 to 0.8), LVESD improved by -1.7 mm (95% CI -2.8 to -0.7), heart rate variability improved by 17 ms (95% CI 6.5 to 28), and 6-minute walk distance improved by 56 m (95% CI 37 to 75). Given there was no sham comparator group, it is unclear if the observed improvements may be attributed to VNS or some other confounding factor.

## **Nonrandomized Studies**

Several small case series describe VNS treatment outcomes in patients with heart failure; however, for the reasons noted above, evidence from non-randomized studies is considered unreliable in the study of VNS as a treatment for any indication.<sup>[44,45]</sup>

## **OTHER INDICATIONS**

### **Nonrandomized Studies**

Small case series (n ≤ 40 patients) and one non-randomized comparison study described experiences with VNS in patients with bulimia, anxiety, Alzheimer's disease<sup>[46,47]</sup>, migraine headaches<sup>[48,49]</sup>, obesity, essential tremor<sup>[50]</sup>, and eating disorders including obesity and food cravings<sup>[51]</sup>. The utility of VNS added to behavioral management of autism and autism spectrum disorders has been posited but there are no RCTs. For the reasons noted above, evidence from non-randomized studies is considered unreliable in the study of VNS as a treatment for any indication.

## **TRANSCUTANEOUS VAGUS NERVE STIMULATORS**

Only conditions for which there is at least one RCT will be discussed, as case series are inadequate to determine the effect of the technology.

### **REFRACTORY EPILEPSY**

Aihua (2014) reported results from a series of 60 patients with pharmaco-resistant epilepsy treated with a transcutaneous VNS (t-VNS) device, who were randomly assigned to receive stimulation over the earlobe (control group) or the Ramsay-Hunt zone (treatment group), which includes the external auditory canal and the conchal cavity and is considered to be the somatic sensory territory of the vagus nerve.<sup>[52]</sup> Thirty patients were randomized to each group; 4 subjects from the treatment group were excluded from analysis due to loss to follow-up (n=3) or adverse effects (n=1), while 9 subjects from the control group were excluded from analysis due to loss to follow-up (n=2) or increase or lack of decrease in seizures or other reasons (n=7). In the treatment group, compared with baseline, the median monthly seizure frequency was significantly reduced after 6 months (5.5 vs 6.0; p<0.001) and 12 months (4.0 vs 6.0; p<0.001) of t-VNS therapy. At 12-month follow-up, t-VNS group subjects had a significantly lower median monthly seizure frequency compared with the control group (4.0 vs 8.0; p<0.001).

Two small case series were identified that used a t-VNS device for treatment of medication-refractory seizures. In a small case series of 10 patients with treatment-resistant epilepsy, Stefan (2012) reported that 3 patients withdrew from the study, while 5 of 7 patients reported a reduction in seizure frequency.<sup>[53]</sup> In another small case series, He (2013) reported that among 14 pediatric patients with intractable epilepsy who were treated with bilateral t-VNS, of the 13

patients who completed follow-up, mean reduction in self-reported seizure frequency was 31.8% after 8 weeks, 54.1% from week 9 to 16, and 54.2% from week 17 to 24.<sup>[54]</sup>

## **PSYCHIATRIC DISORDERS**

Hein (2013) reported results of two pilot RCTs of a t-VNS device for the treatment of depression, one which included 22 subjects and the other with 15 subjects.<sup>[55]</sup> In the first study, 11 subjects each were randomized to active or sham t-VNS. At 2 weeks follow-up, Beck Depression Inventory (BDI) self-rating scores in the active-stimulation group decreased from 27.0 to 14.0 points ( $p < 0.001$ ), while the sham-stimulated patients did not show significant reductions in the BDI (31.0 to 25.8 points). In the second study, seven patients were randomized to active t-VNS and eight patients were randomized to sham t-VNS. In this study, BDI self-rating scores in the active stimulation group decreased from 29.4 to 17.4 points ( $p < 0.05$ ) after 2 weeks, while the sham-stimulated patients did not show significant change in BDI (28.6 to 25.4 points). The authors do not report direct comparisons in BDI change between the sham- and active-stimulation groups.

Hasan (2015) reported a randomized trial of t-VNS for the treatment of schizophrenia.<sup>[56]</sup> Twenty patients were assigned either to active t-VNS or to sham treatment for 12 weeks. There was no statistically significant difference in the improvement of schizophrenia status during the observation period.

Shiozawa (2014) conducted a systematic review of studies evaluating the evidence related to transcutaneous stimulation of the trigeminal or vagus nerve for psychiatric disorders.<sup>[57]</sup> They found four studies that addressed t-VNS for psychiatric disorders and included a total of 84 subjects. Three of the four studies evaluated physiologic parameters in healthy patients and one evaluated pharmaco-resistant epilepsy (Stefan, previously described<sup>[53]</sup>). The authors also include a fifth study in a data table, although not in their text or reference list (Hein, previously described<sup>[55]</sup>). Overall, the studies included were limited by small size and poor generalizability.

## **HEADACHE**

Goadsby (2014) reported results from an open-label pilot study of t-VNS for the treatment of migraine with or without aura.<sup>[58]</sup> Eighty migraine attacks were self-treated by 27 patients, of an initial sample of 30 patients (two patients treated no migraine attacks with the device, one patient treated only an aura). Of 54 moderate or severe attacks treated, 12 subjects (22%) were pain-free at two hours posttreatment. Thirteen subjects reported adverse events, which were all considered mild or moderate.

## **IMPAIRED GLUCOSE TOLERANCE**

Huang (2014) reported results of a pilot RCT of a t-VNS device that provides stimulation to the auricle for the treatment of impaired glucose tolerance.<sup>[59]</sup> The study included 70 patients with impaired glucose tolerance who were randomized to active or sham t-VNS, along with 30 controls who received no t-VNS treatment. After 12 weeks of treatment, patients who received active t-VNS were reported to have significantly lower 2-hour glucose tolerance test results than those who received sham t-VNS (7.5 mmol/L vs 8 mmol/L;  $p = 0.004$ ).

## **ADVERSE EVENTS**

The most commonly reported adverse effects of VNS have been mild and consist primarily of hoarseness of voice during "on" periods of stimulation, transient throat pain, and coughing.

More serious adverse events reported include, but are not limited to direct delivery of the current to the nerve due to generator malfunction; modified synchronization between cardiac and respiratory activity affecting the oxygen delivery to tissues; heart block with ventricular standstill; bradyarrhythmias and severe asystolia; and changes in respiration during sleep.<sup>[1,29,35,60-63]</sup>

## NON-IMPLANTABLE VAGUS NERVE STIMULATORS

### CLUSTER HEADACHE

#### ACT1 and ACT2 Studies

In 2016, Silberstein reported results from the manufacturer funded ACT1 study – a randomized, double-blind, sham-controlled study of nVNS as a treatment for cluster headache (CH).<sup>[64]</sup> One hundred fifty subjects were randomized to receive sham control or nVNS treatment for less than or equal to one month; completers could enter a 3-month nVNS open-label phase. A considerable proportion of patients correctly guessed their treatment allocation after their first treatment, though blinding was found to have improved by the end of the one-month period. The primary end point was response rate, defined as the proportion of subjects who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first CH attack without rescue medication use through 60 minutes. Secondary end points included the sustained response rate (15-60 minutes). Subanalyses of episodic cluster headache (eCH) and chronic cluster headache (cCH) cohorts were prespecified.

During the randomized phase of one month, 14 participants discontinued participation from the treatment group, and 8 in the control group discontinued. In the three-month open label period, 17 and 11 discontinued from the treatment and control groups, respectively. Application site reactions and nervous system AEs occurred more frequently with sham treatment than with nVNS in the double-blind phase. Adverse device effects (ADEs) were reported by 35/150 (nVNS, 11; sham, 24) subjects in the double-blind phase and 18/128 subjects in the open-label phase.

Intent-to-treat analysis included 133 subjects: 60 nVNS-treated (eCH, n = 38; cCH, n = 22) and 73 sham-treated (eCH, n = 47; cCH, n = 26). Authors reported a response in 26.7% of nVNS-treated subjects and 15.1% of sham-treated subjects. Response rates were significantly higher with nVNS than with sham for the eCH cohort (nVNS, 34.2%; sham, 10.6%;  $p = 0.008$ ) but not the cCH cohort (nVNS, 13.6%; sham, 23.1%;  $p = 0.48$ ). Sustained response rates were significantly higher with nVNS for the eCH cohort and total population.

In 2018, Goadsby reported on the results of randomized, double-blind, sham-controlled study (ACT2) for the treatment of acute cluster headache attacks.<sup>[65]</sup> Ninety-two patients with cluster headaches were randomized to nVNS or sham treatment. Patients were further identified as having episodic cluster headaches or chronic cluster headaches and randomized at approximately 1:1 to the nVNS and sham treatment groups. The primary efficacy end point was the ability to achieve pain-free status within 15 minutes of initiation of treatment without use of rescue treatment. There was no difference between nVNS-treated and sham-treated patients in the overall cluster headache study population. Subgroup analysis of the chronic cluster headache population showed no differences between nVNS-treated and sham-treated patients. For the episodic cluster headaches subgroup, nVNS demonstrated a 48% response rate compared with 6% response rate for sham-treated ( $p < 0.01$ ). The interaction  $p$ -value for the subgroup analysis was statistically significant ( $p = 0.04$ ).

## PREVA Study

Gaul (2016, 2017) reported the results of the PREVA study - a randomized open-label study of nVNS as a prophylactic therapy for chronic cluster headache (CH) in patients diagnosed at least one year prior to enrollment.<sup>[66,67]</sup> The study was funded by the device manufacturer. In a two-week baseline period, all 97 participants received only their individualized standard of care (SoC). Patients were then randomized to a four-week period of SoC with nVNS (n=48) or SoC alone, i.e., control (n=49). Four participants from the SoC with nVNS chose to withdraw; one control participant was removed from the study for failing to meet enrollment criteria. In an optional four-week period following, all participants received SoC with nVNS (n=92); 70 completed the optional period (11 controls discontinued from each group).

Efficacy was evaluated by the mean number of CH attacks per week, defined as the number of attacks during the last two weeks of the randomized phase minus the number of attacks during baseline divided by two. Safety and tolerability were assessed in those who were assigned treatment; and the intent-to-treat (ITT) population was those who had more than one efficacy recording in their home diary after randomization.

In the ITT population (n=45 SoC plus nVNS, n=48 in control) authors reported a mean therapeutic gain of 3.9 fewer CH attacks per week (95% confidence interval (CI): 0.5, 7.2;  $p=0.02$ ). However, the proportion of participants receiving SoC plus nVNS in the ITT population from the randomized phase with more than 50% response to treatment was 40.0, and in controls who went on to receive treatment in the extension phase, the proportion was 16.7.

During the randomization phase, 38% participants in the SoC plus nVNS group experienced adverse events (AEs), and 27% of controls experienced AEs. In the extension phase, 25% and 24% experienced AEs, respectively. Overall, the most common AEs for any treatment were CH attacks, headache, nasopharyngitis, dizziness, oropharyngeal pain, and neck pain. No serious AEs were considered related to the nVNS device.

The study is limited by a sham placebo control group, which may result in placebo response in the nVNS group.

## MIGRAINE

One RCT has evaluated nVNS for prevention of migraine headache compared to sham and one RCT has evaluated nVNS for treatment of acute migraine headache compared to sham nVNS.

The EVENT trial (Silberstein, 2016) was a feasibility study of prevention with a sample size of 59.<sup>[68]</sup> It was not powered to detect differences in efficacy outcomes. About twenty percent of participants discontinued treatment after the first two months. The study was supposed to be blinded, but the sham did not deliver electrical stimulation, which may have compromised the blinding. For the outcome of response, defined as 50% or more reduction in the number of headache days, 10% of the patients in the nVNS group versus 0% in the sham group were responders; statistically testing was not performed.

PRESTO was a multicenter, double-blind, randomized, sham-controlled trial of acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura reported by Tassorelli (2018), Grazi (2018), and Martelletti (2018).<sup>[69-71]</sup> The primary efficacy outcome was the proportion of participants who were pain-free without using rescue medication at 120

minutes. There was not a statistically significant difference in the primary outcome (30% vs 20%;  $p = 0.07$ ) although it favored the nVNS group. The nVNS group had a higher proportion of patients with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs 28%;  $p=0.03$ ) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs 18%;  $p=0.02$ ). PRESTO results did not include quality of life or functional outcomes and the double-blind treatment and follow-up period was 4 weeks. In the additional 4 weeks of acute nVNS in the open-label period, rates of pain-free response after the first treated attack (28%,) and pain relief (43.4%) were similar to the rates in the double-blind period. Given the marginally significant primary outcome, lack of quality of life or functional outcomes and limited follow-up, further RCTs are needed.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN PSYCHIATRIC ASSOCIATION

The American Psychiatric Association (APA) (2010, reaffirmed 2015) has level III\* recommendations regarding the use of vagus nerve stimulation (VNS) for patients with major depressive disorder.<sup>[72]</sup> Strategies to address nonresponse during an acute phase of depression include VNS as an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT (electroconvulsive therapy). Maintenance treatment with VNS is also appropriate for individuals whose symptoms have responded to this treatment modality.

\* [III] May be recommended on the basis of individual circumstances (As opposed to level I or II which are recommended with substantial and moderate clinical confidence, respectively.)

### AMERICAN ACADEMY OF NEUROLOGY

The American Academy of Neurology (AAN) 2013 consensus statement states VNS may be considered for seizures in children, for LGS (Lennox-Gastaut-syndrome)- associated seizures, and for improving mood in adults with epilepsy; and VNS may be considered to have improved efficacy over time.<sup>[73]</sup> These statements are based on Level C evidence, which is defined as, “possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population.”

## SUMMARY

Although the current evidence is limited, vagus nerve stimulation (VNS) has evolved to a standard of care as a treatment of medically refractory seizures. Therefore, VNS for medically refractory seizures may be considered medically necessary for patients who have had inadequate response to or are intolerant of at least two antiepileptic drugs.

There is not enough research to make conclusions about the benefit of VNS as a treatment for conditions other than medically refractory seizures. Therefore, VNS is considered investigational for all indications other than selected patients with refractory seizures.

There is not enough research to know if transcutaneous vagus nerve stimulation (tVNS) improves health outcomes as a treatment for any condition. In addition, no tVNS devices have received approval from the U.S. Food and Drug Administration (FDA). Therefore,

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transcutaneous vagus nerve stimulation is considered investigational as a treatment for all indications.

There is not enough research to know if or how well non-invasive vagus nerve stimulation (nVNS) works to treat people with any condition, including but not limited to cluster headache. This does not mean that it does not work, but more research is needed to know. No clinical guidelines based on research recommend nVNS for people with cluster headache or any other condition. Therefore, non-invasive vagus nerve stimulation is considered investigational as a treatment for all indications.

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## CODES

Codes	Number	Description
CPT	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array

Codes	Number	Description
	61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to two or more electrode arrays
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
	64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
	64568	Incision for implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
	64569	Revision or replacement of cranial nerve (e.g., vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
	64570	Removal of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
	95974	<del>Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, first hour (Deleted 1/1/2019)</del>
	95975	<del>;complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, each additional 30 minutes after first hour (list separately in addition to code for primary procedure) (Deleted 1/1/2019)</del>
	95976	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
	95977	;with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
	0466T	Insertion of chest wall respiratory sensor electrode or electrode array, including connection to pulse generator (List separately in addition to code for primary procedure)
HCPCS	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension

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<b>Codes</b>	<b>Number</b>	<b>Description</b>
	L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only

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**Date of Origin:** February 1998

## Deep Brain Stimulation

**Effective:** July 1, 2020

**Next Review:** March 2021

**Last Review:** May 2020

### IMPORTANT REMINDER

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

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

### DESCRIPTION

Deep brain stimulation (DBS) involves the stereotactic placement of an electrode into the brain (i.e., hypothalamus, thalamus, globus pallidus or subthalamic nucleus [STN]).

### MEDICAL POLICY CRITERIA

**Note:** The use of spinal cord stimulation as a treatment of chronic pain is addressed in a separate policy (see Cross References section below).

- I. When a multidisciplinary evaluation has confirmed both the medical intractability of the patient's symptoms and the potential value of deep brain stimulation (DBS), unilateral or bilateral DBS may be considered **medically necessary** when **both** of the following criteria (A. and B.) are met:
  - A. One of the following is met:
    1. The request is for stimulation of the thalamus in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease. Disabling, medically unresponsive tremor defined as tremor causing significant limitation in daily activities AND inadequate symptom

control despite optimal medical management for at least three months before implant.

2. The request is for stimulation of the subthalamic nucleus or globus pallidus in patients with previously levodopa-responsive Parkinson's disease and symptoms such as rigidity, bradykinesia, dystonia or levodopa-induced dyskinesias.
3. The request is for stimulation of the subthalamic nucleus or globus pallidus in patients seven years of age or above with disabling, medically unresponsive primary dystonias including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis). Disabling, medically unresponsive dystonia defined as dystonia causing significant limitation in daily activities AND inadequate symptom control despite optimal medical management for at least three months before implant.

B. The patient does not have any of the following contraindications:

1. Patients who are not good surgical risks because of comorbid medical problems or because of the presence of a cardiac pacemaker; and
2. Patients who have medical conditions that require repeated MRI; and
3. Patients who have dementia that may interfere with the ability to cooperate.

II. Unilateral or bilateral deep brain stimulation revision(s) or replacement(s) may be considered **medically necessary** after the device has been placed

III. Deep brain stimulation is considered **not medically necessary** for essential tremor, Parkinson's disease, medically unresponsive primary dystonias including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis) when Criterion I. is not met.

IV. Deep brain stimulation is considered **investigational** for all other conditions (see Policy Guidelines).

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

## POLICY GUIDELINES

Deep brain stimulation is considered investigational for indications that do not meet the policy criteria above including but not limited to the following:

- Cerebral Palsy
- Chronic pain (e.g., nociceptive pain; neuropathic pain)
- Cognitive decline/dementia due to Parkinson's Disease
- Epilepsy/intractable seizures
- Huntington's disease
- Multiple sclerosis
- Neuropsychiatric applications, including but not limited to the following:
  - Anorexia nervosa
  - Anxiety

- Bipolar Disorder
- Depression
- Obsessive-compulsive disorder
- Schizophrenia
- Tourette syndrome
- Other movement disorders
- Post-traumatic tremor
- Tardive dyskinesia and tardive dystonia
- Traumatic brain injury (TBI)

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and physical/chart notes
- Multidisciplinary evaluations
- Indication for DBS

## CROSS REFERENCES

1. [Spinal Cord and Dorsal Root Ganglion Stimulation](#), Surgery, Policy No. 45
2. [Implantable Peripheral Nerve Stimulation for Chronic Pain of Peripheral Nerve Origin](#), Surgery, Policy No. 205
3. [Responsive Neurostimulation](#), Surgery, Policy No. 216

## BACKGROUND

Deep brain stimulation (DBS) involves the stereotactic placement of an electrode into the brain (i.e., hypothalamus, thalamus, globus pallidus or subthalamic nucleus [STN]). The electrode is initially attached to a temporary transcutaneous cable for short-term stimulation to validate treatment effectiveness. Several days later the patient returns to surgery for permanent subcutaneous implantation of the cable and a radiofrequency-coupled or battery-powered programmable stimulator. The electrode is typically implanted unilaterally on the side corresponding to the more severe symptoms. However, the use of bilateral stimulation using two electrode arrays is also used in patients with bilateral, severe symptoms.

After implantation, noninvasive programming of the neurostimulator can be adjusted to the patient's symptoms. This feature may be important for patients with Parkinson's disease, whose disease may progress over time, requiring different neurostimulation parameters. Setting the optimal neurostimulation parameters may involve the balance between optimal symptom control and appearance of side effects of neurostimulation, such as dysarthria, disequilibrium or involuntary movements.

DBS has been investigated for a variety of indications as discussed below:

- Alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy

The technique has been most thoroughly investigated as an alternative to thalamotomy for unilateral control of essential tremor, and tremor associated with Parkinson's disease

(PD). More recently, there has been research interest in the use of deep brain stimulation of the globus pallidus or STN as a treatment of other Parkinsonian symptoms such as rigidity, bradykinesia or akinesia. Another common morbidity associated with PD is the occurrence of motor fluctuations, referred to as "on and off" phenomena, related to the maximum effectiveness of drugs (i.e., the "on" state) and the nadir response during drug troughs (i.e., the "off" state). In addition, levodopa, the most commonly used antiparkinson drug, may be associated with disabling drug-induced dyskinesias. Therefore, the optimal pharmacologic treatment of Parkinson's disease may involve a balance between optimal effects on Parkinson's symptoms vs. the appearance of drug induced dyskinesias. The effect of DBS on both Parkinson's symptoms and drug-induced dyskinesias has also been studied.

- Treatment of primary and secondary dystonia

Dystonia is defined as a neurological movement disorder characterized by involuntary muscle contractions, which force certain parts of the body into abnormal, contorted, and painful movements or postures. In primary dystonia, dystonia is the only symptom and is unassociated with other pathology. Secondary dystonia is a dystonia brought on by an inciting event, such as a stroke, trauma, or drugs. Tardive dystonia is a form of drug-induced secondary dystonia. Dystonia can be classified according to age of onset, bodily distribution of symptoms, and cause. Age of onset can occur during childhood or during adulthood. Dystonia can affect certain portions of the body (focal dystonia and multifocal dystonia) or the entire body (generalized dystonia). Torticollis is an example of a focal dystonia. Treatment options for dystonia include oral or injectable medications (i.e., botulinum toxin) and destructive surgical or neurosurgical interventions (i.e., thalamotomies or pallidotomies) when conservative therapies fail.

- Cluster headaches

Cluster headaches occur as episodic attacks of severe pain lasting from 30 minutes to several hours. The pain is usually unilateral and localized to the eye, temple, forehead, and side of the face. Autonomic symptoms that occur with cluster headaches include ipsilateral facial sweating, flushing, tearing, and rhinorrhea. Cluster headaches occur primarily in men and have been classified as vascular headaches that have been associated with high blood pressure, smoking, and alcohol use. However, the exact pathogenesis of cluster headaches is uncertain. PET scanning and MRI have shown the hypothalamic region may be important in the pathogenesis of cluster headaches. Alterations in hormonal/serotonergic function may also play a role. Treatment of cluster headaches includes pharmacologic interventions for acute episodes and prophylaxis, sphenopalatine ganglion (SPG) blockade and surgical procedures such as percutaneous SPG radiofrequency rhizotomy and gamma knife radiosurgery of the trigeminal nerve.

- Other Neurologic/Psychiatric Conditions

The role of DBS in treatment of other treatment-resistant neurologic and psychiatric disorders, particularly Tourette syndrome, epilepsy, obsessive-compulsive disorder (OCD), major depressive disorders, bipolar disorder, anorexia, and alcohol addiction, is also being investigated. Ablative procedures are irreversible and, though they have been refined, remain controversial treatments for intractable illness. Interest has shifted

to neuromodulation through DBS of nodes or targets within neural circuits involved in these disorders. Currently, a variety of target areas are being studied.

## REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) has approved the Activa® Tremor Control System (Medtronic Corp.) for deep brain stimulation. The Activa® Tremor Control System and the Activa® Dystonia Therapy System consist of the following components:

1. The implantable pulse generator
2. The deep brain stimulator lead
3. An extension that connects the lead to the power source
4. A console programmer
5. A software cartridge to set electrical parameters for simulation
6. A patient control magnet, which allows the patient to turn the pulse generator on and off or change between high and low settings

In February 2009, the FDA approved deep brain stimulation with the Reclaim device (Medtronic, Inc.) via the Humanitarian Device Exemption (HDE) process for the treatment of severe obsessive-compulsive disorder (OCD).

In June 2015, the FDA approved deep brain stimulation with the Brio Neurostimulation System, (St. Jude Medical) under the Premarket Approval Application (PMA) process (#P140009) for the following conditions:<sup>[1]</sup>

- Bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive therapy to reduce some of the symptoms of advanced levodopa-responsive Parkinson's disease that are not adequately controlled by medications.
- Unilateral or bilateral stimulation of the ventral intermediate nucleus (VIM) of the thalamus for the suppression of disabling upper extremity tremor in adult essential tremor patients whose tremor is not adequately controlled by medications and where the tremor constitutes a significant functional disability.

In September 2016, the FDA approved the St. Jude Medical Infinity™ Deep Brain Stimulation (DBS) system under the PMA process (#P140009/S001) for the same indications above. The directional leads enable the clinician to “steer” current to different parts of the brain. This tailored treatment reduces side effects. The Infinity system can be linked to Apple's iPod Touch and iPad Mini.

In December 2017, a second system with directional leads, the Vercise Deep Brain Stimulation System (Boston Scientific), was approved by FDA. This system is to be used as an adjunctive therapy from reducing motor symptoms of moderate-to-advanced levodopa-responsive PD inadequately controlled with medication alone.

In 2018, the FDA approved the Medtronic DBS System for Epilepsy (Medtronic, Inc) through the Premarket Approval (PMA) process. The pivotal study was the SANTÉ (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) study. The intended use is bilateral stimulation of the anterior nucleus of the thalamus as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by

partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

## EVIDENCE SUMMARY

The principal outcome for deep brain stimulation (DBS) for any indication is symptom reduction and improved function. Assessment of the safety and efficacy of DBS requires well-designed and well-executed randomized controlled trials (RCTs) comparing DBS with sham or on-versus off- phases to determine the following:

- whether the benefits of DBS outweigh any risks
- whether DBS offers advantages over conventional treatments.

The evidence base is sufficient that deep brain stimulation (DBS) improves the net health outcomes of selected patients with symptoms related to Parkinson's disease, essential tremor, or primary dystonias. DBS has become a standard of care for these patients and may be considered medically necessary when criteria are met. Therefore, the evidence for DBS for these indications will not be reviewed in this policy. Below is a brief synopsis of the evidence for Parkinson's disease, essential tremor, or primary dystonias.

### SYMPTOMS ASSOCIATED WITH PARKINSON'S DISEASE

#### Systematic Reviews and Technology Assessments

The policy for PD and tremor was initially based on two BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessments; a 1997 TEC Assessment focused on unilateral deep brain stimulation of the thalamus as a treatment for tremor<sup>[2]</sup> and a 2001 TEC Assessment focused on the use of deep brain stimulation of the globus pallidus and subthalamic nucleus for a broader range of Parkinson symptoms.<sup>[3]</sup>

A number of large systematic reviews have been published on the use of DBS for PD and tremor<sup>[4-14]</sup> confirming the efficacy of DBS in the control of motor signs and improvement of patients' functionality and quality of life.

#### Randomized Controlled Trials

There have been additional published RCTs of deep brain stimulation for PD, which continue to report overall positive results <sup>[15-23]</sup>. Some of these trials suggest that subthalamic stimulation was superior to medical therapy in patients with Parkinson's disease and early motor complications, while others did not find significant differences in overall health outcomes for patients. Surgery related adverse effects addressed in these RCTs indicate that the most common adverse effect is infection.

#### Nonrandomized Studies

Two new DBS systems with directional leads are currently available (approved by the Food and Drug Administration [FDA] in 2016 and 2017). Directional leads potentially enable clinicians to target more specific areas of the brain to be treated with the direct current. Published evidence consists of several small observational studies, with sample sizes ranging from 7 to 13.<sup>[24-27]</sup> The studies showed that patients experienced improved tremor scores and improved quality of life (QOL). Compared with historical data from conventional DBS systems, directional DBS widened the therapeutic window and achieved beneficial effects using lower

current level. Comparative, larger studies are needed to support the conclusions from these small studies. Data from a large study of 292 patients are expected in 2018.

## PRIMARY DYSTONIA

DBS for the treatment of primary dystonia received FDA approval through the Humanitarian Device Exemption (HDE) process.<sup>[28]</sup> The HDE approval process is available for those conditions that affect less than 4,000 Americans per year. According to this approval process, the manufacturer is not required to provide definitive evidence of efficacy, but only probable benefit. As noted in the FDA's analysis of risk and probable benefit, the only other treatment options for chronic refractory primary dystonias are neurodestructive procedures. DBS provides a reversible alternative. The FDA summary of Safety and Probable Benefit states, "Although there are a number of serious adverse events experienced by patients treated with deep brain stimulation, in the absence of therapy, chronic intractable dystonia can be very disabling and in some cases, progress to a life-threatening stage or constitute a major fixed handicap. When the age of onset of dystonia occurs prior to the individual reaching their full adult size, the disease not only can affect normal psychological development but also cause irreparable damage to the skeletal system. As the body of the individual is contorted by the disease, the skeleton may be placed under constant severe stresses that may cause permanent disfigurement. Risks associated with DBS for dystonia appear to be similar to the risk associated with the performance of stereotactic surgery and the implantation of DBS systems for currently approved indications Parkinson's Disease and Essential Tremor), except when used in either child or adolescent patient groups."

The FDA HDE approval was based on the results of DBS in 201 patients represented in 34 manuscripts. There were three studies that reported at least ten cases. Clinical improvement ranged from 50 to 88%. A total of twenty-one pediatric patients were studied; 81% were older than seven years. Among these patients there was approximately a 60% improvement in clinical scores.

Since the FDA approval, there have been additional published randomized controlled trials of deep brain stimulation for dystonia, which continue to report positive results.<sup>[29-31]</sup> These trials included one with a long-term follow-up of five years. Two of the trials reported on the serious adverse effects of DBS, the majority of which were related to the implantation procedure. Dysarthria, involuntary movements and depression were common non-serious adverse events reported.<sup>[32]</sup>

In 2017, Moro published a systematic review of literature published through November 2015 on primary dystonia (also known as isolated dystonia).<sup>[33]</sup> Reviewers included studies with at least 10 cases. Fifty-eight articles corresponding to 54 unique studies were identified; most involved bilateral DBS of the GPi. There were only two controlled studies, one RCT (described below) and 1 study that included a double-blind evaluation with and without stimulation. Twenty-four studies reported data using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and were included in a meta-analysis. These studies enrolled a total of 523 patients (mean per study, 22 patients) and had a mean follow-up of 32.3 months (range, 6 to 72 months). In a pooled analysis of BFMDRS motor scores (scale range, 0 to 120) from 24 studies, the mean increase in scores at six months compared with baseline was 23.8 points (95% CI, 18.5 to 29.1 points). The mean increase in the motor score at last follow-up compared with baseline was 26.6 points (95% CI, 22.4 to 30.9 points). The mean percentage improvement was 59% at six months and 65% at last follow-up. Fourteen studies reported

BFMDRS disability scores (scale range, 0 to 30). Compared with baseline, the mean absolute change in the score was 4.8 points (95% CI, 3.1 to 6.6 points) at six months and 6.4 points (95% CI, 5.0 to 7.8 points) at last follow-up. The mean percentage improvement was 44% at six months and 59% at last follow-up. Rodrigues (2019) performed a Cochrane systematic review of RCTs and identified the same two RCTs.<sup>[32]</sup>

The remaining literature review below will focus on the use of DBS for the investigational indications in this policy.

## **TARDIVE DYSKINESIA AND TARDIVE DYSTONIA**

### **Systematic Review**

Tardive dyskinesia and dystonia (TDD) are severe side effects of dopamine-blocking agents, particularly antipsychotics. Little is known about the possible psychiatric complications of DBS in psychiatric patients. The mean improvement of TDD of the combined patients 3 to 76 months after implantation was 77.5% (95% CI, 71.4%-83.3%;  $p < 0.000$ ) on the Burke-Fahn-Marsden Dystonia Rating Scale.<sup>[34]</sup> The data suggest DBS could be effective and relatively safe for patients with treatment-resistant TDD; however, these results should be interpreted with caution, as most of the data are from case reports and small trials.

Mentzel performed a systematic review to assess the effects and side-effects of deep brain stimulation (DBS) in patients that have developed a severe debilitating treatment-resistant form of TDD.<sup>[35]</sup> This review included 19 case-reports and small-scale trials without randomization or blinding ( $n = 52$  patients). Using the Burke Fahn Marsden Dystonia Rating Scale (BFMDRS), the Abnormal Involuntary Movement Scale (AIMS) and the Extrapyrimal Symptoms Rating Scale (ESRS), the investigators assessed the average improvement in the patients' condition, reporting that improvement as a result of DBS was statistically significant ( $p < 0.00001$ ) on all scales. However, limited conclusions can be drawn from this review on the efficacy and safety of DBS in this population, since there were no randomized controlled trials identified.

### **Randomized Controlled Trials**

Stimulation of the globus pallidus has been examined as a treatment of tardive dyskinesia in a phase II double-blinded (presence and absence of stimulation) multicenter study.<sup>[36]</sup> The trial was stopped early due to successful treatment (greater than 40% improvement) in the first 10 patients.

Gruber (2018) assessed dystonia/dyskinesia severity using the Burke-Fahn- Marsden-Dystonia-Rating-Scale, BFMDRS at three months between active versus sham DBS.<sup>[37]</sup> Twenty-five patients were randomized. In the intention-to-treat analyses, the between group difference of dystonia severity was not significant at three months. Adverse events occurred in 10 of the 25 patients; three of the adverse events were serious. The study was originally powered to include 48 patients but only 25 were randomized and analyses may be underpowered.

### **Nonrandomized Studies**

Pouclet-Courtemanche (2016) reported on a case series of 19 patients with severe pharmaco-resistant tardive dyskinesia treated with DBS.<sup>[38]</sup> Patients were assessed after 3, 6, and 12 months after bilateral globus pallidus stimulation. At six months, all patients had experienced greater than 40% reduction in symptoms as measured on the Extrapyrimal Symptoms

Rating Scale (ESRS). At 12 months, the mean decrease in ESRS score was 58% (range, 21%-81%). An additional small (n=9) case series reported improvement in motor and disability scores.<sup>[39]</sup>

## **CEREBRAL PALSY**

Koy (2013) reported data on the therapeutic outcomes of DBS in cerebral palsy.<sup>[40]</sup> Twenty articles comprising 68 patients with cerebral palsy undergoing deep brain stimulation assessed by the Burke-Fahn-Marsden Dystonia Rating Scale were identified. Most articles were case reports reflecting great variability in the score and duration of follow-up. The mean Burke-Fahn-Marsden Dystonia Rating Scale movement score was  $64.94 \pm 25.40$  preoperatively and dropped to  $50.5 \pm 26.77$  postoperatively, with a mean improvement of 23.6% ( $p < 0.001$ ) at a median follow-up of 12 months. The mean Burke-Fahn-Marsden Dystonia Rating Scale disability score was  $18.54 \pm 6.15$  preoperatively and  $16.83 \pm 6.42$  postoperatively, with a mean improvement of 9.2% ( $p < 0.001$ ). There was a significant negative correlation between severity of dystonia and clinical outcome ( $p < 0.05$ ). Authors suggest DBS can be an effective treatment option for dyskinetic cerebral palsy. In view of the heterogeneous data, a prospective study with a large cohort of patients in a standardized setting with a multidisciplinary approach would be helpful in further evaluating the role of deep brain stimulation in cerebral palsy.<sup>[41]</sup>

## **EPILEPSY/INTRACTABLE SEIZURES**

DBS has been investigated for the treatment of intractable seizures in patients who are not surgical candidates. To date studies show promise but these early reports of therapeutic success are not confirmed by controlled clinical trials. Questions regarding the best structures to stimulate, the most effective stimuli, and the contrasting effects of high-frequency and low-frequency stimulation remain unanswered.

### **Systematic Review**

Two systematic reviews published in 2018 on the use of DBS for drug-resistant epilepsy assessed many of the same studies. The larger review, by Li (2018), identified 10 RCTs and 48 uncontrolled studies.<sup>[42]</sup> The literature search date was not reported. Meta-analyses were not performed. Summaries of the studies were discussed by area of the brain targeted by DBS. A review of the studies showed that DBS might be effective in reducing seizures when DBS targets the anterior nucleus of the thalamus or the hippocampus. Across studies, more than 70% of patients experienced a reduction in seizures by 50% or more. However, there were very few RCTs and the observational studies had small sample sizes. Individual responses varied, depending on seizure syndrome, presence or absence of structural abnormalities, and electrode position. Results were inconclusive when DBS targeted the centromedian nucleus of the thalamus, the cerebellum, and the subthalamic nuclei. Safety data on DBS was limited due to the small population sizes. The RCT in which DBS targeted the anterior nucleus of the thalamus (Fisher [2010] described below) reported paresthesias (23%), implant site pain (21%), and implant site infection (13%). Reviewers concluded that more robust clinical trials would be needed.

In a 2014 Cochrane review, updated in 2017, the safety, efficacy and tolerability of DBS and cortical stimulation were assessed in patients with refractory epilepsy.<sup>[43,44]</sup> The reviews included RCTs comparing DPS to sham stimulation, resective surgery or further treatment with antiepileptic drugs. Of the 10 RCTs identified for inclusion in the 2014 review, three trials were specific to DBS (one anterior thalamic DBS trial, n=109 treatment periods; two centromedian

thalamic DBS trials, n=20, 40 treatment periods). The studies added in the 2017 update were a cross-over RCT of bilateral anterior thalamic stimulation (n=4) and a double blind RCT of hippocampal stimulation (n=6) that was not included in the meta-analysis due to missing detailed methodology. The primary outcome measures included the proportion of patients who were disease free and a 50% or greater reduction in seizure frequency after one to three months. The evidence was rated as moderate quality and no statistical or clinically significant differences were reported based upon the primary outcome measures. Authors concluded that there is insufficient evidence upon which to draw conclusions regarding the efficacy and safety of hippocampal DBS or centromedian DBS as a treatment for epilepsy.

## Randomized Controlled Trials

Fisher (2010) reported results of a multicenter, RCT of bilateral stimulation of the anterior nuclei of the thalamus for epilepsy (SANTE).<sup>[45]</sup> Fisher randomized patients who had failed at least three antiepileptic drugs to one of two groups, stimulation on or stimulation off. This was a 3-month double blind phase. After this phase, all patients received unblinded stimulation. During the first and second months of the blinded phase, the difference in seizure reduction between stimulation on and stimulation off was not significantly different (-42.1% vs. -28.7%, respectively). In the last month of the blinded phase, the stimulated group had a significantly greater reduction in seizures compared with the control group (-40.4% vs. -14.5%, respectively p=0.0017). During the blinded phase, the stimulation group experienced significantly fewer seizure-related injuries than patients in the control group (7.4% vs. 25.5%, respectively p=0.01). Cognition and mood showed no group differences, but participants in the stimulated group were more likely to report depression (8 vs. 1, respectively) or memory problems (7 vs. 1, respectively) as adverse events. Depression symptoms resolved in four of the eight stimulated patients over an average of 76 days (range 14-145). There was a progressive reduction in seizure frequency over long-term follow-up. On intention-to-treat analysis, the median change in seizure frequency was -44% at 13 months and -57% at 25 months. By two years, 54% of patients had a seizure reduction of at least 50%, and 14 patients (13%) were seizure-free for at least six months. The most common device-related adverse events were paresthesias in 18.2% of participants, implant site pain in 10.9%, and implant site infection in 9.1%. Eighteen participants (16.4%) withdrew from the study after the implantation because of adverse events. There were five deaths, none of which were considered to be device-related. Although some patients appeared to have benefited from treatment during the extended follow-up phase, the difference between groups in the blinded portion of the study, while significant, was modest.

Troster (2017) assessed neuropsychological adverse events from the SANTE trial during the three-month blinded phase, and at seven-year follow-up during the open-label noncomparative phase.<sup>[46]</sup> At baseline, there were no differences in depression history between groups. During the three-month blinded phase of the trial, depression was reported in eight (15%) patients from the stimulation group and in one (2%) patient from the no stimulation group (p=0.02). Memory adverse events also occurred at significantly different rates between the treatment groups during the blinded phase (seven in the active group, one in the control group; p=0.03). At seven-year follow-up, after the treatment groups had been combined, there was no statistically significant difference in Profile of Mood State depression score compared with baseline and most cognitive function tests did not improve over baseline measurements.

A seven-year follow-up of SANTE was reported in the FDA SSED.<sup>[47]</sup> Seventy-three (66% of implanted) patients completed the year seven visit. Reasons for withdrawals from the study

after implantation were: death (6), withdrawal of consent (5), investigator decision (3), therapeutic product ineffective (13), implant site infection or pain (6), other adverse event (7) and elective device removal (1). Fifty patients were included in the year 7 analysis of responder rate. Seventy-four percent of the 50 patients were responders (50% or greater reduction in seizure frequency). QOLIE-31 scores (n=67) improved by a mean of 4.9 (SD=11) points at year 7. LSSS scores (n=67) improved by a mean of 18 points (SD=23) at year 7. As the FDA documentation notes, interpretation of the long-term follow-up is limited by several factors: patients were aware they were receiving DBS, only 66% of implanted patients completed the year 7 visit and those who did not do well may be more likely to leave the study, and changes in anti-epileptic drugs were allowed in long-term follow-up.

Cukiert (2017) conducted a double-blind, placebo-controlled randomized trial evaluating outcomes of hippocampal stimulation in 16 patients with refractory temporal lobe epilepsy.<sup>[48]</sup> Prior to treatment, all patients had focal impaired awareness seizures (FIAS, complex partial seizures), and 87% had focal aware seizures (FAS, simple partial seizures). All patients underwent DBS device implantation, and were followed for six months. Patients were seen weekly to receive the treatment or placebo. To maintain double-blind status, programming was performed by a nontreating assistant. Patients kept a seizure diary during the study period. Patients were considered seizure-free if no seizures occurred during the last 2 months of the trial. Responders were defined as patients experiencing a reduction of 50% or more in frequency reduction. There was a significant difference in FIAS frequency from the first month of full stimulation until the end of the blinded phase ( $p < 0.001$ ) and FAS frequency for the same period except for the third month of the blinded phase.

## Nonrandomized Studies

Kim (2017) conducted a retrospective chart review of 29 patients with refractory epilepsy treated with DBS.<sup>[49]</sup> Patients' mean age was 31 years, they had had epilepsy for a mean of 19 years, and had a mean preoperative frequency of tonic-clonic seizures of 27 per month. Mean follow-up was 6.3 years. Median seizure reduction from baseline was 71% at year one, 74% at year two and ranged from 62% to 80% through 11 years of follow-up. Complications included one symptomatic intracranial hemorrhage, one infection requiring removal and reimplantation, and two lead disconnections.

Long-term outcomes of the SANTE trial, described above, were reported by Salanova in 2015.<sup>[50]</sup> The uncontrolled open-label portion of the trial began after three months and, beginning at 13 months, stimulation parameters could be adjusted at the clinician's discretion. Of the 110 implanted patients, 105 (95%) completed the 13-month follow-up, 98 (89%) completed the three-year follow-up, and 83 (75%) completed five years. Among patients with at least 70 days of diary entries, the median change in seizure frequency from baseline was 41% at one year and 69% at five years ( $p < 0.001$  for both). During the study, 39 (35%) of 110 patients had a device-related serious adverse event, most of which occurred in the first several months after implantation. The most frequently reported serious adverse events were implant site infection (10% of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the study and none were considered to be device-related. Depression was reported in 41 (37%) patients over the study; in three cases, this was considered device-related. Memory impairment (nonserious) was reported in 30 (27%) patients during the study, half of which had a history of the condition. Although some patients appear to have benefited from treatment during the extended follow-up phase, the difference between groups in the blinded portion of the study, while significant, was overall modest.

## TRAUMATIC BRAIN INJURY

Central thalamic deep brain stimulation (CT-DBS) has been investigated as a therapeutic option to improve behavioral functioning in patients with severe traumatic brain injury (TBI)<sup>[41]</sup>; however, there are no RCTs for this indication.

## NEUROPSYCHIATRIC APPLICATIONS

In addition to the areas of research discussed above, DBS is being investigated for the treatment of Tourette syndrome, depression, addiction, alcohol addiction, anorexia, and obsessive compulsive disorder.<sup>[51]</sup> Evidence remains insufficient to evaluate the efficacy of DBS for these disorders.<sup>[52]</sup>

### Tourette Syndrome

#### Systematic Reviews

Baldermann conducted a systematic review that included 57 studies on DBS for Tourette syndrome, four of which were randomized crossover studies. The studies included a total of 156 cases.<sup>[53]</sup> Twenty-four studies included a single patient each and four had sample sizes of 10 or more (maximum, 18). Half of the patients (n=78) were stimulated in the thalamus and the next most common areas of stimulation were the global pallidus internus anteromedial part (n=44) and postventrolateral part (n=20). Two of the RCTs used thalamic stimulation, one used bilateral globus pallidus stimulation, and one used both. The primary outcome was the Yale Global Tic Severity Scale (YGTSS). In a pooled analysis of within subject pre-post data, there was a median improvement of 53% in the YGTSS, a decline from a median score of 83 to 35 at last follow-up. Moreover, 81% of patients showed at least a 25% reduction in the YGTSS and 54% and more than a 50% improvement. In addition, data were pooled from the four crossover RCTs; there were a total of 27 patients receiving DBS and 27 receiving a control intervention. Targets included the thalamus and the globus pallidus. In the pooled analysis, there was a statistically significant between-group difference, favoring DBS (SMD=0.96; 95% CI, 0.36 to 1.56). The authors noted that the effect size of 0.96 is considered to be a large effect.

A 2012 systematic review by Pansaon identified 25 published studies, representing data from 69 patients that reported on the efficacy of DBS in the treatment of Tourette syndrome.<sup>[54]</sup> However, only three studies with methodological quality ratings of fair to poor met the inclusion criteria for evidence-based analysis. The authors recommend that DBS continues to be considered an experimental treatment for severe, medically refractory tics.

#### Randomized Controlled Trials

Kefalopoulou (2015) reported on double-blind crossover trial that included 15 patients with severe medically refractory Tourette syndrome.<sup>[55]</sup> They received surgery for bilateral globus pallidus internus DBS and were randomized to the off-position first or the on-position first for three months followed by the opposite position for the next three months. Fifteen patients underwent surgery 14 were randomized and 13 completed assessments after both on- and off-phases. For the 13 study completers, the mean YGTSS scores were 80.7 (SD=12.0) in the off-stimulation phase and 68.3 (SD=18.6) in the on-stimulation phase. Mean difference in YGTSS scores was 12.4 (95% CI, 0.1 to 24.7) which was statistically significant (p=0.048) after Bonferroni correction. There was no between-group difference in YGTSS scores in patients who were randomized to the on-phase first or second. Three serious adverse events

were reported, two related to surgery and one related to stimulation. The authors noted that the most effective target for DBS in Tourette syndrome patients needs additional study.

Piedad (2012) analyzed patient and target selection for DBS of Tourette syndrome. The majority of clinical trials for DBS in Tourette syndrome have targeted the medial thalamus at the crosspoint of the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus.<sup>[56]</sup> Other targets that have been investigated include the subthalamic nucleus, caudate nucleus, globus pallidus internus, and the anterior limb of the internal capsule and nucleus accumbens. The review found no clear consensus in the literature for the best target or for which patients should be treated. Additional study is needed to clarify these issues.

In 2011, Ackermans reported preliminary results of a double-blind crossover trial of thalamic stimulation in six patients with refractory Tourette syndrome.<sup>[57]</sup> Tic severity during three months of stimulation was significantly lower than during the three months with the stimulator turned off, with a 37% improvement on the Yale Global Tic Severity Scale (mean 25.6 vs. 41.1) and a decrease in tic severity of 49% at one year after surgery compared to preoperative assessments (mean 21.5 vs. 42.2 – both respectively). Secondary outcomes (change in associated behavioral disorder and mood) were not altered by the stimulation. Serious adverse events included one small hemorrhage ventral to the tip of the electrode, one infection of the pulse generator, subjective gaze disturbances, and reduction of energy levels in all patients. The interim analysis led to the termination of the trial. The authors commented that further RCTs on other targets are urgently needed since the search for the optimal one is still ongoing.

## **Depression**

### Systematic Reviews

A variety of target areas are being investigated for use of DBS for treatment-resistant depression (TRD). In a recent systematic review, the literature was identified and reviewed for research findings related to treatment-resistant BD.<sup>[58]</sup> Therapeutic trials for treatment-resistant bipolar mania are uncommon, and provide few promising leads other than the use of clozapine. Far more pressing challenges are the depressive-dysthymic-dysphoric-mixed phases of BD and long-term prophylaxis. Therapeutic trials for treatment-resistant bipolar depression have assessed various pharmacotherapies, behavioral therapies, and more invasive therapies including electroconvulsive therapy (ECT), transcranial magnetic stimulation, and deep brain stimulation—all of which are promising but limited in effectiveness. Most studies identified in the review were small, involved supplementation of typically complex ongoing treatments, varied in controls, randomization, and blinding, usually involved brief follow-up, and lacked replication. Clearer criteria for defining and predicting treatment resistance in BD are needed, as well as improved trial design with better controls, assessment of specific clinical subgroups, and longer follow-up. Due to significant limitations within literature the effectiveness of DBS for bipolar treatment is not known at this time.

### Controlled Trials

Crowell (2019) reported long-term follow-up of a within-subject trial with 28 participants with TRD or bi-polar II disorder who were treated with DBS of the subcallosal cingulate.<sup>[59]</sup> Patients were included who had depression for at least 12 months with non-response to at least three antidepressant medications, a psychotherapy trial, and electroconvulsive therapy (lifetime). Seventeen of the patients had a one-month sham-controlled period and 11 patients had a

one-month open label period before the stimulation was turned on. Eight-year follow-up was available for 14 of the 28 participants. The primary outcome measure was the Illinois Density Index, which assesses the longitudinal area under the curve for behavioral measures; in this study these included response (>50% decrease from baseline) and remission (score <7) on the HAM-D. More than 50% of patients maintained a response and 30% in remission, over the eight years of follow-up. The physician-rated Clinical Global Impressions severity score improved from 6.1 (severely ill) at baseline to less than 3 (mildly ill or better) in this open label trial.

In 2016, a crossover RCT evaluating active and sham phases of DBS stimulation in patients with treatment-resistant depression was published by Bergfeld.<sup>[60]</sup> Twenty-five patients were enrolled. Prior to the randomized phase, all patients received 52 weeks of open-label DBS treatment with optimization of the settings. Optimization ended when patients achieved a stable response of at least four weeks or after the 52-week period ended. At the end of the open-label phase, 10 (40%) patients were classified as responders ( $\geq 50\%$  decrease in the Hamilton Depression Rating Scale [HAM-D] score) and 15 (60%) patients were classified as nonresponders. After the 52 weeks of open-label treatment, patients underwent six weeks of double-blind active and sham stimulation. Sixteen (64%) of 25 enrolled patients participated in the randomized phase (nine responders, seven nonresponders). Nine patients were prematurely crossed over to the other intervention. Among all 16 randomized patients, HAM-D scores were significantly higher at the end of the active stimulation phase (mean HAM-D score, 16.5) than the sham stimulation phase (mean HAM-D score, 23.1;  $p < 0.001$ ). Mean HAM-D scores were similar after active and sham phases in initial nonresponders (19.0 vs 23.0, respectively). Among initial responders, mean HAM-D score was 9.4 after active stimulation and 23 after sham stimulation. Trial limitations include a small number of patients in the randomized phase and potential bias from having an initial year of open-label treatment; patients who had already responded to DBS over a year of treatment were those who were likely to respond to active than sham stimulation in the double-blind randomized phase; findings may not be generalizable to treatment-resistant depressed patients who are DBS-naive.

Dougherty published an industry-sponsored, double-blind RCT evaluating DBS of the ventral capsule/ventral striatum in patients with chronic treatment resistant depression, including 30 patients with a major depressive episode lasting at least two years and inadequate response to at least four trials of antidepressant therapy.<sup>[61]</sup> Participants were randomized to 16 weeks of active ( $n=16$ ) versus sham ( $n=14$ ) DBS, followed by an open-label continuation phase. One patient, who was assigned to active treatment, dropped out of the study during the blinded treatment phase. The primary outcome was clinical response at 16 weeks, defined as 50% or greater improvement from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS). A response was identified in 3 (20%) of 15 patients in the active treatment group and 2 (14%) of 14 patients in the sham control group. The between-group difference in response was not statistically significant ( $p=0.53$ ). During the blinded treatment phase, psychiatric adverse events occurring more frequently in the active treatment group included worsening depression, insomnia, irritability, suicide ideation, hypomania, and mania. Psychiatric adverse events occurring more frequently in the sham control group were early morning awakening and purging. Findings of this study do not support the conclusion that DBS is effective for treating treatment-resistant depression.

## Obsessive-compulsive Disorder

## Systematic Reviews

Vicheva (2020) conducted a systematic review and meta-analysis of the use of DBS for treatment-resistant OCD.<sup>[62]</sup> Eight studies including 80 patients total met inclusion criteria. There was significant heterogeneity across studies. A meta-analysis of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores found a 38.68% pooled mean reduction. There were five severe surgery-related adverse events (intracerebral hemorrhage in three patients and infection in two patients) and eight severe mood-related serious adverse events (one completed suicide, three suicide attempts in two patients, and suicidal thoughts and depression in four). There were additional mild and transient adverse events.

Kisely conducted a systematic review and meta-analyses pooling study findings evaluating DBS for OCD, including only double-blind RCTs of active versus sham DBS.<sup>[63]</sup> Five trials (total N=50 patients) met eligibility criteria and data on 44 patients were available for meta-analysis. Three were parallel group RCTs with or without a crossover phase and two were only crossover trials. The site of stimulation was the anterior limb of the internal capsule (3 studies), the nucleus accumbens (1 study) and the subthalamic nucleus (1 study). Duration of treatment ranged from 2 to 12 weeks. All studies reported scores on the Y-BOCS. This is a 10-item scale in which higher scores reflect more intense symptoms, and a score of 24 or more (of a possible 40) is considered severe illness. Most studies designate a therapeutic response as a Y-BOCS reduction of 35% or more from the pretreatment baseline, with a reduction of 25-35% or more considered a partial response. Only one of the five studies reported proportion of responders Y-BOCS as an outcome measure and that study did not find a statistically significant difference between active and sham stimulation groups. All studies reported the outcome measure, mean reduction in Y-BOCS. When data from the five studies were pooled, there was a statistically significantly greater reduction in the mean Y-BOCS in the active versus sham group (mean difference, -8.49; 95% CI, 12.18 to -4.80). The outcome measure, however, does not allow conclusions on whether the difference between groups is clinically meaningful. Trial authors reported 16 serious adverse events including one cerebral hemorrhage and two infections requiring electrode removal. Additionally, nonserious transient adverse events were reported including 13 reports of hypomania, five of increase in depressive or anxious symptoms and six of headaches.

A 2015 systematic review and meta-analysis by Alonso included studies of any type (including case reports) evaluating DBS for OCD and reporting changes on the Y-BOCS.<sup>[64]</sup> The authors identified 31 studies (total N=116 patients). They did not report study type (ie, controlled vs uncontrolled); however, the meta-analysis was only of patients who received active treatment. Twenty-four (77%) studies included 10 or fewer patients. Most studies (24, including 83 patients) involved DBS of striatal areas including the anterior limb of the interior capsule, the ventral capsule and ventral striatum, the nucleus accumbens or the ventral caudate nucleus. Of the remaining studies, five (27 patients) addressed subthalamic nucleus stimulation and two (6 patients) addressed stimulation of the inferior thalamic peduncle. Data were available from 14 studies (105 patients) on percentage of responders (ie, >35% reduction in posttreatment Y-BOCS scores). Twelve studies provided patient-level data. A pooled analysis yielded a global percentage of responders of 60% (95% CI, 49% to 69%). The most frequent adverse events reported were worsening anxiety (25 patients), disinhibition (23 patients), throbbing or flushing (12 patients) and feeling the extension leads (10 patients). The study reported benefits and risks of DBS stimulation but conclusions cannot be drawn about stimulation to any particular region or about the safety or efficacy of DBS for OCD compared with sham stimulation or an alternative therapy.

In 2014, the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons conducted a systematic review which served as the basis of their evidence-based guideline regarding DBS as a treatment of OCD.<sup>[65]</sup> The group made the following conclusions:

1. There is Level I evidence, based on a single Level I study, for the use of bilateral subthalamic nucleus DBS for the treatment of medically refractory OCD.
2. There is Level II evidence, based on a single Level II study, for the use of bilateral nucleus accumbens DBS for the treatment of medically refractory OCD.
3. There is insufficient evidence to make a recommendation for the use of unilateral DBS for the treatment of medically refractory OCD.

However, the Level I and II evidence used to support the groups conclusions were based upon studies with small sample sizes (n=18, 16) which limit the ability to rule out the possibility of chance as an explanation of findings.

In 2011, de Koning published a systematic review of clinical trials for DBS for treatment resistant obsessive-compulsive disorder (OCD).<sup>[66]</sup> Nine case studies and seven controlled studies with a blinded on-off phase were included. Inclusion criteria were use of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) as an outcome measure, and “some estimate of efficacy” included in the study report. The authors concluded that DBS may be a beneficial and safe therapy for refractory OCD, but further research is needed to establish appropriate patient selection criteria, determine the more effective target location, and optimize postoperative patient management. Of note, the systematic review discussed the reported outcomes of the selected studies, but failed to critically appraise their quality.

Of the studies included in the systematic review:

- Nine case studies consisted of observational case reports of one to two patients, or small (<10 patients) non-comparative case series. Conclusions cannot be reached from these studies as randomized trials with an appropriate comparison group are needed to control for any placebo effect and for potential patient selection and treatment bias. In addition, the lack of blinding of patients and investigators fails to control for the placebo effect and potentially leads to additional bias.
- All seven RCTs included in the systematic review were double-blind crossover studies in which both the patient and the investigators were blinded to whether the DBS was turned on or off.<sup>[67-73]</sup> However, these RCTs are considered unreliable for the following reasons:
  - Small study populations (n= 4 to 16) limit the ability to rule out the role of chance as an explanation of findings
  - Heterogeneity of study participants (e.g., comorbidities) and procedures (e.g., five different brain target areas) limits meaningful comparison of outcomes
  - Inability to isolate the contribution of DBS from the impact of other treatments (e.g., medications) during the study period
  - Short-term follow-up does not permit conclusions related to the durability of any initial beneficial effects

## **Anorexia Nervosa**

Anorexia nervosa is an eating disorder characterized by a chronic course that is refractory to treatment in many patients and has one of the highest mortality rates of any psychiatric

disorder. In a recent systematic review by McClelland et al., two case series and two case reports that applied DBS to anorexic patients were identified and reviewed with mixed results.<sup>[74]</sup> There are no RCTs investigating DBS for this indication.

### **Alcohol Addiction**

Alcohol dependency can be considered as a chronic mental disorder characterized by frequent relapses even when treated with appropriate medical or psychotherapeutic interventions.

A 2012 systematic review by Herremans and Baeken investigated several neuromodulation techniques including deep brain stimulation in the treatment of alcohol addiction.<sup>[75]</sup> Previous studies investigating these neuromodulation techniques in alcohol addiction remain to date rather limited. Overall, the clinical effects on alcohol addiction were modest. Neuromodulation techniques have only recently been subject to investigation in alcohol addiction and methodological differences between the few studies restrict clear conclusions. Nevertheless, the scarce results encourage further investigation in alcohol addiction.

### **OTHER APPLICATIONS**

There is interest in applications of DBS beyond that for essential tremors, primary dystonia and Parkinson's disease. Clinical trials are being pursued; however, at this time, FDA approval is limited to the above indications and severe obsessive-compulsive disorder. The following discussion focuses on randomized controlled trials (RCTs) for the investigational indications noted in Policy Criteria II. above.

### **Chronic Pain, Pain Syndromes, and Cluster Headaches**

DBS for the treatment of chronic pain was investigated and largely abandoned in the 1980's due to poor results in two trials. With improved technology and surgical techniques there has been a resurgence of interest in DBS for intractable pain. DBS of the posterior hypothalamus for the treatment of chronic cluster headaches has also been investigated as functional studies have suggested cluster headaches have a central hypothalamic pathogenesis. Outcomes and treatment protocols have been heterogenous.<sup>[76,77]</sup> Additionally, due to the limited RCTs and small sample sizes, conclusions cannot be reached on the effectiveness of DBS as a treatment of any type of pain, including but not limited to cluster headaches, chronic spinal pain, failed back surgery syndrome, phantom limb pain, facial deafferentation pain, and central or peripheral neuropathic pain.

### **Morbid Obesity**

The study of DBS of the hypothalamus and nucleus accumbens for cluster headache and obsessive-compulsive disorder (OCD) has prompted interest in DBS for obesity and addiction, which are thought to be associated with those brain regions. However, patients with unilateral subthalamic nucleus or globus pallidus internus DBS for PD were found to have gained a mean 4.86 pounds following initiation of DBS.<sup>[78]</sup> There are currently no studies of DBS in any brain region for the treatment of obesity.

### **Multiple Sclerosis**

No randomized controlled trials were found for DBS in the treatment of multiple sclerosis (MS) tremors. Three small nonrandomized comparative trials were found, one<sup>[79]</sup> comparing

stimulation off versus on (n=9), and two<sup>[20,80]</sup> comparing thalamic stimulation versus thalamotomy (n=12 total MS patients). The small study populations do not permit conclusions on efficacy of DBS for MS tremors.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN ACADEMY OF NEUROLOGY

2019 guidelines from AAN provide recommendations on the assessment for and use of deep brain stimulation in adults with severe, treatment-refractory tics.<sup>[81]</sup> AAN notes that patients with severe Tourette syndrome resistant to medical and behavioral therapy may benefit from DBS, but there is no consensus on the optimal brain target. Brain regions that have been stimulated in patients with Tourette Syndrome include the centromedian thalamus, the globus pallidus internus (ventral and dorsal), the globus pallidus externus, the subthalamic nucleus, and the ventral striatum/ventral capsular nucleus accumbens region. AAN concludes that DBS of the anteromedial globus pallidus is possibly more likely than sham stimulation to reduce tic severity.

In the 2013 American Academy of Neurology (AAN) guidelines on the treatment for tardive syndromes (TDS), indicated there is insufficient evidence to support or refute DBS for TDS.<sup>[82]</sup> This recommendation is based on Level U evidence (evidence is insufficient to support or refute the use of any other treatment over another). The 2011 AAN guideline regarding essential tremor was reaffirmed in 2014 indicating that, “no high quality, long-term studies exist regarding the efficacy and safety of (DBS) for ET.”<sup>[83]</sup>

The American Academy of Neurology (AAN) updated its guidelines on the treatment of essential tremor (ET) in 2011.<sup>[83]</sup> This update did not change the conclusions and recommendations of AAN 2005 practice parameters on DBS for ET.<sup>[84]</sup> The guidelines stated that bilateral DBS of the thalamic nucleus may be used to treat medically refractory limb tremor in both upper limbs (level C, possibly effective), but that there were insufficient data on the risk/benefit ratio of bilateral vs unilateral DBS in the treatment of limb tremor. There was insufficient evidence to make recommendations on the use of thalamic DBS for head or voice tremor (level U, treatment is unproven).

The 2010 guidelines from AAN on the treatment of nonmotor symptoms of PD found insufficient evidence for the treatment of urinary incontinence with DBS of the STN.<sup>[85]</sup> AAN found that DBS of the STN possibly improves sleep quality in patients with advanced PD. However, none of the studies performed DBS to treat insomnia as a primary symptom, and DBS of the STN is not currently used to treat sleep disorders.

### AMERICAN PSYCHIATRIC ASSOCIATION

In a 2007 the American Psychiatric Association (APA) published an evidence-based guideline, which was reaffirmed in 2012, on the treatment of patients with obsessive-compulsive disorder.<sup>[86]</sup> The APA gave their lowest level recommendation for DBS, among a list of other therapies with limited published evidence, for OCD that remains refractory “after first- and second-line treatment and well-supported augmentation strategies have been exhausted.” In the 2010 APA guideline for the treatment of major depression, DBS is listed as a search term in the literature review; however, no recommendations for DBS are mentioned.<sup>[87]</sup>

### CONGRESS OF NEUROLOGIC SURGEONS

2018 evidence-based guidelines from the Congress of Neurologic Surgeons (CNS) compared the efficacy of bi-lateral deep brain stimulation of the subthalamic nucleus and globus pallidus internus for the treatment of patients with Parkinson disease.<sup>[88]</sup>

**Table 1. Recommendations of the Congress of Neurologic Surgeons for DBS for Parkinson Disease**

Goal	Most Effective Area of Stimulation (subthalamic nucleus or globus pallidus internus)	Level of Evidence
Improving motor symptoms	subthalamic nucleus or globus pallidus internus are similarly effective	I
Reduction of dopaminergic medication	subthalamic nucleus	I
Treatment of "on" medication dyskinesias	globus pallidus internus if reduction of medication is not anticipated	I
Quality of life	no evidence to recommend one over the other	I
Lessen impact of DBS on cognitive decline	globus pallidus internus	I
Reduce risk of depression	globus pallidus internus	I
Reduce adverse effects	insufficient evidence to recommend one over the other	Insufficient

## SUMMARY

There is enough research to show that deep brain stimulation (DBS) improves health outcomes in select patients with symptoms related to Parkinson's disease, essential tremor, or primary dystonias. DBS has become a standard of care for these patients. Therefore, DBS, including revision(s) or replacement(s), may be considered medically necessary when policy criteria are met.

Deep brain stimulation (DBS) is not clinically appropriate in patients with symptoms related to Parkinson's disease, essential tremor, or primary dystonias when criteria are not met. Therefore, DBS is considered not medically necessary for these indications when criteria are not met.

There is not enough research to determine the safety and effectiveness of deep brain stimulation (DBS) for other conditions. Current practice guidelines do not recommend the use of deep brain stimulation for the treatment of various neurologic and psychiatric disorders. Therefore, DBS is considered investigational for all other indications when policy criteria are not met.

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## CODES

Codes	Number	Description
CPT	61850	Twist or burr hole(s) for implantation of neurostimulator electrode(s), cortical
	61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
	61863	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
	61864	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of

Codes	Number	Description
		intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure).
	61867	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
	61868	Twist drill, burr hole, craniotomy, or craniectomy for stereotactic implantation of neurostimulator array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61886	;with connection to two or more electrode arrays
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulsewidth, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95983	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional
	95984	;with brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure)
HCPCS	C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension

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<b>Codes</b>	<b>Number</b>	<b>Description</b>
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator

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**Date of Origin:** April 1998

## ***Radiofrequency Ablation (RFA) of Tumors Other than Liver***

**Effective:** March 1, 2020

**Next Review:** November 2020

**Last Review:** January 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Radiofrequency ablation kills cells using the heat produced by radiofrequency energy delivered into the tumor via a probe.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy does not address liver tumors (primary or metastatic). See Cross References.

- I. Radiofrequency ablation may be considered **medically necessary** to treat tumors when one or more of the following criteria are met:
  - A. Localized renal cell carcinoma that is no more than 4 cm in size when one or both of the following criteria are met:
    1. Preservation of kidney function is necessary (i.e., the patient has one kidney or renal insufficiency defined by a glomerular filtration rate (GFR) of less than 60 mL/min per m<sup>2</sup>) and standard surgical approach (i.e., resection of renal tissue) is likely to substantially worsen kidney function; or
    2. Patient is not considered a surgical candidate.

- B. Osteoid osteomas that are unresponsive to initial medical treatment.
  - C. To palliate pain in patients with osteolytic bone metastases who have failed or are poor candidates for standard treatments (e.g., radiation).
  - D. Isolated peripheral non-small cell lung cancer (NSCLC) lesion that is no more than 3 cm in size when both of the following criteria are met:
    - 1. Surgical resection or radiation treatment with curative intent is considered appropriate based on stage of disease, however, medical co-morbidity renders the individual unfit for those interventions; and
    - 2. Tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.
  - E. Malignant non-pulmonary tumor(s) metastatic to the lung that are no more than 3 cm in size when all of the following criteria (1. – 3.) are met:
    - 1. In order to preserve lung function when surgical resection or radiation treatment is likely to substantially worsen pulmonary status, or the patient is not considered a surgical candidate; and
    - 2. There is no evidence of extrapulmonary metastases; and
    - 3. The tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.
  - F. Renal angiomyolipomas when one or more of the following criteria are met:
    - 1. Symptomatic lesion (e.g., hemorrhage), or
    - 2. Asymptomatic lesion larger than 4 cm.
- II. Radiofrequency ablation is considered **investigational** as a technique for ablating all other benign or malignant tumors other than liver tumors that do not meet the policy criteria above including but not limited to breast tumors, initial treatment of osteoid osteomas and painful bony metastases, and all primary or metastatic lung (pulmonary) tumors that do not meet medical necessity.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION

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

1. Specific description of the tumor(s) targeted for treatment including the following:
  - Tumor type (primary vs. metastatic; primary tumor type)
  - The location of tumor(s)
  - The number and size(s) of lesion(s) being treated
2. Rationale for the determination that the patient is not a surgical candidate or the tumor is unresectable

3. Whether the goal of treatment is curative or palliative
4. Comorbidities and any contraindicated treatments (e.g., surgery; radiation therapy)
5. Prior treatments, if any, and tumor response
6. Documentation of whether this treatment is to preserve organ function

## CROSS REFERENCES

1. [Radioembolization, Transarterial Embolization \(TAE\), and Transarterial Chemoembolization \(TACE\)](#), Medicine, Policy No. 140
2. [Cryosurgical Ablation of Miscellaneous Solid Tumors](#), Surgery, Policy No. 132
3. [Magnetic Resonance \(MR\) Guided Focused Ultrasound \(MRgFUS\) and High Intensity Focused Ultrasound \(HIFU\) Ablation](#), Surgery, Policy No. 139
4. [Microwave Tumor Ablation](#), Surgery, Policy No. 189
5. [Ablation of Primary and Metastatic Liver Tumors](#), Surgery, Policy No. 204

## BACKGROUND

Radiofrequency ablation (RFA) was initially developed to treat inoperable tumors of the liver (see Cross References). Recently, studies have reported on the use of RFA to treat other tumors. For some of these, RFA is being investigated as an alternative to surgery for operable tumors. Well-established local or systemic treatment alternatives are available for each of these malignancies. The hypothesized advantages of RFA for these cancers include improved local control and those common to any minimally invasive procedure (eg, preserving normal organ tissue, decreasing morbidity, decreasing length of hospitalization).

Goals of RFA may include 1) controlling local tumor growth and preventing recurrence; 2) palliating symptoms; and 3) extending survival duration for patients with certain cancerous tumors. The effective volume of RFA depends on the frequency and duration of applied current, local tissue characteristics, and probe configuration (eg, single vs multiple tips). RFA can be performed as an open surgical procedure, laparoscopically or percutaneously, with ultrasound or computed tomography guidance.

Potential complications associated with RFA include those caused by heat damage to normal tissue adjacent to the tumor (e.g., intestinal damage during RFA of kidney), structural damage along the probe track (e.g., pneumothorax as a consequence of procedures on the lung), and secondary tumors (if cells seed during probe removal).

## REGULATORY ISSUES

The U.S. Food and Drug Administration (FDA) issued the following statement September 24, 2008 concerning the regulatory status of radiofrequency ablation.<sup>[1]</sup> “The FDA has cleared RF ablation devices for the general indication of soft tissue cutting, coagulation, and ablation by thermal coagulation necrosis. Some RF ablation devices have been cleared for additional specific treatment indications, including partial or complete ablation of nonresectable liver lesions and palliation of pain associated with metastatic lesions involving bone. The FDA has not cleared any RF ablation devices for the specific treatment indication of partial or complete ablation of lung tumors, citing lack of sufficient clinical data to establish safety and effectiveness for this purpose. The FDA has received reports of death and serious injuries associated with the use of RF ablation devices in the treatment of lung tumors.”

## EVIDENCE SUMMARY

## RENAL CELL CARCINOMA

### BACKGROUND

Radical nephrectomy, partial nephrectomy, or nephron-sparing surgery remains the principal treatments of renal cell carcinoma (RCC).

RFA may be considered a treatment option when surgical excision is not an option such as the following:

- When preservation of renal function is necessary (e.g., in patients with marginal renal function, a solitary kidney, bilateral tumors)
- In patients with comorbidities that would render them unfit for surgery.
- In patients at high risk of developing additional renal cancers (as in von Hippel-Lindau disease).

### SYSTEMATIC REVIEWS

In their systematic review and meta-analysis, Uhlig (2019) compared oncologic, perioperative, and functional outcomes for partial nephrectomy (PN) with outcomes for various ablative techniques, including RFA and others, for small renal masses (mean diameter=2.53-2.84 cm).<sup>[2]</sup> They identified 47 moderate-quality studies, mostly retrospective, published from 2005-2017, including one RCT. A total of 24,077 patients were included, of whom 15,238 received PN and 1,877 received RFA. The network meta-analysis used PN as the reference point. Cancer-specific mortality and local recurrence were calculated as incidence rate ratio. According to the meta-analysis, for RFA and PN, respectively, cancer-specific mortality was 2.03 and 1.00 (95% CI 0.81 to 5.08), local recurrence was 1.79 and 1.00 (95% CI 1.16 to 2.76), complications OR was 0.89 and 1.00 (95% CI 0.59 to 1.33), and renal function decline (mean difference in glomerular filtration rate) was 6.49 and 0.00 (95% CI 2.87 to 10.10). The overall results indicated that PN had better overall survival (OS) and local control over ablative techniques, but it was not significantly better for cancer-related mortality. In addition, ablation had fewer complications and better renal function outcomes. Across the studies included, patients treated by PN tended to be younger with less comorbidity compared with patients receiving thermal ablation—a consideration when assessing the outcomes for survival and local control.

A 2019 systematic review reported by Favi included a descriptive summary of ablative therapy for renal allograft tumors.<sup>[3]</sup> The 28 studies that met inclusion criteria assessed RFA (n=78), cryoablation (n=15), MWA (n=3), HIFU (n=3), and irreversible electroporation (n=1) for mainly papillary renal cell carcinoma (RCC) and clear cell RCC. All but two neoplasms were stage T1a N0 M0. In this population, three cases of primary treatment failure, a single case of recurrence, and no cancer-related deaths were reported. Complication rate was mostly below 10% and graft function remained stable in the majority of patients. No meta-analyses were performed and due to the limited sample size the authors were not able to determine a clear benefit of one procedure over the others.

An AHRQ Evidence Report, most recently amended in 2016, included thermal ablation (RFA or cryoablation; surgical or image-guided) as an available management strategies for stage I or II RCC.<sup>[4]</sup> The report noted that better oncologic outcomes were believed to be achieved with

partial or radical nephrectomy; however, these procedures were associated with significantly higher complication rates than thermal ablation or active surveillance.

In 2014 Wang published a meta-analysis of 145 studies published through July 2013 comparing effectiveness and complications of radiofrequency ablation and partial nephrectomy (PN) for treatment of stage T1 renal tumors.<sup>[5]</sup> The rate of local progression was greater with RFA than laparoscopic/robotic or open partial nephrectomy (4.6%, 1.2%, 1.9%, respectively;  $p < 0.001$ .) RFA had more frequent minor complications than laparoscopic/robotic or open partial nephrectomy (13.8%, 7.5%, 9.5%, respectively;  $p < 0.001$ ). However, the rate of major complications was greater with open partial nephrectomy than laparoscopic/robotic partial nephrectomy or RFA (7.9%, 7.9%, 3.1%, respectively,  $p < 0.001$ ). Several limitations to this meta-analysis were discussed in the article. These included the limited follow-up duration of the included studies and the unavailability of the original study data. Despite the limitations, the data was sufficient for the authors to conclude that both RFA and PN were viable in terms of short-term outcomes and low complication rates. RFA showed a higher risk of local tumor progression but lower complication rates.

## **RANDOMIZED CONTROLLED TRIALS**

Since the systematic reviews reported above, no additional randomized controlled trials evaluating RFA as a treatment for renal cell carcinoma were identified.

## **NONRANDOMIZED STUDIES**

Published studies have consistently reported fairly high success rates at up to six years follow-up; two to five re-ablation sessions were often necessary to achieve 95% tumor necrosis.<sup>[6-29]</sup> Numerous case series, while unreliable, consistently suggest that the benefits of RFA outweigh the risks in patients for whom nephrectomy is not possible. Current studies suggest that physician specialty (i.e., interventional radiology, urology) and experience, and procedure approach (i.e., percutaneous, open, laparoscopic) may impact tumor recurrence and patient survival outcomes, and authors have recommended further study on these variables.

## **ADVERSE EVENTS**

Reported complication rates have been low.<sup>[6-28,30]</sup> Complications reported in the literature to date have included the following:

- Perinephric hematomas
- Hemorrhage
- Ureteral strictures
- Percutaneous urinary fistula
- Appendiceal perforation

## **BREAST TUMORS**

### **BACKGROUND**

The standard treatment for breast cancer is surgical excision by lumpectomy or mastectomy. Adjuvant radiation therapy, chemotherapy, and/or hormone therapy may also be used. If treated, fibroadenomas, benign tumors of the breast, are typically surgically excised.

### **SYSTEMATIC REVIEWS**

In 2016, Chen reported results from a meta-analysis of clinical trials assessing the effect of radiofrequency ablation for breast cancer.<sup>[31]</sup> The authors pooled data from fifteen nonrandomized studies that were published between 2001 and 2012. Of the 15 studies, eight studies reported that the tumor size was <2 cm, five studies reported <3 cm, and the remaining two studies reported <5 cm; eleven studies reported complete ablation rate, from which pooled estimates were 89% (95% CI: 85-93%) of patients receiving RFA achieved a complete ablation. Five studies reported recurrence rate, from which pooled data suggest no local recurrence at a maximum follow-up of 76 months. A statistical test of publication bias showed no potential publication bias ( $Z=0.78$ ,  $p=0.436$ ). The analyses were limited by small sample size of the included studies, and heterogeneity in patient selection; the authors conclude large, well-designed studies are necessary.

In 2010, Zhao conducted a systematic review of 38 studies on ablation techniques for breast cancer treatment published from 1994 to 2009.<sup>[32]</sup> Nine of the studies reviewed focused on RFA for small breast tumors ranging in size from 0.5 – 7 cm. Tumor resection was performed immediately after ablation or up to four weeks after RFA. Complete coagulation necrosis rates of 76% to 100% were reported. These studies were limited to feasibility or pilot studies that were difficult to compare due to heterogeneous patient and tumor characteristics and energy sources. In addition, the studies were conducted in the research setting rather than in clinical practice. The authors concluded that RFA for breast cancer tumors was feasible but further studies with longer follow-up on survival, tumor recurrence and cosmetic outcomes are needed.

Similarly, another 2010 review of 17 studies by Soukup reported that RFA for the treatment of breast tumors was feasible and promising.<sup>[33]</sup> However, while minimal adverse effects and complications occurred with breast RFA, the authors noted that incomplete tumor ablation remained a concern. Additional studies of health outcomes and refinement of the procedure were recommended.

## **RANDOMIZED CONTROLLED TRIALS**

No randomized controlled trials of RFA as a treatment for breast tumors were identified.

## **NONRANDOMIZED STUDIES**

Current published evidence is limited to preliminary nonrandomized pilot and feasibility studies with small numbers of patients.<sup>[34-48]</sup> These studies preclude conclusions due to methodologic limitations such as non-random allocation of treatment and a lack of appropriate comparison groups.

The bulk of the published studies measured secondary outcomes such as tissue analysis for viable cancer cells less than one month following RFA. No long-term follow-up data has been reported on local control and survival rates for RFA of breast cancer compared with conventional breast-conserving treatment. Small study populations limit the ability to rule out the role of chance as an explanation of study findings. The heterogeneity of the patient selection criteria between studies limits meaningful comparison of outcomes. The role of various patient characteristics (e.g., tumor size and location; number of tumors) cannot be ruled out as an explanation for study findings.

## **LUNG (PULMONARY) TUMORS**

## BACKGROUND

Surgery is the preferred treatment for primary non-small cell lung carcinoma (NSCLC). Patients with early stage NSCLC who are not surgical candidates may be candidates for radiation treatment with curative intent. RFA is being investigated as a treatment of small primary lung cancers or lung metastases in patients who are not surgical candidates.

## SYSTEMATIC REVIEWS

In a 2013 Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review on local nonsurgical therapies for stage I non–small-cell lung cancer (NSCLC), no comparative RFA studies were identified.<sup>[49]</sup> The AHRQ report found available evidence is insufficient to draw conclusions on the comparative effectiveness of local nonsurgical therapies for NSCLC including RFA.

In a 2013 systematic review of RFA, surgical excision and stereotactic radiotherapy (SBRT) for colorectal cancer lung metastases, no randomized trials were identified and evidence was also insufficient to draw conclusions on the comparative effectiveness of these therapies.<sup>[50]</sup>

A 2011 systematic review also reported low quality evidence consisting of nonrandomized observational case series with no control group. The review included 46 studies with a total of 2,905 ablations in 1,584 patients.<sup>[51]</sup> The mean tumor size of  $2.8 \pm 1.0$  cm. Local recurrence occurred in 282 cases (12.2%) and ranged from 0% to 64% as reported in 24 studies. Overall survival rates ranged from 25% to 100% with a mean of 59.4% as reported in 21 studies with a mean of  $17.7 \pm 12.4$  months follow-up. The mean cancer-specific survival rate was 82.6% as reported in 24 studies with a range of 55% to 100% with a mean of  $17.4 \pm 14.1$  months follow-up. Mean overall morbidity was 24.6% and most commonly included pneumothorax, pleural effusion and pain. Mortality related to the RFA procedure was 0.21% overall. The authors concluded RFA for the treatment of lung tumors demonstrated promise but that higher quality studies comparing RFA to other local treatment options “are urgently needed.”

In a 2012 review of evidence from 16 studies, Bilal compared RFA to stereotactic ablative radiotherapy (SABR) in patients with inoperable early stage non-small cell lung cancer (NSCLC).<sup>[52]</sup> The authors found overall survival rates for RFA and SABR were similar in patients at one year (68.2–95% vs. 81–85.7%) and three years (36–87.5% vs. 42.7–56%). However, survival rates at five years were lower with RFA (20.1–27%) than with SABR (47%). Caution must be used in interpreting these findings drawn from comparisons of results from uncontrolled, case series and retrospective reviews.

## RANDOMIZED CONTROLLED TRIALS

No randomized controlled trials of RFA as a treatment for pulmonary tumors were identified.

## NONRANDOMIZED STUDIES

Current studies consist of small case series, retrospective reviews, or uncontrolled cohort studies which focused primarily on technical feasibility and initial tumor response.<sup>[53-85]</sup>

One larger nonrandomized case series was published in 2011. Huang prospectively followed 329 consecutive patients treated with RFA for lung tumors.<sup>[86]</sup> Complications were experienced by 34.3% (113) patients and was most commonly pneumothorax (19.1%). Overall survival at

two and five years was 35.3% and 20.1%, respectively. The risk of local progression was not significantly different in tumors < 4 cm but became significant in tumors > 4 cm.

In 2015 de Baere review of a database from two cancer centers that included all consecutive patients (N=566) with lung metastases treated with RFA.<sup>[87]</sup> Median follow-up was 35.5 months (range 20-53 months) with 235 patients followed for more than two years. During follow-up, 176 patients died, of which 112 had progression of their lung tumor disease. Disease progression was also found in 227 of the 390 patients who were alive at last follow-up. Four-year local efficacy was 89% and lung disease control was 44.1%. Median overall survival was 62 months. Limitations of this study included the lack of a control group, and the lack of consideration of the impact of adjuvant chemotherapy.

Study quality concerns include lack of long-term follow-up; significant interstudy heterogeneity in terms of study design, patient populations and RFA methods used; and, non-uniformity of reporting and efficacy scoring criteria. These differences limit meaningful comparison between studies because they may significantly impact study findings.

## ADVERSE EVENTS

Acute, delayed or recurrent pneumothorax is the most commonly reported complication of lung RFA for primary or metastatic tumors (30-56% of treatment sessions).<sup>[78,86,88-91]</sup> Most cases resolved without chest tube placement.

Other complications reported in the literature to date are considered uncommon and include the following:<sup>[90-95]</sup>

1. Pleural effusion
2. Intrathoracic hemorrhage with or without hemothorax
3. Hemoptysis
4. Pneumonia
5. Fever
6. Post procedure chest pain
7. Exacerbation of interstitial pneumonia
8. Bronchopleural fistula
9. Seeding of the needle tract with cancer cells
10. Lung inflammation; aseptic pleuritis
11. Infection or abscess
12. Cough
13. Subcutaneous emphysema
14. Pain duration ablation procedure
15. Pleuritic chest pain
16. Pneumonitis
17. Stellate ganglion injury
18. Brachial plexus injury
19. Death

## OSTEIOD OSTEOMAS

### BACKGROUND

Osteomas usually heal spontaneously in three to four years and standard initial treatment includes medical management with NSAIDs. Invasive procedures including open surgery, laser photocoagulation, radiofrequency ablation, or core drill excision may be necessary if symptoms cannot be managed with NSAIDs.

## **SYSTEMATIC REVIEWS**

Lanza (2014) reported on a systematic review of various ablative techniques for osteoid osteomas.<sup>[96]</sup> Included in the review were 23 articles on RFA, three on interstitial laser ablation, and one with a combination of ablation techniques, totaling 27 articles (total N=1772 patients). The mean technical success was 100% and clinical success, defined as being pain-free, ranged from 94% to 98%, depending on the length of follow-up. Complications occurred in 2% of patients and included skin or muscle burn in nine patients, four infections, nerve lesions or tool breakage in three patients each, delayed skin healing, hematoma, and failure to reach target temperature in two patients each, and fracture, pulmonary aspiration, thrombophlebitis, and cardiac arrest in one patient each. Eighty-six patients had tumor recurrence.

## **RANDOMIZED CONTROLLED TRIALS**

No randomized controlled trials of RFA as a treatment for osteoid osteomas were identified.

## **NONRANDOMIZED STUDIES**

Numerous nonrandomized uncontrolled case series have consistently suggested that the benefits of RFA outweigh the risks in patients who require treatment due to failed response to nonsurgical treatments.<sup>[97-104]</sup>

## **SECTION SUMMARY**

Despite the weaknesses in the published clinical evidence, RFA of osteomas has become a standard of care for osteomas that have failed standard treatments. This was based on the lower morbidity and quicker recovery time associated with the procedure compared with open surgery. The risk of osteoma recurrence with RFA is 5–10%; recurrent tumors can be retreated with RFA. There are minimal clinical trial data on the risks and benefits of RFA as initial treatment of osteoid tumors. Since most of these tumors heal spontaneously with medical treatment, the necessity of surgical intervention as initial treatment is unclear.

## **PALLIATION OF PAIN FROM BONE METASTASES**

### **BACKGROUND**

External beam irradiation is often the initial palliative therapy for osteolytic bone metastases. However, pain from bone metastases is refractory to radiation therapy in 20% to 30% of patients, while recurrent pain at previously irradiated sites may be ineligible for additional radiation due to risks of normal tissue damage. Other alternatives include hormonal therapy, radiopharmaceuticals such as strontium-89, and bisphosphonates. Less often, surgery or chemotherapy may be used for palliation and intractable pain may require opioid medications. RFA may be considered another alternative for palliating pain from bone metastases.

### **SYSTEMATIC REVIEWS**

A systematic review reported by Gennaro (2019) assessed four percutaneous thermal ablation techniques for pain reduction in patients with bone metastases.<sup>[105]</sup> A total of eleven studies addressing RFA (n=3), MWA (n=1), cryoablation (n=2), and MRgFUS (n=5) were included (total n=364 patients). Mean pain reduction for all techniques combined ranged from 25 to 91% at four weeks and from 16 to 95% at 12 weeks. There were no complications in the MWA group while the MRgFUS group had the highest complication rate. Overall, the number of minor complications reported ranged from 0 to 59 and the number of significant adverse events ranged from 0 to 4.

Lanza reported on a systematic review of various ablative techniques for osteoid osteomas in 2014.<sup>[96]</sup> Included in the review were 23 articles on RFA, three on interstitial laser ablation, and one with a combination of ablation techniques, totaling 27 articles (total n=1,772 patients). The mean technical success was 100% and clinical success, defined as being pain-free, ranged from 94% to 98%, depending on length of follow-up. Complications occurred in 2% of patients and included skin or muscle burn in nine patients, four infections, nerve lesions or tool breakage in three patients each, delayed skin healing, hematoma, and failure to reach target temperature in two patients each, and fracture, pulmonary aspiration, thrombophlebitis, and cardiac arrest in one patient each. Eighty-six patients had tumor recurrence.

## **RANDOMIZED CONTROLLED TRIALS**

No randomized controlled trials of RFA as a treatment for palliation of pain from bone metastases were identified.

## **NONRANDOMIZED STUDIES**

Current evidence is limited to data from small, poorly designed case series.<sup>[106-110]</sup> However, though small and uncontrolled, available studies consistently reported significant improvement in pain following RFA in patients who failed or were poor candidates for standard treatments. Clinical trial data is lacking for use of RFA as an alternative to conventional techniques for initial treatment of painful bony metastases.

# **ANGIOMYOLIPOMA**

## **BACKGROUND**

Angiomyolipomas (AMLs) or angiomyolipomata are rare benign tumors that contain blood vessels, smooth muscle, and fat. They are usually associated with the kidneys but may also be in the liver or other locations. They are more frequently seen in patients with tuberous sclerosis complex (TSC). These lesions are usually asymptomatic but may hemorrhage, particularly if large (4 cm or larger). Treatment consists of surveillance as long as the lesion remains small and asymptomatic. Treatment or prevention of hemorrhage may include surgical resection, arterial embolization, or laparoscopic or percutaneous ablation.

## **PUBLISHED STUDIES**

Due to the rare nature of these tumors, there is limited published evidence on the tumor management.<sup>[111-116]</sup> The current studies have significant methodological limitations including retrospective records review, small size (n=4-32), heterogeneity of patients and treatment modalities, and short-term follow-up. However, the available studies consistently reported low rates of complications and high rates of successful ablation, generally without recurrence at

mean follow-up ranging between 9 and 45 months. Some larger tumors (>3.5 cm) required two RFA sessions. Minor complications included transient perinephric hematoma, intercostal nerve transection. A patient in one early study developed a small skin metastasis at the electrode insertion site which was resected and did not recur.

## **SECTION SUMMARY**

Because this is a rare tumor that is often identified incidentally and may not require treatment, it is unlikely that large randomized controlled trials or comparative studies will become available. Due to the risk of potentially life-threatening hemorrhage in large ( $\geq 4$  cm) AMLs and the low rate of adverse effects, treatment of symptomatic or large lesions may be warranted.

## **HEAD AND NECK TUMORS**

### **BACKGROUND**

Tumors of the head and neck arise in the lip, oral cavity, pharynx, larynx, paranasal sinuses and salivary glands. Treatment depends on the location and extent of the disease.<sup>[117]</sup> Standard treatment for patients with early-stage disease (stage I or II) is single-modality with surgery or radiation therapy. The two modalities result in similar survival. Combined modality therapy is required for locally advanced disease. In patients with recurrent head and neck cancer, surgical salvage attempts are poor in terms of local control, survival and quality of life, and these recurrent tumors are often untreatable with standard salvage therapies. Palliative chemotherapy or comfort measures may be offered.

### **SYSTEMATIC REVIEWS RANDOMIZED CONTROLLED TRIALS**

No systematic reviews or randomized trials evaluating the safety and effectiveness of RFA for treatment of head and neck tumors were identified.

### **NONRANDOMIZED STUDIES**

Current published evidence is limited to poorly designed case series, feasibility, and retrospective studies that are considered unreliable due to lack of a control group for comparison and lack of randomization to control for bias.<sup>[118-122]</sup>

In addition to these methodological limitations, prospective case series included small numbers of patients. Small study populations limit the ability to rule out the role of chance as an explanation of study findings.

### **ADVERSE EVENTS**

Complications and adverse events are reported to be uncommon, but are often severe. They are generally related to burning of local soft tissue (e.g., fistula formation).<sup>[118-121]</sup>

## **THYROID TUMORS**

### **BACKGROUND**

Thyroid carcinoma is uncommon, with a lifetime risk of being diagnosed with thyroid carcinoma less than 1%. Thyroid carcinoma occurs two to three times more often in women than men. The main histological types of thyroid carcinoma include: 1) differentiated (including papillary,

follicular, and Hürthle); 2) medullary; 3) anaplastic (aggressive undifferentiated tumor). All anaplastic thyroid carcinomas are considered stage IV and are almost uniformly lethal, however most deaths are from papillary, follicular, and Hürthle cell carcinomas, which account for nearly 95% of thyroid carcinoma cases. The treatment of choice for differentiated thyroid carcinoma is surgery followed by radioiodine in selected patients and thyroxine therapy in most patients. There is no effective therapy for anaplastic thyroid carcinoma; most are unresectable, but EBRT may improve local control and provide palliation. Surgical resection is the primary treatment choice for medically unresponsive, symptomatic benign thyroid tumors and thyroid carcinomas. However, techniques for ablation of thyroid tumors (eg, RFA, microwave ablation) are being investigated.

## SYSTEMATIC REVIEW

**Benign Tumors:** A 2019 systematic review and meta-analysis was reported by Trimboli on the efficacy of thermal ablation for benign non-functioning solid thyroid nodules.<sup>[123]</sup> Twelve studies per therapy were identified addressing RFA and laser ablation, with three RCTs on RFA and four on laser ablation. The remainder were prospective and retrospective cohort studies. Overall there was high heterogeneity. Only studies with six months or longer follow-up were included and median follow-up was 12 months. The primary outcome was the volume reduction rate at 6, 12, 24, and 36 months. The volume reduction rate for the RFA group was 68%, 75%, and 87%, respectively, with insufficient 36-month reporting for analysis. The volume reduction rate for the laser ablation group was 48%, 52%, 45%, and 44%, respectively.

In 2014 Fuller reported on a systematic review and meta-analysis of studies on RFA for benign thyroid tumors.<sup>[124]</sup> Included in the review were nine studies (five observational studies<sup>[125-129]</sup>, four randomized studies<sup>[130-133]</sup>) totaling 306 treatments. After RFA, statistically significant improvements were reported in nodule size reduction (29.77 mL; 95% CI -13.83 to -5.72), combined symptom improvement and cosmetic scores on the 0 to 6 scale (mean, -2.96; 95% CI -2.66 to -3.25) and withdrawal from methimazole (odds ratio, 40.34; 95% CI 7.78 to 209.09). Twelve adverse events were reported, two of which were considered significant but did not require hospitalization.

**Malignant Tumors:** No systematic reviews of studies for malignant thyroid tumors were identified.

## RANDOMIZED CONTROLLED TRIALS

No new RCTs were published since those included in the 2014 systematic review summarized above.

## NONRANDOMIZED STUDIES

In 2016, Kim reported on a comparative review of 73 patients with recurrent thyroid cancer smaller than 2 cm who had been treated with RFA (n=27) or repeat surgery (n=46).<sup>[134]</sup> RFA was performed in cases of patient refusal to undergo surgery or poor medical condition. Data were weighted to minimize potential confounders. The three-year recurrence-free survival rates were similar for RFA (92.6%) and surgery (92.2%, p=0.681). Posttreatment hoarseness rate did not differ between the RFA (7.3%) and surgery (9.0%) groups. Posttreatment hypocalcemia occurred only in the surgery group (11.6%).

## ADVERSE EVENTS

In 2017, Chung reported results of a systematic review and meta-analysis evaluating the safety of RFA for benign thyroid nodules and recurrent thyroid cancers.<sup>[135]</sup> Twenty-four studies were included, totalling 2,421 participants and 2,786 thyroid nodules. Overall, 41 major complications and 48 minor complications (as defined by the Society of Interventional Radiology) of RFA were reported, giving a pooled proportion of 2.38% for overall RFA complications [95% confidence interval (CI) 1.42%-3.34%] and 1.35% for major RFA complications (95% CI 0.89%-1.81%). Subgroup analysis found major complication rates were significantly higher for malignant thyroid nodules than for benign. Major complications included voice change, nodule rupture, permanent hypothyroidism, and brachial plexus injury. Minor complications included pain, haematoma, vomiting, skin burns, and transient thyroiditis.

## CHOLANGIOCARCINOMAS

### BACKGROUND

Cholangiocarcinomas are tumors that originate in the bile duct epithelium; 90% are adenocarcinomas. Intrahepatic cholangiocarcinomas (ICC) are located within the hepatic parenchyma and are reviewed under Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204 (see Cross References for a link to the policy). They may also be referred to as peripheral cholangiocarcinomas. Extrahepatic cholangiocarcinomas (ECC) are more common than intrahepatic cholangiocarcinoma and are located within the extrahepatic bile duct. Complete resection with negative margin is potential curative, though recurrence is common and most cases are unresectable due to advanced disease when diagnosed. For unresectable or metastatic cholangiocarcinomas at any location, the primary treatment may include chemotherapy, treatment within a clinical trial, or best supportive care. RFA and other locoregional therapies may be an option. Biliary drainage with biliary stenting may be warranted for unresectable or metastatic extrahepatic disease. Liver transplantation is potentially curative in carefully selected patients with lymph node negative, nondisseminated locally advanced hilar cholangiocarcinomas and otherwise normal biliary and hepatic function or underlying liver disease precluding surgery.

### SYSTEMATIC REVIEWS AND RANDOMIZED CONTROLLED TRIALS

No systematic reviews or randomized controlled trials regarding radiofrequency ablation for the treatment of extrahepatic cholangiocarcinomas were identified.

### NONRANDOMIZED STUDIES

The evidence for ECC consists of a single short-term case series.<sup>[136]</sup> This study included 11 patients with hilar ECC. At one-month follow-up after RFA, the reduction in tumor size was 30% in six tumors, 20% in two tumors, and size was unchanged in three tumors. At six months following RFA, the overall size reduction was 35%, with the largest reduction 60%. Overall survival ranged from 10-30 months.

## UTERINE FIBROIDS (LEIOMYOMAS OR MYOMAS)

### BACKGROUND

Uterine fibroids, also known as leiomyomas or myomas, are benign smooth muscle tumors of the uterus occurring in women during their reproductive years. They frequently occur in multiples, and the tumor location within the uterus is often used to describe the fibroids

(intramural, submucosal, subserosal, or cervical myomas). Surgery, including hysterectomy and various myomectomy procedures, is considered the criterion standard treatment for symptom resolution. There has been long-standing research interest in developing minimally invasive alternatives for treating uterine fibroids, including procedures that retain the uterus and allow for future childbearing. Various techniques to induce myolysis have also been studied including Nd:YAG lasers, bipolar electrodes, cryomyolysis, and radiofrequency ablation. With these techniques, an energy source is used to create areas of necrosis within uterine fibroids, reducing their volume and thus relieving symptoms.

## SYSTEMATIC REVIEWS

Bradley (2019) performed a systematic review and meta-analysis of RFA for the treatment of uterine fibroids.<sup>[137]</sup> A total of 32 studies met inclusion criteria. A meta-analysis of data at the 12-month follow-up, calculated a decrease in fibroid volume of 66%, an increase in health-related quality of life by 39 points, and a decrease in symptom severity score of 42 points (all  $p < 0.001$  versus baseline). The annual cumulative rates of reintervention due to fibroid-related symptoms were 4.2%, 8.2%, and 11.5% at one, two, and three years, respectively.

A systematic review and meta-analysis by Sandberg (2018) evaluated the risk of reintervention for hysterectomy and QOL after uterine-sparing interventions for fibroids.<sup>[138]</sup> Risk of reintervention at 12 months was 0.3% for radiofrequency volumetric thermal ablation (RFVTA) compared with 3.6% for UAE and 1.1% for myomectomy. Symptom severity and QOL scores were similar for the three treatments. Only one RFVTA study was identified on reintervention risk at 36 months; none was identified on reintervention risk at 60 months.

A systematic review by Havryliuk (2017) that did not separate outcomes by the length of follow-up found a reintervention rate of 5.2% after RFVTA (four studies, 12- to 36-month follow-up) compared to 4.2% after myomectomy (six studies, 12- to 52-month follow-up).<sup>[139]</sup> There was no significant difference in complication rates between RFVTA (6.3%) and myomectomy (7.9%). The length of stay after myomectomy was two days (range 0.5 to 6.0). No data were provided on length of stay after RFVTA.

Lin (2018) conducted a meta-analysis of improvement in symptom severity, QOL, and reintervention after laparoscopic radiofrequency ablation.<sup>[140]</sup> The review included one RCT and seven non-comparative trials. The recurrence risk at a weighted mean follow-up of 24.65 months (range, 3 to 36 months) was 4.4%. Improvements in symptoms and QOL were maintained out to 24 months in three studies and out to 36 months in one study. No studies were identified that had follow-up longer than 36 months.

## RANDOMIZED CONTROLLED TRIALS

In Germany in 2014, Brucker published a single-center manufacturer-sponsored randomized controlled trial (RCT) comparing radiofrequency volumetric thermal ablation (RFVTA) with the Acessa system to laparoscopic myomectomy.<sup>[141]</sup> The trial included 51 premenopausal women at least 18 years old with symptomatic uterine fibroids less than 10 cm in any diameter and a uterine size of less than 17 weeks of gestation. Pregnancy and lactation were exclusion criteria. Prior to randomization, all women underwent laparoscopic ultrasound mapping. Data on 50 of the 51 women were analyzed. The primary study outcome, mean (SD) time to hospital discharge, was 10.0 (5.5) hours in the RFVTA group and 29.9 (14.2) hours in the myomectomy group. The criterion for noninferiority (no more than 10% longer hospital stay with RFVTA than

laparoscopic myomectomy) was met at a significance level of  $p < 0.001$ . All patients in the myomectomy group were hospitalized overnight; although not explicitly stated, this appeared to be the standard procedure at the study hospital. In the Acessa group, there was one unplanned hospitalization due to unexplained vertigo and four hospitalizations as standard procedure because the patients also underwent adhesiolysis.

Secondary outcomes of the RCT were reported in a 2015 publication by Hahn <sup>[142]</sup> (12-month outcomes) and a 2016 publication by Kramer <sup>[143]</sup> (24-month outcomes). Analysis was per protocol and 43 (84%) of 51 randomized participants were available for both the 12- and 24-month analyses. Each publication reported on 12 symptoms: heavy menstrual bleeding, increased abdominal gait, dyspareunia, pelvic discomfort/pain, dysmenorrhea, urinary frequency, urinary retention, sleep disturbance, backache, localized pain, and “other symptoms” (not specified). At 12 months, no participants reported four of the symptoms (dyspareunia, urinary retention, sleep disturbance, uterine pain) and there were no statistically significant between-group differences in the frequency of any of the remaining eight symptoms (at the  $p < 0.05$  level). The most commonly reported symptom at 12 months (heavy menstrual bleeding) occurred in seven (33%) of women in the RFVTA group and two (9%) of women in the laparoscopic myomectomy group ( $p = 0.069$ ) after controlling for baseline bleeding. At 24 months, no participants reported urinary retention or “other” symptoms, and there were no statistically significant between-group differences in any of the 10 reported symptoms. The most commonly reported symptom at 24 months (dysmenorrhea) occurred in eight (38%) in the RFVTA group and in seven (32%) in the laparoscopic myomectomy group ( $p = 0.67$ ). Patients were also assessed using several validated questionnaires (eg, the Uterine Fibroid Symptom and Quality of Life). There were no statistically significant between-group differences at 12 or 24 months on these validated questionnaires. In addition, the authors described pregnancy outcomes. Three patients in the RFVTA group conceived and all delivered a healthy neonate; the number of women who desired to become pregnant was not reported. Limitations of the 12- and 24-month analyses included lack of intention-to-treat analysis and failure to describe secondary study hypotheses and statistical analyses clearly. The RCT was relatively small in size and thus may have been underpowered to detect clinically meaningful differences in secondary outcomes, so these results do not rule out potential differences between treatments.

## **NONRANDOMIZED STUDIES**

A large retrospective case series was published by Yin in 2015.<sup>[144]</sup> The study was conducted in China and used Chinese gynecologic radiofrequency ablation devices. It included 1216 consecutive patients treated at a single hospital over a 10-year period. All fibroids were less than 6 cm in size and mean diameter was 4.5 cm (range, 3.1-6.0 cm). Mean follow-up time was 36.5 months. Among the 476 premenopausal women, the mean reduction in myoma diameter was 2.7 cm at six months, 2.4 cm at 12 months, and 2.2 cm at 24 months. Among the 740 peri- or postmenopausal women, mean reduction was 3.3 cm at six months, 2.3 cm at 12 months, and 2.3 cm at 24 months. Myoma diameter was significantly lower at each of these time points posttreatment compared with pretreatment. In the premenopausal subgroup, the proportion of women with dysmenorrhea decreased from 43.7% at baseline to 7.6% at 12 months and to 6.7% at 24 months; rates were significantly lower after treatment.

In 2013, Chudnoff published a prospective industry-funded multicenter study.<sup>[145]</sup> It included 135 premenopausal women at least 25 years old with symptomatic uterine fibroids, a uterine size of 14 weeks of gestation or less, and six or fewer treatable fibroids, with no single fibroid

larger than 7 cm. In addition, women desired to preserve their uteri but not to have children in the future. RFVTA was conducted using the Acessa system. According to the study protocol, most fibroids less than 1 cm in diameter were not treated. The primary efficacy outcomes were change in the volume of menstrual bleeding and the surgical reintervention rate after 12 months. A total of 127 (94%) of 135 women completed the study. From baseline to 12 months, 53 (42%) of 127 women (95% confidence interval, 32% to 49%) experienced at least a 50% reduction in the volume of menstrual bleeding. Most women (104/127 [82%]) experienced a decrease in menstrual bleeding at 12 months. Only one woman underwent a surgical reintervention through 12 months (this woman had been lost to follow-up and was not included in the other efficacy analyses). Three-year outcomes were reported by Berman in 2014.<sup>[146]</sup> A total of 104 (77%) of the 135 women who participated in the study were evaluable at three years. Fourteen underwent reintervention over the three years to treat uterine fibroid symptoms. Eleven women had hysterectomies, two had myomectomies, and one had uterine artery embolization. Bleeding outcomes were not reported at three years, but the authors stated that quality-of-life variables improved from baseline to 36 months and that most of the improvement in quality of life occurred within three months of the procedure.

## MISCELLANEOUS TUMORS

### BACKGROUND

The standard treatment of miscellaneous tumors depends on the type, location, and extent of the cancer. A large number of phase II or III clinical trials involving the use of RFA in the treatment of primary or metastatic cancers are underway.<sup>[147]</sup>

### PUBLISHED STUDIES

Thomson (2019) published a systematic review on non-surgical treatments for Morton's neuroma.<sup>[148]</sup> A total of 22 studies, addressing nine non-operative treatment modalities, met inclusion criteria. In addition to RFA, treatment modalities included corticosteroid injection, alcohol injection, extra-corporeal shockwave therapy (ESWT), cryoablation, capsaicin injection, Botulinum toxin, orthosis and YAG laser therapy. All showed statistically significant improvements, but the pain-relieving results for alcohol injection were only short-term and orthotics, capsaicin injections, cryoablation, Botulinum toxin, RFA and ESWT had limitations to their application.

A prospective observational study by Rey (2019) assessed the effectiveness of transvaginal ultrasound-guided RFA of myomas (TRFAM) in reducing tumor volume and eliminating metrorrhagia associated with myomas.<sup>[149]</sup> The study included 205 women with symptomatic type II/III uterine submucosal or intramural cavity-distorting myomas undergoing RFA. The preoperative mean standard deviation (SD) volume of the myomas was 122.4 (182.5) cm<sup>3</sup> (95% CI, 82.1 to 162.8). Mean myoma volume decreased significantly at one (85.2 [147.9] cm<sup>3</sup>; p=0.001), three (67.3 [138.0] cm<sup>3</sup>; p=0.001), six (59.3 [135.3] cm<sup>3</sup>; p=0.001), and 12 months (49.6[121.4] cm<sup>3</sup>; p=0.001). At 12 months, the mean volume reduction was 60% compared with preoperative volume. All patients returned to normal menstruation at a mean follow-up of three months and 12 months. Of the 205 patients, 201 (98.04%) were satisfied with the procedure. The investigators conceded that a larger population with a longer follow-up is needed, but their study suggests that transvaginal ultrasound-guided RFA of myomas TRFAM is effective and safe for treating select patients with metrorrhagia secondary to myomas.

The remainder of the current published evidence on RFA for other tumors is limited to unreliable data from small case series and retrospective reviews. Evidence from these studies is considered unreliable due to methodological limitations such as non-random allocation of treatment and a lack of appropriate comparison groups.<sup>[118,125,126,150-163]</sup>

## PRACTICE GUIDELINE SUMMARY

### NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines for thyroid carcinoma (v.2.2019) state that for papillary, Hurthle Cell, medullary, or follicular carcinoma with locoregional recurrence surgery is preferred if resectable, and/or local therapies when available, including RFA.<sup>[164]</sup> For the same subtypes of thyroid carcinoma, RFA may also be considered in recurrent or persistent disease or distant metastases (soft tissue or bone). (category 2A)

NCCN guidelines for colon cancer (v.1.2020) indicate that “ablative techniques can be considered [in patients whose primary colon tumor was resected for cure when metastatic lung tumors are] unresectable and amenable to complete ablation” (category 2A).<sup>[165]</sup> The guidelines also state that “ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.”

NCCN guidelines for kidney cancer (v.2.2020) indicate RFA is an ablative option for the treatment of kidney cancer in select patients with clinical stage T1 lesions who are not candidates for surgery, though ablative techniques have shown higher local recurrence rates than surgery and may require more treatments.<sup>[166]</sup> RFA is also an option for relapse or Stage IV and in select patients (e.g., elderly patients, others) with competing health risks.

NCCN guidelines for the treatment of non-small cell lung cancer (v.2.2020) state: “For medically operable disease, resection is the preferred local treatment modality (other modalities include SABR, thermal ablation such as radiofrequency ablation and cryotherapy).”<sup>[167]</sup>

### AMERICAN COLLEGE OF RADIOLOGY

The 2014 American College of Radiology (ACR) Appropriateness Criteria<sup>®</sup> considers RFA to be an alternative to partial nephrectomy for small (<4 cm) RCC tumors.<sup>[168]</sup>

The 2014 ACR Appropriateness Criteria on early-stage NSCLC that current evidence from a number of retrospective series involving varied patient populations reported a wide range of responses to RFA, ranging from 38% to 93%.<sup>[169]</sup> Primary tumor relapse rate after RFA ranged from 8% to 43% and two-year cancer-specific survival after RFA ranged from 57% to 93%, with three-year OS of 15% to 46%. Predictors of complete response included smaller tumor size metastases, and ablation zone four times the tumor diameter. The document quoted the 2012 ACCP/STS guidelines<sup>[170]</sup> summarized above.

### AMERICAN COLLEGE OF CHEST PHYSICIANS

The American College of Chest Physicians (ACCP) guidelines on the treatment of stage I and II NSCLC indicate RFA has been used effectively in clinical stage 1 NSCLC. Therefore, in

medically inoperable patients, peripheral NSCLC tumors less than 3 cm may be treated with RFA.<sup>[171]</sup>

The ACCP also joined with the Society of Thoracic Surgeons (STS) to develop consensus guidelines on the treatment of high-risk patients with stage I NSCLC.<sup>[170]</sup> These consensus guidelines indicate RFA is an alternative treatment option in patients who are not surgical candidates due to severe medical comorbidity.

## **AMERICAN THYROID ASSOCIATION**

The 2012 American Thyroid Association (ATA) guidelines consider the evidence to be insufficient to allow conclusions as to the role of RFA, cryoablation, and embolization for the management of anaplastic thyroid cancer (ATC).<sup>[172]</sup> Therefore, a definitive recommendation could not be made for these treatments. (Strength of Recommendation: Weak; Quality of Evidence: Insufficient)

## **AMERICAN UROLOGICAL ASSOCIATION**

The 2017 American Urological Association (AUA) Guidelines state that “Physicians should consider TA [thermal ablation] as an alternate approach for the management of cT1a renal masses <3 cm in size.” and “Both radiofrequency ablation and cryoablation are options for patients who elect thermal ablation.” Both are rated as “Conditional Recommendation; Evidence Level Grade C.”<sup>[173]</sup>

# **SUMMARY**

## **RENAL CELL CARCINOMA**

Although there are currently no high-quality studies of radiofrequency ablation (RFA) of renal cell carcinoma (RCC), the overall body of published evidence suggests RFA may be beneficial in the short- to mid-term for small (4 cm or smaller), localized RCCs in patients who are not considered candidates for partial or complete surgical removal of the kidney. Therefore, RFA may be medically necessary for small RCCs in patients who are not surgical candidates or when preservation of kidney function is necessary, such as in patients with only one kidney.

Surgical excision is the preferred treatment for renal cell carcinoma (RCC) in patients who are considered to be healthy enough for surgery. There is insufficient evidence to determine whether radiofrequency ablation (RFA) is effective as surgical excision for treatment of RCC tumors. Therefore, RFA is considered investigational for treatment of RCC tumors for which surgical resection is an option.

## **BREAST TUMORS**

There is insufficient evidence to determine the effectiveness of radiofrequency ablation for treatment of benign or malignant breast masses. Therefore, this treatment is considered investigational for the treatment of these tumors.

## **LUNG TUMORS**

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Surgical resection is the treatment of choice for primary non-small cell lung cancer (NSCLC) or metastatic tumors in the lung. For those patients who are unable to tolerate surgery, radiofrequency ablation (RFA) may be a treatment option in certain cases. While available studies are limited by study design, accumulating evidence suggests that RFA may be similar to surgery in survival rates, and rates of procedure-related complications and mortality. Therefore, in patients with NSCLC or metastatic tumors in the lung who are ineligible for surgical treatment, RFA may be medically necessary when the policy criteria are met. There is not enough evidence to show that radiofrequency ablation (RFA) is effective as alternative treatments when criteria are not met. Therefore, RFA is considered investigational when the policy criteria are not met.

## **OSTEOID OSTEOMAS**

Although the published evidence is limited to studies of lower methodological quality, radiofrequency ablation (RFA) of osteomas has become a standard of care based on expert opinion that the potential benefits of RFA outweigh risks in patients with osteoid tumors who have failed nonsurgical treatments. Therefore, RFA may be medically necessary for select patients when policy criteria are met.

The current preferred treatment of osteoid osteomas is non-surgical medical treatment. There is insufficient evidence to determine the effectiveness of radiofrequency ablation (RFA) for initial (first-line) treatment of osteoid tumors. RFA is, therefore, considered investigational as initial treatment of these tumors in patients who have not undergone standard medical management.

## **ANGIOMYOLIPOMAS**

The current published evidence on radiofrequency ablation (RFA) of angiomyolipomas (AMLs) is limited to studies of lower methodological quality. However, because these tumors are rare, it is unlikely that evidence from large comparative studies will become available. Given the potential for life-threatening hemorrhage from large AMLs (4 cm or larger), and the consistent reports that the potential benefits of treatment outweigh any risks, RFA may be medical necessary to treat symptomatic or large asymptomatic AMLs. There is not enough evidence to show that radiofrequency ablation (RFA) is effective as alternative treatments when criteria are not met. Therefore, RFA of asymptomatic AMLs smaller than 4 cm is considered investigational.

## **PALLIATION OF PAIN FOR BONE METASTASES**

The current evidence for radiofrequency ablation (RFA) for treatment of painful metastatic tumors in the bone is limited to studies of lower methodological quality; however, these studies have consistently reported significant improvement in pain following RFA in patients who have failed or are poor candidates for standard treatments. In light of this evidence, the unlikelihood of randomized controlled trials in these patients, and the lack of treatment options, the potential benefits of RFA appear to outweigh risks. Therefore, RFA may be medically necessary in patients with painful metastatic bone lesions who have failed or are poor candidates for standard treatments.

Because of the lack of data on the effectiveness of radiofrequency ablation (RFA) for initial (first-line) treatment of painful bony metastases, this indication is considered investigational.

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## HEAD AND NECK CANCERS

There is insufficient evidence to determine whether radiofrequency ablation (RFA) is effective for treatment of tumors of the head and neck. Therefore, RFA is considered investigational for the treatment of head and neck cancers.

## THYROID TUMORS

While radiofrequency ablation (RFA) has been shown to reduce the size of thyroid tumors and improve clinical symptoms, complications can be common. The available evidence is insufficient to determine whether any beneficial effects of RFA outweigh the risks. Therefore, RFA for the treatment of benign or malignant thyroid tumors is considered investigational.

## UTERINE FIBROIDS

There is not enough research to show that radiofrequency ablation (RFA) improves health outcomes for people with uterine fibroids. Additionally, no clinical guidelines based on evidence recommend this treatment option. Therefore, RFA is considered investigational for treating uterine fibroids.

## MISCELLANEOUS TUMORS

There is insufficient evidence to determine whether radiofrequency ablation (RFA) is effective for treatment of other tumors. Therefore, RFA is considered investigational for all other tumors.

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175. BlueCross BlueShield Association Medical Policy Reference Manual "Laparoscopic and Percutaneous Techniques for the Myolysis of Uterine Fibroids." Policy No. 4.01.19

## CODES

Codes	Number	Description
	31641	Ablation therapy for reduction or eradication of 1 or more bone tumors (eg, metastasis) including adjacent soft tissue when involved by tumor extension, percutaneous, including imaging guidance when performed; radiofrequency Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with destruction of tumor or relief of stenosis by any method other than excision (eg, laser therapy, cryotherapy)
	32998	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; radiofrequency

<b>Codes</b>	<b>Number</b>	<b>Description</b>
	50542	Laparoscopy, surgical; ablation of renal mass lesion(s), including intraoperative ultrasound guidance and monitoring, when performed
	50592	Ablation, one or more renal tumor(s), percutaneous, unilateral, radiofrequency
	58674	Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency
	0404T	Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency
HCPCS	None	

**Date of Origin:** December 1998

## Varicose Vein Treatment

**Effective:** July 1, 2020

**Next Review:** March 2021

**Last Review:** May 2020

### IMPORTANT REMINDER

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

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

### DESCRIPTION

Varicose veins are dilated, tortuous veins that may cause pain or skin ulcers; however, the majority of treatment is done for cosmetic reasons. Invasive treatment may include surgical removal and/or destruction using lasers, heat, or injection of sclerosing solution.

### MEDICAL POLICY CRITERIA

#### Notes:

- Member contracts for covered services vary. Member contract language takes precedence over medical policy. In addition, when there is a contract denial for treatment of varicose veins, the denial not only includes treatment but also the associated venous imaging studies (i.e. CPT 93970 or 93971) for treatment planning.
- This policy addresses treatment of the superficial system veins of the lower extremity (e.g., great and small saphenous veins, saphenous tributaries, varicose veins and associated lower extremity perforator veins), upper extremity varices, and vulvar varices.
- Embolization, ablation, and sclerotherapy of the ovarian, internal iliac, or gonadal veins for treatment of pelvic congestion syndrome or varicoceles are addressed separately (see Cross References below).

- This policy uses the nomenclature great saphenous vein and small saphenous vein. Great saphenous veins are also known as long saphenous veins (CPT nomenclature) or greater saphenous veins. Small saphenous veins are also known as short saphenous veins (CPT nomenclature) or lesser saphenous veins.

I. **ALL** of the following **general criteria** (see Policy Guidelines) must be met for varicose vein treatment to be considered for coverage:

A. One or more of the following indications must be documented:

1. Functional impairment, attributed to varicose veins, which limits performance of instrumental activities of daily living (ADLs). Instrumental ADLs are defined as feeding, bathing, dressing, grooming, meal preparation, household chores, and occupational tasks that are required as a daily part of job functioning. Clinical records **must specifically document** ALL of the following:
  - a. The specific instrumental ADL that is impaired; and
  - b. A description of how performance of the instrumental ADL is limited; and
  - c. Progress notes must document patient compliance with medically supervised conservative therapy, including the current use for a minimum of 3 months of compression (minimum 15 mmHg) stockings and the patient's response; or
2. Venous imaging study documented recurrent attacks of superficial phlebitis; or
3. Recurrent or persistent hemorrhage from ruptured varix, which does not include bleeding caused by scratching or shaving; or
4. Documentation of ulceration from venous stasis where incompetent varices are a significant contributing factor; and

B. A complete venous imaging study in the superficial system veins (e.g., great and small saphenous veins, perforator veins, and saphenous tributaries) is performed including documentation of the diameter of the vein and the reflux in seconds measured at multiple levels in the thigh and calf. Vein diameter and incompetence measurements must be in the actual superficial vein and not in the deep vein junctions (e.g., saphenofemoral junction and saphenopopliteal junction).

II. Procedures

A. Endovenous ablation

1. Endovenous radiofrequency or laser ablation of incompetent great or small saphenous veins may be considered **medically necessary** when **ALL** of the following are met:
  - a. Documentation by venous imaging study of minimum vein diameter measurements for:
    - i. Great saphenous vein diameter 5.5 mm or greater

- ii. Small saphenous vein diameter is 4 mm or greater; and
    - b. Incompetence exceeding 0.5 seconds; and
    - c. Clinical documentation that all incompetent segments of the same vein will be treated in the same session; and
    - d. Criterion I. is met.
  - 2. If Criterion II.A.1. is not met, endovenous radiofrequency or laser ablation of incompetent great or small saphenous veins is considered **not medically necessary**.
  - 3. Separate sessions for ablation of segments of a continuous vein are considered **not medically necessary** (See Policy Guidelines).
  - 4. Endovenous ablation is considered **investigational** for ALL of the following:
    - a. Cryoablation of any vein; and
    - b. Radiofrequency or laser ablation of veins other than the great or small saphenous veins, including but not limited to the following:
      - i. accessory saphenous veins
      - ii. branch tributaries
      - iii. perforator veins; and
    - c. Ablation of any other veins (e.g., vulvar varices); and
    - d. Mechanochemical ablation of any vein; and
    - e. Microwave ablation of any vein; and
    - f. Steam injection ablation of any vein.
- B. Ligation/stripping and phlebectomy (i.e., stab, hook, transilluminated powered)
- 1. Ligation/stripping and phlebectomy of incompetent superficial system veins (including the great and small saphenous veins and saphenous tributaries including accessory saphenous veins) and varicose veins 4 mm or greater in diameter may be considered **medically necessary** when ALL of the following Criteria are met:
    - a. The incompetent superficial veins proximal to the vein to be treated either have been treated or are being treated concurrently; and
    - b. Criterion I. is met; and
    - c. Incompetence exceeding 0.5 seconds.
  - 2. If Criterion II.B.1. is not met, ligation/stripping or phlebectomy (including perforator veins) is considered **not medically necessary**.
- C. Sclerotherapy
- 1. Sclerotherapy (liquid, foam, or microfoam) of the following superficial system veins: great saphenous vein below the knee, small saphenous vein, and saphenous tributaries including accessory saphenous veins, and

other varicose veins may be considered **medically necessary** when ALL of the following criteria are met:

- a. Documentation by venous imaging study of minimum vein diameter of 4mm or greater; and
  - b. The incompetent superficial veins proximal to the vein to be treated either have been treated or are being treated concurrently; and
  - c. Criterion I. is met.
2. If Criterion II.C.1. is not met, sclerotherapy is considered **not medically necessary**.
  3. Venous imaging study guidance (see Policy Guidelines) may be considered **medically necessary** for liquid, foam, or microfoam sclerotherapy of the great saphenous vein below the knee, small saphenous vein, accessory saphenous veins and saphenous tributaries.
  4. Venous imaging study guidance is considered **not medically necessary** for sclerotherapy of all other superficial system veins.
  5. Sclerotherapy is considered **investigational** for ALL of the following:
    - a. Vulvar, including labial and buttock varices; and
    - b. Upper extremity varices; and
    - c. Great saphenous vein from the saphenous femoral junction (SFJ) to knee; and
    - d. Perforator veins
  6. Sclerotherapy of small (less than 4 mm in diameter) superficial veins, including but not limited to reticular veins and/or telangiectasias (spider veins) is considered **cosmetic**.
- D. Endovenous glue/adhesive (e.g. cyanoacrylate adhesives)
1. The use of endovenous glue or adhesives to treat incompetent great or small saphenous veins may be considered **medically necessary** when the **ALL** of the following are met:
    - a. Documentation by venous imaging study of minimum vein diameter measurements for:
      - i. Great saphenous vein diameter 5.5 mm or greater
      - ii. Small saphenous vein diameter is 4 mm or greater; and
    - b. Incompetence exceeding 0.5 seconds; and
    - c. Clinical documentation that all incompetent segments of the same vein will be treated in the same session; and
    - d. Criterion I. is met.
  2. If Criterion II.D.1. is not met, the use of endovenous glue or adhesive of incompetent great or small saphenous veins are considered **not medically necessary**.

- III. Treatment sessions (see Policy Guidelines): When applicable medical necessity criteria detailed above are met, either initial or subsequent treatment may be considered **medically necessary** when performed within either of the following numbers of treatment sessions:
  - A. One treatment session; or
  - B. Two treatment sessions for endovenous ablation (with associated procedures) of bilateral veins (a separate session for each of the right and left legs).
- IV. Treatment sessions not meeting Criterion III. above are considered **not medically necessary**.
- V. Varicose vein treatment is considered **not medically necessary** when Criterion I. is not met.
- VI. Follow-up venous imaging studies performed within 6 months following the most recent ipsilateral treatment, in the absence of complications, are considered **not medically necessary**, including but not limited to routine confirmation studies following endovenous ablation. Focused venous imaging studies to confirm ablation or rule out deep vein thrombosis or endovenous heat-induced thrombosis are considered a component of and incidental to the procedure or follow-up evaluation.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History of present illness and physical examination.
- Impact on activities of daily living (including the specific ADL) impaired, how it impacts performance, and what is done to alleviate it. Conservative therapy treatment plan (including units of compression stocking strength documented in mmHg and timeframe) with documented results and evidence of medical supervision.
  - Note: Impact on ADLs and conservative therapy plan are not required when there are documented recurrent attacks of superficial phlebitis, recurrent or persistent hemorrhage from ruptured varix, which does not include bleeding caused by scratching or shaving, and/or ulceration from venous stasis where incompetent varices are a significant contributing factor)
- Complete venous imaging studies including vein names with measurements of seconds of reflux and average vein diameters not including focal dilations (i.e. valve).
- Documentation of ulceration from venous stasis where incompetent varices are a significant contributing factor which may include photographs.
- Procedures requested:
  - Specific procedures to be performed
  - Specific veins to be treated
  - Number of treatment session(s) being requested
  - If bilateral endovenous ablation is requested, document whether a bilateral or two unilateral sessions are being requested

- Specify the veins to be treated in each session
- For ablations, specify how all incompetent segments of the same vein are to be treated

## ADDITIONAL INFORMATION

- Additional Venous Imaging Studies
  - For additional treatment sessions after previous varicose vein procedures, additional imaging is only required when the previous imaging did not identify the veins requested in the additional treatment session(s). Additional imaging is not required when an initial request was denied (for criteria not related to imaging) and the member is seeking subsequent approval. Initial imaging will be considered adequate unless there is a relevant intervening venous procedure(s), in which case new imaging studies may be requested.
- Conservative Therapy
  - Compression stockings should be worn daily while the patient is out of bed. *Unna boot* or *compression wrap* may be utilized in lieu of compression stockings when there is documentation of an open venous stasis ulcer of the leg to be treated. For additional treatment requests after initial treatment, there must have been 3 months of conservative therapy after the most recent varicose vein procedure which has not successfully treated the patient's symptoms.
- Treatment Sessions
  - Each treatment session should address as much abnormality as is appropriate and reasonable and may include more than one vein and/or modality.
  - Endovenous laser or radiofrequency ablation of the entire incompetent saphenous vein usually can be accomplished in a single treatment session. Although additional procedures, including ligation or sclerotherapy, performed in the same treatment session on the same ablated saphenous vein are considered included components of the ablation procedure, procedures on other saphenous venous systems may be distinct procedural services.

## CROSS REFERENCES

1. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12
2. [Ovarian Internal Iliac, and Gonadal Vein Embolization as a Treatment of Pelvic Congestion Syndrome](#), Surgery, Policy No.147

## BACKGROUND

The venous system of the lower extremities consists of the superficial system (e.g., great and small saphenous veins and accessory or tributary veins that travel in parallel with the great and small saphenous veins) and the deep system (e.g., popliteal and femoral veins). These two parallel systems are interconnected via perforator veins and at the saphenofemoral and the saphenopopliteal junctions.

One-way valves are present within all veins to direct the return of blood up the lower limb. Larger varicose veins, many protruding above the surface of the skin, typically are related to valve incompetence. As the venous pressure in the deep system is generally greater than that of the superficial system, valve incompetence leads to increased hydrostatic pressure transmitted to the unsupported superficial vein system. Backflow (venous reflux) with pooling of blood ultimately results in varicosities. In addition, clusters of varicosities may appear related

to incompetent perforating veins, such as Hunter and Dodd, located in the mid- and distal thigh, respectively and/or associated with incompetence at the saphenofemoral junction. In some instances, the valvular incompetence may be isolated to a perforator vein, such as the Boyd perforating vein located in the anteromedial calf. These varicosities are often not associated with saphenous vein incompetence since the perforating veins in the lower part of the leg do not communicate directly with the saphenous vein.

Although many varicose veins are asymptomatic, when present, symptoms include itching, burning, heaviness, fatigue, and pain. In addition, chronic venous insufficiency secondary to venous reflux can lead to peripheral edema, hemorrhage, thrombophlebitis, venous ulceration, and chronic skin changes. In an effort to improve the consistency in diagnosing chronic venous disorders, particularly for patient selection in clinical trials, an international consensus committee developed CEAP classification.<sup>[1]</sup> In this system, classification is based on clinical manifestations (C), etiology (E), anatomical distribution (A), and underlying pathophysiology (P). (See Appendix 1)

**Note:** The term "varicose veins" does not apply to the telangiectatic dermal veins, which may be described as "spider veins" or "broken blood vessels." While abnormal in appearance, these veins typically are not associated with any symptoms, such as pain or heaviness, and their treatment is considered cosmetic.

## TREATMENT OF SUPERFICIAL VARICOSE VEINS

### Conservative Therapy

Treatment of venous reflux/venous insufficiency is aimed at reducing abnormal pressure transmission from the deep to the superficial veins. Varicose veins can usually be treated with non-surgical measures. Symptoms often decrease when the legs are elevated periodically, when prolonged standing is avoided, and when elastic compression stockings are worn.

### Operative Therapy

If conservative treatment measures fail, additional treatment options typically focus first on identifying and correcting the site of reflux, and second on redirecting venous flow through veins with intact valves. Thus, conventional surgical treatment of varicosities is based on the following three principles:

- Control of the most proximal point of reflux, typically at the saphenofemoral junction, as identified by preoperative Doppler ultrasonography. Surgical ligation and division of the saphenofemoral or saphenopopliteal junction is performed to treat the valvular incompetence.
- Removal or occlusion by ablation of the refluxing great and/or small saphenous vein from the circulation. The classic strategy for isolation is vein stripping in conjunction with vein ligation and division.
- Removal or occlusion of the refluxing varicose tributaries. Strategies for removal include phlebectomy (i.e., ligation/division/stripping, powered phlebectomy, or stab avulsion) or occlusion by injection sclerotherapy; either at the time of the initial treatment, or subsequently. Over the years various minimally invasive alternatives to ligation and stripping have been investigated, including sclerotherapy and thermal ablation using

radiofrequency energy (high frequency radiowaves), laser energy, or cryoablation (also called cryotherapy).

## **Endovenous Ablation**

The objective of endovenous ablation techniques is to cause injury to the vessel, causing retraction and subsequent fibrotic occlusion of the vein.

### Thermal Ablation

Three endovenous thermal ablation techniques have been investigated as minimally invasive alternatives to vein ligation and stripping.

- Radiofrequency (RF) ablation is performed by means of a specially designed catheter inserted through a small incision in the distal medial thigh to within 1-2 cm of the saphenofemoral junction. High frequency radio waves (200-300 kHz) are delivered through the catheter electrode and cause direct heating of the vessel wall, causing the vein to collapse. The catheter is slowly withdrawn, closing the vein.
- Laser ablation is performed similarly; a laser fiber is introduced into the saphenous vein under ultrasound guidance; the laser is activated and slowly removed along the course of the saphenous vein. Laser ablation may be referred to as endovenous laser ablation (EVLA) or endovenous laser treatment (EVLV).
- Cryoablation uses extreme cold to cause injury to the vessel. Technical developments since thermal ablation procedures were initially introduced include the use of perivenous tumescent anesthesia which allows treatment of veins larger than 12 mm in diameter and helps to protect adjacent tissue from thermal damage during treatment of the lesser saphenous vein.
- There are two technologies that are not available in the United States:
  - Microwave ablation is performed via endovenous catheter using microwave energy to heat the vessel walls.
  - Steam ablation is catheter-based endovenous thermal ablation that uses high pressure pulses of steam to heat the vein to 120°C.

### Mechanochemical Ablation

Endovenous mechanochemical ablation (MOCA) utilizes both sclerotherapy and mechanical damage to the lumen. Following ultrasound imaging, a disposable catheter with a motor drive is inserted into the distal end of the target vein and advanced to the saphenofemoral junction. As the catheter is pulled back, a wire rotates at 3500 rpm within the lumen of the vein, abrading the lumen. At the same time, a liquid sclerosant (sodium tetradecyl sulphate) is infused near the rotating wire. It is proposed that mechanical ablation allows for better efficacy of the sclerosant, without the need for the tumescent anesthesia used in thermal ablation.

## **Cyanoacrylate Adhesive**

Cyanoacrylate adhesive is a clear, free-flowing liquid that polymerizes in the vessel via an anionic mechanism (i.e. polymerizes into a solid material upon contact with body fluids or tissues). The adhesive is gradually injected along the length of the vein in conjunction with

ultrasound and manual compression. The acute coaptation halts blood flow through the vein until the implanted adhesive becomes fibrotically encapsulated and establishes chronic occlusion of the treated vein. Cyanoacrylate glue has been used as a surgical adhesive and sealant for a variety of indications, including gastrointestinal bleeding, embolization of brain arteriovenous malformations, and to seal surgical incisions or other skin wounds.

## **Sclerotherapy**

The objective of sclerotherapy is to destroy the endothelium of the target vessel by injecting an irritant solution (either a detergent, osmotic solution, or a chemical irritant), ultimately resulting in the complete obliteration of the vessel. The success of the treatment depends on accurate injection of the vessel, an adequate injectant volume and concentration of sclerosant, and post-procedure compression. Compression theoretically results in direct apposition of the treated vein walls to provide more effective fibrosis and may decrease the extent of the thrombosis formation.

Sclerotherapy is an accepted and effective treatment of telangiectatic vessels. Historically, larger veins and very tortuous veins were not considered to be good candidates for sclerotherapy. Technical improvements in sclerotherapy, including the routine use of Duplex ultrasound to target refluxing vessels, luminal compression of the vein with anesthetics, and foam sclerosant in place of liquid sclerosant, have improved its effectiveness in these veins. Other concerns have arisen with these expanded uses of sclerotherapy. For example, use of sclerotherapy in the treatment of varicose tributaries without prior ligation, with or without vein stripping creates issues regarding its effectiveness in the absence of the control of the point of reflux and isolation of the refluxing saphenous vein. Sclerotherapy of the great saphenous vein raises issues regarding appropriate volume and concentration of the sclerosant and the ability to provide adequate post-procedure compression. Moreover, the use of sclerotherapy, as opposed to the physical removal of the vein with stripping, raises the issue of recurrence due to recanalization.

## **TREATMENT OF PERFORATOR VEINS**

Perforator veins cross through the fascia and connect the deep and superficial venous systems. Incompetent perforating veins were originally addressed with an open surgical procedure, called the Linton procedure, which involved a long medial calf incision to expose all posterior, medial, and paramedial perforators. While this procedure was associated with healing of ulcers, it was largely abandoned due to a high incidence of wound complications. The Linton procedure was subsequently modified by using a series of perpendicular skin flaps instead of a longitudinal skin flap to provide access to incompetent perforator veins in the lower part of the leg. The modified Linton procedure may be occasionally utilized for the closure of incompetent perforator veins that cannot be reached by less invasive procedures. Subfascial endoscopic perforator surgery (SEPS) is a less-invasive surgical procedure for treatment of incompetent perforators and has been reported since the mid-1980s. Guided by Duplex ultrasound scanning, small incisions are made in the skin and the perforating veins are clipped or divided by endoscopic scissors. The operation can be performed as an outpatient procedure. Endovenous ablation of incompetent perforator veins with sclerotherapy and radiofrequency has also been reported.

## **OTHER**

Deep vein valve repair or reconstruction and replacement are being investigated.

Venous “glue” or “superglue” is not cleared for use in the United States for this indication. This is an adhesive delivered via endovenous catheter as a method for sealing the vein.

## REGULATORY STATUS

Devices that have received specific U.S. Food and Drug Administration (FDA) marketing clearance for the endovenous treatment of superficial vein reflux include:

- The VenClose® radiofrequency system received FDA approval in 2016 and is approved for endovascular coagulation for superficial vein reflux.
- The Alma 810 nm diode tabletop laser received FDA approval in 2016 and is indicated for endoluminal or endovenous laser surgery for incompetent saphenous veins.
- The VenaSeal™ (Medtronic) Closure System was FDA approved in 2015. The system includes a liquid adhesive, catheter, guidewire, dispenser gun and tips, and syringes. The clear liquid adhesive, cyanoacrylate adhesive, is injected into the diseased vein and polymerizes into a solid material to permanently seal the vein.
- The CERMAVEIN Steam Vein Sclerosis (SVS™) system is being studied outside of the United States but does **not** have FDA approval or clearance for marketing.
- The ClariVein® Infusion Catheter (Vascular Insights) received marketing clearance through the 510(k) process in 2008 (K071468). It is used for mechanochemical ablation. Predicate devices were listed as the Trellis® Infusion System (K013635) and the Slip-Cath® Infusion Catheter (K882796). The system includes an infusion catheter, motor drive, stopcock and syringe and is intended for the infusion of physician-specified agents in the peripheral vasculature.
- Polidocanol is an injectable sclerosing agent that may be used for intravenous treatment of varicose veins.
  - Varithena® (Biocompatibles, Inc, a BTG group company), formerly Varisolve®, is a polidocanol sclerosant microfoam made with a proprietary gas mix that is dispersed from a canister with a controlled density and more consistent bubble size. FDA approval in 2013 was for the treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein system above and below the knee.
  - In 2010, Asclera® (Merz North America, Inc) is an injectable solution with FDA approval for the treatment of uncomplicated spider veins (varicose veins  $\leq$  1mm in diameter) and reticular veins (varicose veins 1-3 mm in diameter) in the lower extremities.
- A modified Erbe Erbokryo® cryosurgical unit (Erbe USA) received FDA clearance for marketing in 2005. A variety of clinical indications are listed, including cryostripping of varicose veins of the lower limbs.
- The Trivex system is a device for transilluminated powered phlebectomy that received FDA clearance through the 510(k) process in October 2003. According to the label, the intended use is for “ambulatory phlebectomy procedures for the resection and ablation of varicose veins.”

- In 2002, the Diomed 810 nm surgical laser and EVLT™ (endovenous laser therapy) procedure kit received FDA clearance through the 510(k) process, "... for use in the endovascular coagulation of the greater saphenous vein of the thigh in patients with superficial vein reflux."
- In 1999, the VNUS® Closure™ system (a radiofrequency device) received FDA clearance through the 510(k) process for "endovascular coagulation of blood vessels in patients with superficial vein reflux." The VNUS RFS and RFS*Flex* devices received FDA clearance in 2005 for "use in vessel and tissue coagulation including: treatment of incompetent (i.e., refluxing) perforator and tributary veins. The modified VNUS® ClosureFAST™ Intravascular Catheter received FDA clearance through the 510(k) process in 2008.

## EVIDENCE SUMMARY

Outcomes of interest for venous interventions include symptom control, healing and recurrence, recanalization of the vein, and neovascularization. Recanalization is the restoration of the lumen of a vein after it has been occluded; this occurs more frequently following treatment with endovenous techniques. Neovascularization is the proliferation of new blood vessels in tissue, and occurs more frequently following vein stripping. Direct comparisons of durability for endovenous and surgical procedures are complicated by these different mechanisms of recurrence. Relevant safety outcomes include the incidence of paresthesia, thermal skin injury, thrombus formation, thrombophlebitis, wound infection, and transient neurologic effects.

### VARICOSE VEIN TREATMENT

#### Systematic Reviews

Kheirelseid (2017) published a systematic review (SR) of nine randomized control trials (RCTs) that evaluated long-term outcomes (five years or more) of endovenous laser therapy, radiofrequency ablation, or ultrasound guided foam sclerotherapy for great saphenous vein-related varicose veins.<sup>[2]</sup> No difference in recurrence rate was seen for endovenous laser therapy or radiofrequency ablation versus conventional surgery. The authors concluded this study was too small to make a definitive determination on long-term effectiveness for varied varicose vein procedures.

Hamann (2017) published a SR of RCTs evaluating the long-term ( $\geq$  five years) impact on health outcomes for different types of treatment for the great saphenous vein, including ligation and stripping, endovenous thermal ablation and ultrasound guided foam sclerotherapy, for great saphenous vein incompetence.<sup>[3]</sup> Three RCTs and 10 follow-up reports on RCTs were included, of which one could not be included in the meta-analysis. At five years, endovenous thermal ablation and ligation stripping were more successful than ultrasound guided foam sclerotherapy. The reoccurrence of reflux was lower for ligation and stripping, than for endovenous thermal ablation and ultrasound guided foam sclerotherapy. Venous clinical severity scores were similar for ligation and stripping and endovenous thermal ablation. The authors stated the included studies had methodological limitations including unknown or high risk of bias and that more long-term RCTs are needed to compare success rates and clinical outcomes.

Vemulapalli (2017) published a SR that evaluated treatments for lower extremity varicose veins and/or venous insufficiency, reflux, or incompetence.<sup>[4]</sup> Included in the review were 53 RCTs (10, 034 patients), which were poor to good quality and four additional studies. Various therapy comparisons could not be made because of heterogeneity in therapies, populations and outcomes. Long-term symptom scores were no different between high ligation/stripping and endovascular laser ablation. There were no short-term bleeding differences between high ligation/stripping and radiofrequency ablation. The authors stated there is lack of high quality evidence on the safety and effectiveness of treatments for chronic lower extremity venous disease. Additional studies must compare effectiveness and provide practice parameters.

Boersma (2016) published results from a SR and meta-analysis that compared the anatomical success rates and complication rates of six treatment modalities for small saphenous vein incompetence: surgery (n=9), endovenous laser ablation (EVLA) (n=28), radiofrequency ablation (RFA) (n=9), ultrasound-guided foam sclerotherapy (UGFS) (n=6), and mechanochemical endovenous ablation (MOCA) (n=1).<sup>[5]</sup> Although the review included 49 articles (five RCTs and 44 cohort studies), nine were specific to RFA and were cohort studies. The pooled anatomical success rate for RFA in 386 incompetent small saphenous veins was 97.1% (95% CI 94.3% to 99.9%). RFA had a relatively low neurological complication rate (mean 9.7%) when compared to the overall neurological complication rate (mean 19.6%). The pooled anatomical success rate for UGFS in 494 incompetent small saphenous veins was 63.6% (95% CI 47.1% to 80.1%); however, more research is needed to determine these effects. The 28 articles specific to EVLA included both RCT's and cohort studies. The pooled anatomical success rate for EVLA in 2,950 incompetent small saphenous veins was 98.5% (95% CI 97.7% to 99.2%). EVLA had a low neurological complication rate (mean 4.8%) when compared to the overall neurological complication rate (mean 19.6%). There was one study on mechanochemical ablation (MOCA) and although the authors reported an anatomical success rate of 94%, more research is needed to determine these effects. The authors concluded that EVLA/RFA should be a preferred treatment over surgery and foam sclerotherapy in small saphenous vein incompetence. An updated Cochrane review from 2014 compared RFA, EVLA, and foam sclerotherapy versus ligation/stripping for saphenous vein varices.<sup>[6]</sup> Included in the review were 13 randomized studies with a combined total of 3081 patients. The overall quality of the evidence was moderate. For EVLA versus surgery, there were no significant differences between the treatment groups for clinician noted or symptomatic recurrence, or for recanalization. Neovascularization and technical failure were reduced in the laser group (OR=0.05, p<0.001; and OR=0.29, p<0.001, respectively). For RFA versus surgery, there were no significant differences between the groups in clinician noted recurrence, recanalization, neovascularization, or technical failure. The authors concluded that sclerotherapy, EVLA, and RFA were at least as effective as surgery in the treatment of long saphenous vein varicose veins.

In 2012, a SR of RCTs and meta-analysis was published that compared the clinical outcomes of EVLA, RFA, UGFS, and surgery.<sup>[7]</sup> The review included 28 RCTs and reported no significant difference in primary failure and clinical recurrence with EVLA and RFA compared with surgery. The advantages of the endovenous ablation techniques over surgery were a lower rate of wound infections and hematoma, and a shorter recovery period.

## **RANDOMIZED CONTROL TRIALS**

Lawaetz (2017) published a five-year follow-up on an RCT in which 500 patients (580 legs) received either endovenous radiofrequency ablation, endovenous laser ablation, ultrasound

guided foam sclerotherapy or high ligation and stripping for great saphenous vein reflux.<sup>[8]</sup> Recanalization occurred more often after ultrasound guided foam sclerotherapy, but there was no difference in technical efficacy between the procedures. There was a higher unknown reason for reoccurrence after endovenous laser ablation and high ligation and stripping.

van der Velden (2015) published results from a five-year follow-up comparing conventional surgery, endovenous laser ablation, and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins.<sup>[9]</sup> A total of 224 legs were included (69 conventional surgery, 78 EVLA, and 77 UGFS), and 193 were evaluated at final follow up (86.2%). At the five-year follow-up, the Kaplan-Meier analysis showed obliteration or absence of the great saphenous vein in 85% of patients who underwent conventional surgery and 77% of patients who underwent EVLA (not significantly different). Grade I neovascularization was higher in the conventional surgery group (27% vs 3%,  $p < 0.001$ ), while grade II neovascularization was similar in the two groups (17% vs 13%).

Brittenden (2014) reported a multicenter randomized trial that compared foam sclerotherapy, EVLA, and surgical treatment in 798 patients.<sup>[10]</sup> The study was funded by U.K.'s Health Technology Assessment Programme of the National Institute for Health Research.<sup>[11]</sup> Veins greater than 15 mm were excluded from the study. At the six-week follow-up visit, patients who were assigned to treatment with foam or laser had the option of treatment with foam for any residual varicosities; this was performed in 38% of patients in the foam group and 31% of patients in the EVLA group. Six months after treatment, mean disease-specific quality of life was slightly worse after sclerotherapy than after surgery ( $p = 0.006$ ), and there were more residual varicose veins, although the differences were small. Disease-specific quality of life was similar for the laser and surgery groups. The frequency of procedural complications was similar for the foam sclerotherapy (6%) and surgery (7%) groups, but was lower in the laser group (1%). The rate of complications at 6 months (primarily lumpiness and skin staining), was highest for the sclerotherapy group.

Five-year follow-up data from the Brittenden trial was published in 2019 on disease-specific and generic quality of life.<sup>[12]</sup> Disease-specific quality of life after five years was significantly better for those who received laser ablation or surgery compared to foam sclerotherapy.

Biemans (2013) published results from the MAGNA trial, which randomized 223 consecutive patients (240 legs) with long saphenous vein reflux to EVLA, ligation and stripping, or physician compounded foam sclerotherapy (1 ml aethoxysclerol 3#: 3ml air).<sup>[13]</sup> At one-year follow-up, the anatomic success rates were similar between EVLA and stripping (88.5% and 88.2%, respectively), which were superior to foam sclerotherapy (72.2%). Ten percent of the stripping group showed neovascularization. Health-related quality of life improved in all groups. The CEAP classification improved in all groups with no significant difference between the groups. Transient adverse events were reported in 11 patients after stripping, seven after EVLA, and five after sclerotherapy.

## **ENDOVENOUS ABLATION**

Endovenous ablation of varicose veins has been proposed as an alternative to ligation and/or stripping. Outcomes of interest include short and long term functional improvement and recurrence rates related either to recanalization of the saphenous vein or neovascularization. In terms of safety, relevant outcomes include the incidence of paresthesias, thermal skin or nerve injuries, thrombus formation, thrombophlebitis, and wound infection.

## Vein Diameter

There is currently no standardized range for saphenous vein diameter most likely to be associated with severe symptoms or for which endovenous ablation is recommended. In studies of the correlation between great saphenous vein diameter and the presence or absence of reflux, the best cutoff measurement to predict reflux varied between studies from 5.05 mm to 7.3 mm.<sup>[14-17]</sup> Sensitivity and specificity ranged from 76% to 87% and 60% to 87%, respectively. It is important to note that there is heterogeneity among the populations included in the studies. In addition, there was heterogeneity between studies in measurement techniques (e.g., location, position).

## Endovenous Laser and Radiofrequency Ablation

### Systematic Reviews

He (2017) conducted a SR which evaluated the effectiveness and safety of endovenous laser ablation compared to radiofrequency ablation for the treatment of varicose veins.<sup>[18]</sup> The SR included a total of 12 studies (N=1,577) (10 RCTs and 2 nonrandomized studies). The meta-analysis of the combined studies concluded that there were no significant differences in effectiveness and safety outcomes between the two groups.

Woźniak (2016) also evaluated laser ablation compared to radiofrequency ablation.<sup>[19]</sup> The study included 510 adults with five year follow-up and reported similar conclusions to He (2017) summarized above. A SR of EVLA versus surgery was published in 2009.<sup>[20]</sup> Fifty-nine studies were included, with seven studies that directly compared EVLA and surgery. Randomized and nonrandomized studies directly comparing outcomes for EVLA or surgery were included for the assessment of safety or effectiveness, while case series with a minimum patient population of 100 were included for the assessment of safety alone. For all studies, it was calculated that 5,759 patients (6,702 limbs) were treated with EVLA and 6,395 patients (7,727 limbs) underwent surgery. Few differences were apparent between treatments with respect to clinical effectiveness outcomes, although long-term follow-up was lacking. Nonclinical effectiveness outcomes generally favored EVLA over surgery in the first two months after treatment. The authors concluded that while EVLA offers short-term benefits and appears to be as clinically effective as surgery up to 12 months after treatment, clinical trials with a minimum of three years of follow-up are required to establish the enduring effectiveness of EVLA.

A number of SRs of RCTs comparing various types of ablation to surgical treatment have been published. These reviews consistently reported moderate quality of evidence. Most of the reviews compared EVLA, RFA, and surgical treatment of varicose veins. Overall, these techniques had similar, statistically significant improvement in function and in pain relief compared to preoperative scores. RFA and EVLA had low rates of technical procedure failure rates, and short-term recannulization rates. Adverse effects were generally minor for all techniques. Though intraoperative pain was not reported, EVLA consistently resulted in significantly greater pain and bruising when compared to RFA for one to two weeks following the procedure. RFA had significantly more occurrences of superficial phlebitis. Recanalization was similar for EVLA and RFA at one-year follow-up.

The primary limitation of the current evidence is the lack of long-term data on recanalization rates for ablation techniques and neovascularization rates for ligation and stripping. In addition, many of the available studies used first-generation technology and, therefore, do not provide

data on newer devices. For example, newer laser technology may result in decreased pain during and after the procedure. Newer RFA technology (e.g., ClosureFast RF catheter) may result in higher rates of vein occlusion.

### Randomized Controlled Trials

The ongoing, and largest randomized study on EVLA, comparing endovenous laser ablation with costectomy and stripping of the great saphenous vein (RELACS), schedule to follow patients for five years, randomized 400 patients to EVLA performed by a surgeon at one site or to ligation and stripping performed by a different surgeon at a second location.<sup>[21]</sup> Fifty-four patients withdrew from the study after receiving the randomization result (from an independent site), due primarily to preference for the other treatment. At the two-year follow-up there was no significant difference between the groups for clinically recurrent varicose veins, medical condition on the Homburg Varicose Vein Severity Score, or disease-related quality of life. Saphenofemoral reflux was detected by ultrasonography more frequently after EVLA (17.8% vs 1.3%). At 5-year follow-up, Kaplan-Meier analysis showed obliteration or absence of the great saphenous vein in 85% of patients who underwent conventional surgery and 77% of patients who underwent EVLA (not significantly different).<sup>15</sup> Grade I neovascularization was higher in the conventional surgery group (27% vs 3%,  $p < 0.001$ ), while grade II neovascularization was similar in the 2 groups (17% vs 13%).

Rasmussen (2012) reported the five-year follow-up data comparing EVLA ( $n=121$ ) with ligation and stripping ( $n=68$ ).<sup>[22]</sup> Data was available on 98% of the patients. There was no significant difference between the two groups for clinical recurrence (EVLA 36%, stripping 35%) or in the percentage of reoperations (EVLA 38.6%, stripping 37.7%).

Literature on isolated treatment of the anterior accessory saphenous vein is limited. In a 2009 study, outcomes from a cohort of 33 patients who underwent EVLA of the anterior accessory saphenous vein were compared with 33 matched controls undergoing EVLA of the greater saphenous vein.<sup>[23]</sup> In 21 of the patients (64%) in the accessory saphenous vein group there had been no previous treatment of the greater saphenous vein. At 12-month follow-up there was no evidence of reflux in these patients, and the treated accessory saphenous vein was not visible with ultrasound. The Aberdeen Varicose Vein Symptom Severity Score had improved in both groups, with no significant difference between the two groups. Patient satisfaction scores were also similar.

### Nonrandomized Trials

Several case series have reported on endoluminal radiofrequency ablation.<sup>[24-27]</sup> The largest was reported by Merchant and colleagues, who analyzed the four-year data collected in the ongoing Closure Study Group registry focusing on the treatment of reflux of the long saphenous vein.<sup>[24]</sup> Data were available on 890 patients and 1,078 limbs treated at 32 centers. Clinical and duplex ultrasound follow-up was performed at one-week, six-months, and yearly for four-years. The vein occlusion rates were 91% at one week and 88.8% at four-years, although only 98 limbs had been followed up to the four-year mark. These results suggest that radiofrequency ablation results in durable occlusion. Radiofrequency ablation has typically been limited to vessels less than 12 mm in diameter. The rationale behind this patient selection criterion is that the electrodes must remain in direct contact with the vein wall during treatment and the largest diameter of the deployed radiofrequency electrodes is 12 mm. The authors noted that exsanguinations, perivenous tumescent infiltration, and external compression may promote electrode and vessel wall contact such that larger veins can be treated. However, in

this large case series, there were only 58 limbs with vein sizes larger than 12 mm, and only 29 available for follow-up at six-months or one-year. While the occlusion rate was similar to that seen in smaller vessels, long-term data are inadequate to determine if this effect is durable.

Merchant and Pichot (2005) also reported the 5-year Closure Study Group registry data.<sup>[28]</sup> There were 1222 limbs in 1006 patients treated at 34 centers with radiofrequency ablation of various levels of the long saphenous vein, the short saphenous vein, and the accessory saphenous vein. At five-year follow-up using duplex ultrasound examination, 185 limbs were considered failures due to nonocclusion (12.4%), recanalization of a previously occluded vein (69.7%), or groin reflux of a vein with occluded trunk (17.8%). In the latter group, the groin reflux often involved an accessory vein. Logistic regression analysis of risk factors of gender, age, body mass index [BMI], vein diameter, and catheter pullback speed showed that each unit increase in BMI over 25 was associated with increasing risk of long-term failure. In addition, a catheter pull-back speed over the standard speed of 3 cm/min was associated with failure to occlude or recanalization. The authors pointed out that this anatomical failure did not necessarily result in clinical failure; most patients experienced initial symptom relief that was maintained over 5 years.

Many other clinical trials on laser ablation of varicose veins are case series<sup>[29-33]</sup> and registry data<sup>[28]</sup>. Using historical controls for comparison is difficult since treatment outcomes are variably reported. There are no consistent definitions of success versus failure, either based on patient or clinical assessment. In general, recurrence rates after ligation and stripping are estimated at around 20%. Doppler or Duplex ultrasound are perhaps the most objective form of assessment of recurrence, but many of the reports of the long-term outcomes of ligation and stripping did not use ultrasound studies for postoperative assessment. Only two studies have reported objective results of ligation and stripping at 12 and 24 months. Jones and colleagues reported on the results of a study that randomized 100 patients with varicose veins to undergo either ligation alone or ligation in conjunction with stripping.<sup>[34]</sup> The results of the ligation and stripping group are relevant to this discussion. At one year, reflux was detected in 9% of patients, rising to 26% at two years. Rutgers and Kitslaar reported on the results of a trial that randomized 181 limbs to undergo either ligation and stripping or ligation combined with sclerotherapy.<sup>[35]</sup> At two years, Doppler ultrasound demonstrated reflux in approximately 10% of patients, increasing to 15% at three years. Therefore, based on this crude assessment, the reflux rate of 13% for radiofrequency ablation at one year<sup>[36]</sup> and 6% for laser ablation at two years<sup>[29]</sup> is roughly comparable to the reflux rate of 9-10% reported by Jones et al and Rutgers and Kitslaar.

## **Cryoablation**

Disselhoff (2008, 2011) reported two and five-year outcomes from a randomized trial that compared cryostripping with EVLA.<sup>[37,38]</sup> One hundred and twenty patients were included with symptomatic uncomplicated varicose veins (CEAP C2) with saphenofemoral incompetence and greater saphenous vein reflux. At 10 days after treatment, EVLA had better results than cryostripping with respect to pain score over the first 10 days (2.9 vs. 4.4), resumption of normal activity (75% vs. 45%) and induration (15% vs. 52%). At the two-year follow-up, freedom from recurrent incompetence was observed in 77% of patients after EVLA and 66% of patients after cryostripping (not significantly different). At five years, 36.7% of patients were lost to follow-up; freedom from incompetence and neovascularization was found in 62% of patients treated with EVLA and 51% of patients treated with cryostripping (not significantly different). Neovascularization was more common after cryostripping, but incompetent

tributaries were more common after EVLA. There was no significant difference between groups in the Venous Clinical Severity Score or Aberdeen Varicose Vein Severity Score at either two or five years.

Klem (2009) published results from a randomized trial that found endovenous cryoablation (n=249) to be inferior to conventional stripping (n=245) for treating patients with symptomatic varicose veins.<sup>[39]</sup> The percentage of patients with greater saphenous vein remaining was 44% in the endovenous cryoablation group and 15% in the conventional stripping group. The Aberdeen Varicose Vein Questionnaire also showed better results for conventional stripping (score of 11.7) in comparison with cryoablation (score of 8.0). There were no differences between the groups in SF-36 subscores, and neural damage was the same (12%) in both groups.

## **Cyanoacrylate Ablation**

Morrison (2017) published a report on the 12-month outcomes of the VeClose trial that compared endovenous cyanoacrylate closure to radiofrequency ablation for great saphenous vein incompetence.<sup>[40]</sup> Ninety-five patients who underwent endovenous cyanoacrylate closure and ninety-seven patients who underwent radiofrequency ablation presented at the one-year follow-up evaluation. The authors concluded that although endovenous cyanoacrylate closure showed faster closure rates and fewer reopening episodes, quality of life was the same for both procedures. The study was not blinded, but may not have been possible because of the differences in the way the procedures are performed.

Morrison (2018) published thirty-six month follow-up data to the VeClose trial with follow-up on 146 (66%) patients (72 from CAC and 74 from RFA)<sup>[41]</sup>. Loss to follow-up was similar in the two groups. The complete closure rates for CAC and RFA were 94.4% and 91.9% (p=0.005 for non-inferiority), respectively. Recanalization-free survival through 36 months was not statistically different for the two groups. No significant device- or procedure-related adverse events were reported for either group.

Yasmin (2017) published a retrospective review on results of VariClose (n-butyl cyanoacrylate) treatment for varicose veins.<sup>[42]</sup> One hundred and eighty patients with great saphenous vein diameter > 5.5mm and small saphenous vein diameter > 4mm and reflux > 5 s were treated and followed up at between three and seven months. No recanalization was observed and the venous clinical severity scores dropped to an average of 3.9 three months after the procedure versus 10.2 before. No long-term results were reported.

Bozkurt (2016) conducted a one year prospective comparative study (n=310) evaluating cyanoacrylate glue compared to endovenous laser ablation for venous insufficiency.<sup>[43]</sup> The authors concluded that periprocedural pain, ecchymosis, permanent paresthesia were less in the cyanoacrylate ablation group. There were no significant differences in closure rates at 12 months follow-up. In addition, there were no significant differences in severity scores nor the Aberdeen Varicose Vein Questionnaire. Additional studies are needed to evaluate the effectiveness and safety of this technique.

## **Mechanochemical Ablation**

### Systematic Review

Witte (2017) published a SR of 13 studies evaluating the anatomic, technical, and clinical success of mechanochemical endovenous ablation (MOCA) using ClariVein® for the great and

small saphenous veins.<sup>[44]</sup> Studies were of “moderate to good quality”. Two-three year pooled anatomic outcomes for the great saphenous vein and small saphenous vein reported were 91% and 87% respectively. The authors stated MOCA using the ClariVein® and liquid sclerosant is associated with an anatomic success rate of 87%-92% and the risk of complications is low, but no RCTs were available to compare MOCA to endothermal ablation.

Vos (2017) published a SR of 15 prospective studies evaluating the anatomic and technical success of MOCA and cyanoacrylate vein ablation (CAVA) for great saphenous vein incompetence.<sup>[45]</sup> MOCA and CAVA pooled anatomic success were 94.8% and 94.1% at six months and 94.1% and 89% at one year. The authors stated additional RCTs of high quality comparing MOCA and CAVA to conventional procedures are needed. These will assist in establishing clinical outcomes and practice parameters.

### Randomized Controlled Trials

Mohamed (2020) published results of a trial comparing endovenous laser ablation and mechanochemical ablation using ClariVein in the management of superficial venous insufficiency.<sup>[46]</sup> Patients (n=150) were randomized to MOCA with 1.5% sodium tetradecyl sulfate or to EVLA. Occlusion rates were lower in the MOCA group 77% compared to the EVLA group (91%) with no significant difference between the two treatments in intraprocedural pain scores. Clinical severity and quality of life scores were not significantly different between the groups at one year follow-up. Additional follow-up is continuing to evaluate durability of the treatments.

Holewijn (2019) published a non-inferiority trial examining three percent polidocanol in the Mechanochemical endovenous Ablation to RADiOfrequeNcy Ablation (MARADONA).<sup>[47]</sup> The trial included 213 patients who were randomized before reimbursement for the procedure was suspended. Pain scores in the 14 days after the procedure were slightly lower, but hyperpigmentation was higher. Anatomic failures were significantly greater in the MOCA group at 1 year and approached significance at 2-years. The study was underpowered for anatomic failures because of the early stoppage of the study. At 1 and 2-years follow-up, clinical and quality of life outcomes were similar in the two groups.

Lane (2017) published a multi-center RCT evaluating pain levels for 170 patients undergoing either mechanical occlusion chemically assisted ablation or radiofrequency ablation.<sup>[48]</sup> Pain, duplex ultrasound results, clinical outcomes and quality of life were evaluated at one and six months after treatment. Pain after mechanical occlusion chemically assisted ablation was lower than with radiofrequency ablation, but other outcomes including quality of life and safety did not differ.

Bootun (2014) published early one month results from an ongoing study comparing 119 patients randomized to mechanochemical ablation (MCA) (n=60) or RFA (n=59).<sup>[49]</sup> The maximum and average pain scores were significantly lower during MCA compared to RFA (p<0.001). At one-month follow-up, both groups showed complete or proximal occlusion rates of 92%, though data were available for only 67% of participants. These preliminary outcomes do not permit conclusions due to methodological limitations including the short-term follow-up and incomplete data. The authors noted that data from longer follow-up is being collected.

Nonrandomized Studies Thierens (2019) published a prospective cohort study with five year follow up data. Anatomic and clinical follow-ups were performed at 4 weeks, 6 months, and 1, 3, and 5 years after the procedure. Less than half of the study population remained at 5 years.

however 79% had freedom from anatomic failure and clinical measures had worsened. Nearly 15% of the recanalizations occurred in the first year, which the authors considered to be due to technical issues when the procedure was initially introduced. It should be noted, however, that the more recent MARADONA trial from the same group of investigators using 3% polidocanol (described above) also saw a rate of recanalization of 16.5% in the first year and 20% in the second year. Without a control condition, it cannot be determined whether the loss of clinical improvement in this cohort study is due to recanalization or the usual progression of venous disease over time.

Tang (2017) published single-center study outcomes for 300 patients who received ClariVein® treatment for varicose veins.<sup>[50]</sup> Veins treated included great saphenous vein (n=184), bilateral great saphenous veins (n=62), short saphenous vein (n=23), and bilateral short saphenous veins (n=6). Evaluations occurred two months after the procedures. At two months, 13 out of 393 veins or 3.3% had to be retreated with ultrasound-guided foam sclerotherapy. The authors stated there were no adverse findings and results are promising, but these results are from a one surgeon's experience and RCTs with long-term follow-up are needed.

The remainder of the evidence on MCA of varicose veins is limited to nonrandomized series and cohort studies.<sup>[51-56]</sup> In the only comparative study, van Eekeren and colleagues compared postoperative pain and early quality of life in 68 patients treated with either RFA or MCA of great saphenous veins.<sup>[54]</sup> Patients who did not want to be treated with MCA were offered treatment with RFA; this study design could potentially lead to selection bias. There was no significant between-group difference in procedure-related pain. Compared with RFA, patients treated with MCA had a 14.3 mm reduction in pain measured on a 100 mm visual analog scale (VAS) measured over the first 3 postoperative days (6.2 vs. 20.5) and a 13.8 mm reduction in pain (4.8 vs. 18.6 mm;  $p<.001$ ) over the first two weeks. MCA patients treated also had a significantly earlier return to normal activities (1.2 vs. 2.4 days) and return to work (3.3 vs. 5.6 days;  $p=.02$ ). There was a similar improvement in quality of life for the two groups when measured at six weeks. Longer studies are required to determine the durability of these effects.

## **Microwave Ablation**

This technique has not been approved or cleared for marketing by the FDA. Two clinical trial reports were found. The first, a preliminary randomized trial, compared endovenous microwave ablation (EMA) with high ligation and stripping (HLS).<sup>[57]</sup> At 24-months follow-up, there was no significant difference in outcomes between the two groups. The second, a retrospective comparison between laser (n=163 limbs in 138 patients) and microwave (n=143 limbs in 121 patients) ablation of the greater saphenous vein, found significantly lower ecchymosis, skin burn, and paresthesia in the laser ablation.<sup>[58]</sup> However, the recanalization rate was significantly higher in the laser ablation group at one week and six months postoperatively ( $p<0.01$ ). Loss to follow-up at 24-months was about 19% in each group.

## **Steam Ablation**

This technique has not been approved or cleared for marketing by the FDA. There is currently no published clinical trial evidence on this technique.

## **SCLEROTHERAPY**

In general, reported outcomes of uncontrolled studies have varied for sclerotherapy, as have the periods of follow-up. In many studies the outcomes are reported in terms of cure rates, but the criteria for cure or failure are poorly defined. Studies have also reported subjective patient-assessed outcomes or physician assessment, both of which may be poorly defined. More recent studies included results of Doppler or duplex ultrasonography; however, the relationship between finding ultrasonographic evidence of recurrent reflux and clinical symptoms is uncertain. Finally, it should be noted that sclerotherapy of the long saphenous vein is a fundamentally different approach than stripping. With stripping, recurrences are likely related to an incomplete surgical procedure or to revascularization. With sclerotherapy, recurrences may be additionally related to recanalization of an incompletely fibrosed saphenous vein.

Systematic Reviews A SR from 2008 found that foam sclerotherapy of varicose veins is associated with a higher recurrence rate in patients with saphenofemoral incompetence compared to the rates of endovenous laser therapy or radiofrequency obliteration, while a 2009 SR suggested that outcomes from sclerotherapy are worse than those of surgery (ligation and stripping) for saphenous vein reflux.<sup>[59,60]</sup>

### Randomized Controlled Trials

Yin (2017) reported on a randomized control study for patients who received ultrasound guided foam sclerotherapy combined with great saphenous vein high ligation (n= 73) or stripping and multistab avulsion or transilluminated powered phlebectomy of the great saphenous vein (n=90).<sup>[61]</sup> Only 73 patients who received ultrasound guided foam sclerotherapy and 74 patients in the control group completed follow-up at one, six, and 12 months following treatment. At 12 months reflux recurrence rate was 13.8% after ultrasound guided foam sclerotherapy and 13.5% for the control treatment. Minor and major complications, venous filling index, VCSS, and AVVQ scores were similar. Patient satisfaction, operating times, and hospital costs were more favorable for ultrasound guided foam sclerotherapy.

Gibson (2017) reported on a multi-center randomized placebo-controlled trial evaluating the safety and efficacy of Varithena®.<sup>[62]</sup> Patients with symptomatic varicose veins received Varithena® (n=39) or a placebo (n=38). Assessments took place at baseline and at weeks one, four, eight and 12 after treatment. The authors stated Varithena® improves vein appearance and symptoms in patients with varicose veins. The study had methodological limitations including small sample size and potential author conflicts of interest. In addition, outcomes for appearance and symptoms may be viewed as subjective; thus, additional larger RCTs, with long-term follow-up are needed to validate health outcomes for Varithena®.

Several controlled trials comparing sclerotherapy of varicose tributaries or the saphenous vein, with and without associated ligation and stripping, have reported that the absence of ligation and stripping was associated with an increased frequency of recurrence. These trials are difficult to interpret due to the lack of clarity about which vein— either the varicose tributaries or the saphenous vein itself – have undergone sclerotherapy. Nonetheless, these trials established the importance of control of the site of reflux (ligation) and isolation of the refluxing portion of the saphenous vein (stripping). The following are examples of these studies:

Results from the five year follow up published by van der Velden (2015) examined ultrasound-guided foam sclerotherapy in 77 legs.<sup>[9]</sup> The authors found obliteration or absence of the greater saphenous vein was observed in only 23% of patients treated with sclerotherapy compared to 85% of patients who underwent conventional surgery and 77% of patients who underwent EVLA. Thirty-two percent of legs treated initially with sclerotherapy required one or

more reinterventions during follow-up compared with 10% in the conventional surgery and EVLA groups. However, clinically relevant grade II neovascularization was higher in the conventional surgery and EVLA groups (17% and 13%, respectively), compared with the sclerotherapy group (4%). EuroQol-5D scores improved equally in all groups.

King (2015) published results from the VANISH-1 study, a manufacturer-funded multicenter placebo RCT undertaken to evaluate the efficacy of relief of symptoms and safety of Varithena (0.5%, 1%, and 2%) compared with 0.125% (control) and placebo.<sup>[63]</sup> Seven-hundred and eighty patients were screened; 279 patients met the study criteria and were treated with either placebo (n=56), or Varithena 0.125% (n=57), 0.5% (n=51), 1% (n=52), or 2% (n=63). Patients rated the duration and intensity of nine symptoms and activity levels during the previous 24 hours using the VVSymQscore instrument. At week eight VVSymQscores for pool Varithena (0.5% +1%+2%) patients were significantly superior to placebo ( $p<.001$ ), and VVSymQscores decreased significantly ( $p<.001$ ) from baseline at eight weeks for all Varithena individual doses. There were no serious AE's and no PE's; however, patients receiving higher Varithena dose concentrations (1% and 2%) had higher rates of treatment-emergent AE's, which occurred in  $\geq 3\%$  of patients. The most common kinds of treatment-emergent AE's included pain, superficial thrombophlebitis, and hematoma at the injection site.

Vasquez and Gasparis (2015) published results from a manufacturer sponsored multicenter randomized placebo-controlled study. The purpose of the study was to determine the efficacy and safety of Varithena (0.5%, 1.0%) and placebo, each administered with endovenous thermal ablation.<sup>[64]</sup> A total of 234 patients were screened; 117 patients met the study criteria and received treatment (38 placebo, 39 Varithena 0.5%, and 40 Varithena 1%). Patients were assessed using the Quality of Life/Symptoms (mVEINES-QOL/Sym) questionnaire, Patients Self-Assessment of Visible Varicose Veins (PA-V) and the Independent Photography Review-Visible Varicose Veins (IPR-V) instruments. Efficacy showed baseline scores were greater at week eight for pooled Variethena than for placebo for both IPR-V (-1.2 vs. -0.8 points,  $p = 0.001$ ) and PA-V (-1.8 vs. -1.6 points,  $p = 0.16$ ), however, only IPR-V change score reached statistical significance. The comparison of the individual dose concentrations of Variethena (0.5%, 1.0%) with placebo showed a similar pattern for both IPR-V and PA-V scores. Although no patients presented spontaneously with symptoms of thrombus, six patients were found to have venous thrombi, and all occurred during the first eight weeks post treatment. Through six months of follow-up, there were no reports of visual disturbance or migraine among Varithena recipients, no pulmonary emboli, and no AE-related study withdrawals. There was one serious AE, breast cancer, considered unrelated to the study drug.

Microfoam sclerotherapy was studied in the 2014 VANISH-2 study, an ongoing five year manufacturer-funded pivotal double-blind RCT undertaken to obtain FDA marketing approval for Varithena microfoam (BTG).<sup>[65]</sup> The study compared 0.5% or 1.0% polidocanol microfoam with subtherapeutic foam dose (0.125%) and endovenous placebo in 232 patients. The authors reported early eight week follow-up data<sup>[66]</sup> finding elimination of reflux and/or occlusion of the previously incompetent vein in 85.6% of the combined 0.5% and 1.0% groups, 59.6% in the 0.125% "subtherapeutic" group, and 1.8% of the placebo group. The improvement in the venous clinical severity score was significantly greater in the 0.5% and 1.0% groups (-5.10) compared with placebo (-1.52), but was not reported for the 0.125% group. The 1.0% dose of Varithena was selected for the 2013 FDA approval. Adverse events occurred in 60% of patients receiving foam sclerotherapy compared to 39% of placebo; 95% were mild or moderate and transient. The most common adverse events were retained

coagulum, leg pain, and superficial thrombophlebitis. Deep vein thrombosis was detected by ultrasound in 2.8% of Varithena-treated patients with 1% having proximal symptomatic thrombi treated with anticoagulants. No pulmonary emboli were detected and no clinically significant cardiac or cardiopulmonary, neurologic, or visual adverse events were reported. In the short-term the rates of occlusion with this microfoam sclerotherapy were similar to those reported for EVLA or stripping. RCTs comparing EVLA or stripping with microfoam sclerotherapy with long-term outcomes are needed to evaluate comparative effectiveness. In 2015, Todd and Wright published an update to the VANISH-2 study and reported on findings at one year.<sup>[67]</sup> Results at year one showed symptoms improved when compared to week 8 (64% with total VVSymQ scores of 3 or less at week eight vs 85% at year one). Reductions from baseline in the individual symptom scores that compose the VVSymQ score were also demonstrated, with all five HASTI symptoms showing a continued decrease from over time. In addition, improvements from baseline in appearance as assessed by both the patients themselves (PA-V score) and blinded experts reading standardized photographs (IPR-V score) were maintained, with a small trend toward further improvement between week eight and one year. Ten patients of the 232 in the total population had 12 AEs reported during the long-term follow-up period through year one, including one death; however, all were unrelated to treatment. Of the patients who had venous thrombus AEs during the main eight week trial, none had recurrent venous thrombus AEs, and all clots stabilized or resolved completely. No post-thrombotic syndrome or other clinically important sequelae were reported. No patient developed a new venous thrombus AE in the one year follow-up, and no pulmonary emboli were diagnosed at any time through the one year in this study.

A 2012 study was a noninferiority trial of foam sclerotherapy versus ligation and stripping in 430 patients.<sup>[68]</sup> Analysis was per protocol. Forty patients (17%) had repeat sclerotherapy. At two years, the probability of clinical recurrence was similar in the two groups (11.3% sclerotherapy vs 9.0% ligation and stripping), although reflux was significantly more frequent in the sclerotherapy group (35% vs 21%). Thrombophlebitis occurred in 7.4% of patients after sclerotherapy. There were two serious adverse events in the sclerotherapy group (deep venous thrombosis and pulmonary emboli) that occurred within one week of treatment.

Blaise (2010) reported three-year follow-up from a multicenter double-blind randomized trial (143 patients) that compared treatment of the greater saphenous vein with either 1% or 3% polidocanol foam.<sup>[69]</sup> Additional treatment with foam sclerotherapy was carried out at six weeks, three and six months if required to abolish persistent venous reflux. There were 49 additional injections in the 1% polidocanol group and 29 additional injections in the 3% group. At the three-year follow-up, venous reflux was observed in 21% of patients in the 1% group and 22% of patients in the 3% polidocanol group.

Neglen (1993) reported on a "partially randomized" trial that compared the outcomes of three different treatment strategies: 1) sclerotherapy alone; 2) ligation and stripping, or 3) ligation combined with sclerotherapy.<sup>[70]</sup> It was difficult to determine the target of the sclerotherapy. As described in the article, sclerosant was injected into all points of control (presumably at the junction of the perforator veins) and, "if possible, into the main stem of the long saphenous vein." Thus, it seems that the intent of the sclerotherapy was not the obliteration of the long saphenous vein as an alternative to stripping, but as a treatment of the varicose tributaries. Therefore, among those patients who underwent ligation plus sclerotherapy, this trial tested whether or not stripping could be eliminated from the overall approach. In the group who received sclerotherapy alone, almost 70% of patients self-reported a cure immediately postoperatively, which declined to about 30% after five years. This gradual recurrence rate for

sclerotherapy alone is similar to that reported in the above studies. For the ligation and sclerotherapy group, 70% reported a cure immediately postoperatively, dropping to 50% after five years. The best long-term results were reported for the ligation and stripping group, which reported an 80% immediate cure rate, dropping to 70% after five years. The physician assessment of treatment outcome showed greater differences among the three groups. For example, based on physician assessment (observation and foot volumetric measurements), only 5% of the sclerotherapy group were considered cured after 5 years, compared to 10% in the ligation and sclerotherapy group and 60% in the ligation and stripping group.

Rutgers (1994) reported on a trial that randomized 156 patients with varicose veins and saphenofemoral incompetence to undergo either ligation and stripping or ligation and sclerotherapy.<sup>[35]</sup> The site of sclerotherapy was not described. At the three years follow-up, the cosmetic results were better in those limbs that had undergone stripping. Additionally, the clinical and Doppler ultrasound evidence of reflux was significantly less in those undergoing stripping.

### **Nonrandomized Studies**

There has also been interest in injecting sclerosant into the saphenous vein either in conjunction with ligation as an alternative to stripping, as a stand-alone procedure, or as an alternative to both ligation and stripping.

Myers (2007) published results from a three-year follow-up prospective observational study of sclerotherapy in 489 patients with refluxing saphenous veins and related tributaries.<sup>[71]</sup> Out of 807 veins treated, 56% were associated with the great saphenous vein and 22% with the small saphenous vein; 22% were tributaries alone. Ultrasound at three to five days after each treatment showed successful occlusion in an average of 1.5 sessions for the group as a whole (65% in one session and 26% in two sessions). The Kaplan-Meier analysis showed three-year survival rates of 83% for tributaries, 53% for great saphenous veins, and 36% for small saphenous veins. These results do not support the use of sclerotherapy for refluxing saphenous veins.

Kanter and Thibault (1996) published result from a case series, which included 172 patients with 202 limbs who had varicose veins with associated saphenofemoral incompetence.<sup>[72]</sup> Using ultrasound guidance, sclerosant was injected into the long saphenous vein 3-4 cm distal to the saphenofemoral junction. Injections were given at 30- to 90-second intervals, proceeding distally as previously injected segments were observed to spasm. Immediately after therapy, a thigh compression stocking was applied. Two weeks after the initial procedure, patients were reevaluated with Duplex ultrasound and were re-treated if found to have persistent reflux. There was a clinical recurrence rate of 22.8% at one year.

Ninja published two case series (1996; 1997) evaluating sclerotherapy for patients with symptomatic vulvar varicosities.<sup>[73,74]</sup> The first study included seven women and the second study included five women. Both studies concluded that all patients noticed marked improvements in symptoms after treatment. However, the sample sizes in these two studies were very small and they lacked a comparator group.

### **Adverse Effects**

Although long-term sequelae have not been reported with sclerotherapy, transient adverse effects have been found in up to 8% of patients, including cerebrovascular accidents, transient

ischemic attacks, speech and/or visual disturbance, migraine, shortness of breath, dizziness, and numbness.<sup>[75,76]</sup> Bubbles appear in the right side of the heart between 9 and 59 seconds after injection and emboli have been detected in the middle cerebral artery following sclerotherapy of saphenous trunks and varices. Deep venous occlusion after ultrasound-guided sclerotherapy has also been reported; risk was found to be greater when treating veins  $\geq 5$  mm in diameter (odds ratio of 3.7) and injecting 10 mL or more of foamed sclerosant (odds ratio of 3.6).<sup>[77]</sup> A SR of visual disturbance following sclerotherapy found this adverse effect to be rare and transient; further research was recommended to clarify the mechanism of action of sclerosants.<sup>[78]</sup>

## Other Treatments

FDA approval of the VenaSeal™ Closure System, which uses adhesive, was based on three manufacturer-sponsored clinical studies, one of which was a randomized controlled noninferiority trial. In the VeClose Study, 222 subjects with symptomatic long saphenous vein incompetence were randomized to undergo either the VenaSeal closure (n=108) or RFA (n=114).<sup>[79]</sup> A three-month follow-up was conducted during which no adjunctive procedures were allowed. There were a number of methodological limitations in this study, which include but are not limited to, a 14% loss of data, which was accounted for using various methods such as imputing missing data. While these analyses supported noninferiority, their reliability is unclear. These results require validation in large RCTs with lower rates of data loss and longer-term follow-up.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN VEIN AND LYMPHATIC SOCIETY (AVLS)

The AVSL guidelines committee (2016) published a consensus statement on treatment options for incompetent accessory saphenous veins.<sup>[80]</sup> They performed a SR to evaluate clinical outcomes and treatment options. They stated treatment recommendations for symptomatic great saphenous veins should include endovenous thermal ablation (laser or radiofrequency) and ultrasound-guided foam sclerotherapy (Grade 1C-strong recommendation, low quality evidence).

The AVLS (2014) published a practice guideline for treatment of superficial veins of the lower leg.<sup>[81]</sup> Recommendations for the treatment of saphenous veins included laser and radiofrequency ablation, for the small and great saphenous veins and the anterior and posterior accessory of the great saphenous vein (Grade 1B-strong recommendation, moderate quality evidence). Mechanical or Chemical ablation could be used for truncal veins (Grade 2B-weak recommendation, moderate quality evidence). Open surgery is not recommended, unless the conditions do not respond to other recommended treatments (Grade 1B evidence). Nonvisible symptomatic tributary veins could be treated with ultrasound-guided foam sclerotherapy or chemical ablation (Grade 1B evidence).

### NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)

NICE (2013) published a clinical guideline for the diagnosis and management of varicose veins.<sup>[82]</sup> No new evidence was found in 2016 that would change the guideline recommendations.

“1.3.2 For people with confirmed varicose veins and truncal reflux:

- Offer endothermal ablation (see radiofrequency ablation of varicose veins [NICE interventional procedures guidance 8] and endovenous laser treatment of the long saphenous vein [NICE interventional procedures guidance 52]).
- If endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy (see ultrasound-guided foam sclerotherapy for varicose veins [NICE interventional procedures guidance 440]).
- If ultrasound-guided foam sclerotherapy is unsuitable, offer surgery.

If incompetent varicose tributaries are to be treated, consider treating them at the same time.

1.3.3 If offering compression bandaging or hosiery for use after interventional treatment, do not use for more than 7 days.”

## INTERSOCIETAL ACCREDITATION COMMISSION

In 2016, the Intersocietal Accreditation Commission (IAC) published standards and guidelines on vascular testing for accreditation.<sup>[83]</sup> The IAC has recommendations for peripheral venous testing in section 4B. The guideline for documentation of lower extremity venous duplex for reflux states the following (section 4.7.2B):

4.7.2.1B Transverse grayscale images without and with transducer compressions (when anatomically possible or not contraindicated) must be documented as required by the protocol and must include at a minimum:

- i. common femoral vein;
- ii. saphenofemoral junction;
- iii. mid femoral vein;
- iv. great saphenous vein;
- v. popliteal vein;
- vi. small saphenous vein.

4.7.2.2B Spectral Doppler waveforms with the extremity(s) in a dependent position, demonstrating baseline flow and response to distal augmentation and if reflux is present, duration of retrograde flow measured with calipers and documented as required by the protocol and must include at a minimum:

- i. common femoral vein;
- ii. saphenofemoral junction;
- iii. great saphenous vein;
- iv. mid femoral vein;
- v. popliteal vein;
- vi. small saphenous vein.

4.7.2.3B Transverse grayscale images of *diameter measurement* must be documented as required by the protocol and must include at a minimum:

- i. saphenofemoral junction;
- ii. great saphenous vein at proximal thigh;
- iii. great saphenous vein at knee;
- iv. small saphenous vein (at saphenopopliteal junction).

## CYANOACRYLATE GLUE

### National Institute for Health and Care Excellence (NICE)

NICE (2015) published a guidance on cyanoacrylate glue occlusion for varicose veins.<sup>[84]</sup> NICE recommendations included using cyanoacrylate glue occlusion for special circumstances. Evidence was limited in quantity and quality.

## ENDOVENOUS ABLATION

### Society for Vascular Surgery and the American Venous Forum

The 2011 Society for Vascular surgery (SVS) and the American Venous Form (AVF) clinical practice guidelines on varicose veins and chronic venous disease included recommendations for endovenous radiofrequency or laser ablation for the treatment of incompetent long saphenous veins.<sup>[85]</sup>

- A Grade 1B recommendation was made in favor of endovenous thermal ablation over foam sclerotherapy and high ligation and stripping due to the reduced convalescence, pain, and morbidity. A Grade 1B recommendation was defined as a strong recommendation based on moderate quality evidence.
- A Grade 1B recommendation was made against treatment of incompetent perforator veins with CEAP class C2, but recommend treating these veins if they are located underneath a healed or active ulcer (Grade 2B recommendation defined as a weak recommendation based on moderate quality evidence.)
- The guideline does not make recommendations for saphenous vein diameter.

The 2014 SVS/AVF guidelines for management of venous ulcers included the following recommendations in favor of standard compressive therapy and ablation of incompetent superficial veins that have axial reflux directed to the bed of the ulcer<sup>[86]</sup>:

- In a patient with a venous leg ulcer and incompetent superficial veins to 1) improve ulcer healing (Grade 2B recommendation defined as a weak recommendation based on moderate quality evidence), and 2) prevent recurrence (Grade 1C recommendation defined as a strong recommendation based on low- to very low-quality evidence)
- To prevent ulceration in a patient with skin changes at risk for venous leg ulcer, and incompetent superficial veins (Grade 2C recommendation defined as a weak recommendation based on low- to very low- quality evidence)
- To aid in ulcer healing and to prevent recurrence in a patient who also has pathological perforating veins located beneath or associated with the ulcer bed (Grade 2C recommendation defined as a weak recommendation based on low- to very low- quality evidence)
- To prevent ulceration or ulcer recurrence in a patient with skin changes at risk for venous leg ulcer or healed venous ulcer and incompetent superficial veins (Grade 2C recommendation defined as a weak recommendation based on low- to very low-quality evidence).
- If a patient is expected to benefit from pathologic perforator vein ablation, percutaneous ablation with ultrasound-guided sclerotherapy or endovenous RFA or EVLA is recommended over open venous perforator surgery (Grade 1C

recommendation defined as a strong recommendation based on low- to very low-quality evidence)

### **National Institute for Health and Care Excellence (NICE)**

NICE (2016) published guidance on endovenous mechanochemical ablation for varicose veins.<sup>[87]</sup>

“Current evidence on the safety and efficacy of endovenous mechanochemical ablation for varicose veins appears adequate to support the use of this procedure provided that standard arrangements are in place for consent, audit and clinical governance. Clinicians are encouraged to collect longer-term follow-up data.”

NICE published a guidance in 2004 for endovenous laser treatment of the long saphenous vein.<sup>[88]</sup>

“Current evidence on the safety and efficacy of endovenous laser treatment of the long saphenous vein appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. Current evidence on the efficacy of this procedure is limited to case series with up to 3 years follow-up. Clinicians are encouraged to collect longer-term follow-up data.”

NICE published a guidance in 2003 for radiofrequency ablation of varicose veins.<sup>[89]</sup>

“Current evidence on the safety and efficacy of radiofrequency ablation of varicose veins appears adequate to support the use of this procedure as an alternative to saphenofemoral ligation and stripping, provided that the normal arrangements are in place for consent, audit and clinical governance.”

### **American College of Radiology<sup>[90]</sup>**

The 2012 the American College of Radiology (ACR) published appropriateness criteria for the treatment of lower-extremity venous insufficiency considered endovenous radiofrequency or laser ablation at least as effective as surgery. Cryoablation and mechanochemical ablation are not addressed. The criteria do not include patient selection criteria related to vein size. They also stated injection sclerotherapy may be appropriate in specific situations, but has not shown to have long-term effectiveness for the great saphenous veins.

### **Society of Interventional Radiography, Cardiovascular Interventional Radiological Society of Europe, American College of Phlebology, Canadian Interventional Radiology Association<sup>[91]</sup>**

The 2010 the Society of Interventional Radiography (SIR), Cardiovascular Interventional Radiological Society of Europe (CIRSE), American College of Phlebology (ACP), Canadian Interventional Radiology Association (CIRA) published a joint consensus statement on endovenous thermal ablation using either laser or radiofrequency devices under imaging guidance and monitoring an effective treatment of extremity venous reflux and varicose veins under the following conditions:

- I. The endovenous treatment of varicose veins may be medically necessary when one of the following indications (A–E) is present:

- A. Persistent symptoms interfering with activities of daily living in spite of conservative/nonsurgical management. Symptoms include aching, cramping, burning, itching, and/or swelling during activity or after prolonged standing.
  - B. Significant recurrent attacks of superficial phlebitis
  - C. Hemorrhage from a ruptured varix
  - D. Ulceration from venous stasis where incompetent varices are a contributing factor
  - E. Symptomatic incompetence of the great or small saphenous veins (symptoms as in A above)
- II. A trial of conservative, nonoperative treatment has failed. This would include mild exercise, avoidance of prolonged immobility, periodic elevation of legs, and compressive stockings.
- III. The patient's anatomy is amenable to endovenous ablation.

## **SCLEROTHERAPY**

### **National Institute for Health and Care Excellence (NICE)**

NICE published a guidance in 2013 for sclerotherapy.<sup>[92]</sup>

“1.1 Current evidence on the efficacy of ultrasound-guided foam sclerotherapy for varicose veins is adequate. The evidence on safety is adequate, and provided that patients are warned of the small but significant risks of foam embolisation (see section 1.2), this procedure may be used with normal arrangements for clinical governance, consent and audit.”

“1.2 During the consent process, clinicians should inform patients that there are reports of temporary chest tightness, dry cough, headaches and visual disturbance, and rare but significant complications including myocardial infarction, seizures, transient ischaemic attacks and stroke.”

### **Society for Vascular Surgery and the American Venous Forum**

The 2011 Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) published practice guidelines<sup>[85]</sup> and included the following recommendations concerning sclerotherapy in varicose vein treatment:

- Grade 1B (strong recommendation based on moderate quality evidence) recommendation for the use of sclerotherapy to treat varicose tributaries
- Grade 1B recommendation against selective treatment of perforating vein incompetence in patients with simple varicose veins
- Grade 2B (weak recommendation based on moderate quality evidence) for sclerotherapy to treat pathologic perforating veins (i.e., outward flow of  $\geq 500$  ms duration and a diameter of  $\geq 3.5$  mm) located under healed or active ulcers (CEAP class C5-C6)

The 2014 SVS/AVF guidelines<sup>[86]</sup> for management of venous ulcers included the following recommendations:

- Grade 1C (Strong recommendation, low quality or very-low quality evidence) For those patients who would benefit from pathologic perforator vein ablation, we recommend treatment by percutaneous techniques that include ultrasound-guided sclerotherapy or

endovenous thermal ablation (radiofrequency or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromise skin.

## SUMMARY

There is enough research to determine that treatment of certain symptomatic varicose veins using ligation, phlebectomy, endovenous treatment with radiofrequency or laser ablation, endovenous glue/adhesive, and sclerotherapy may improve short-term clinical outcomes (e.g., pain and return to work). Therefore, these procedures may be considered medically necessary in select patients when the policy criteria are met. Procedures not meeting the policy Criteria are considered not medically necessary. In addition, follow-up venous studies performed within six months following the most recent treatment in the absence of complications is considered not medically necessary.

There is not enough research to show improvement in health outcomes for endovenous ablation or sclerotherapy of the investigational indications listed in the medical policy Criteria. Further, the current evidence has limitations including no comparator groups, small study population, and short-term follow-up.

There is not enough research to show that mechanochemical ablation of varicose veins improves patient outcomes and is safe. Therefore, the use of mechanochemical ablation of any vein is considered investigational.

### Appendix 1: CEAP Classification

<b>Clinical classification (C)</b>	C0: no visible or palpable signs of venous disease C1: telangiectasias or reticular veins C2: varicose veins ( $\geq 3$ mm diameter) C3: edema C4: skin and subcutaneous tissue changes C4a: pigmentation or eczema C4b: lipodermatosclerosis or atrophie blanche C5: healed venous ulcer C6: active venous ulcer
Each clinical class is further characterized by a subscript for symptomatic (S) or asymptomatic (A), for example, C2A or C5S.	
<b>Etiologic classification (E)</b>	Ec: congenital Ep: primary Es: secondary (postthrombotic) En: no venous cause identified
<b>Anatomic classification (A)</b>	As: superficial veins Ap: perforator veins Ad: deep veins An: no venous location identified
<b>Pathophysiologic classification</b>	
Basic CEAP	Pr: reflux Po: obstruction Pr,o: reflux and obstruction Pn: no venous pathophysiology identifiable
Advanced CEAP includes the addition of any of following 18 venous segments as locators:	

<b>Superficial veins</b>	Telangiectasias or reticular veins Great saphenous vein above knee Great saphenous vein below knee Small saphenous vein Nonsaphenous veins
<b>Deep veins</b>	Inferior vena cava Common iliac vein Internal iliac vein External iliac vein Pelvic: gonadal, broad ligament veins, other Common femoral vein Deep femoral vein Femoral vein Popliteal vein Crural: anterior tibial, posterior tibial, peroneal veins (all paired) Muscular: gastrocnemial, soleal veins, other
<b>Perforating veins</b>	Thigh Calf

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## CODES

**NOTES:**

- This policy uses the nomenclature great saphenous vein and small saphenous vein, also known as greater or long and lesser or short saphenous veins, respectively. Current CPT nomenclature uses long and short saphenous veins.
- There is no specific CPT code for mechanochemical treatment devices (e.g., the ClariVein® device) which should be reported with an unlisted procedure code such as 37799. Per CPT definitions, it is inappropriate to use codes 37241-37244 or 37475-37479 to report this procedure.
- Varithena is not separately reimbursable using any CPT or HCPCS Code.
- There is no specific CPT code for transilluminated powered phlebectomy. Providers might elect to use CPT codes describing stab phlebectomy (37765 or 37766), excision of varicose vein cluster(s) (37785), or unlisted vascular surgery procedure (37799).
- There is no specific CPT for microfoam sclerotherapy. Providers might elect to use CPT codes describing sclerotherapy (36468-36471) or the unlisted vascular surgery procedure code 37799. Use of codes 36475-36476 would be inappropriate as the procedure is not ablation therapy.

Codes	Number	Description
		Endovenous catheter directed chemical ablation with balloon isolation of incompetent extremity vein, open or percutaneous, including all vascular access, catheter manipulation, diagnostic imaging, imaging guidance and monitoring
	36465	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; single incompetent extremity truncal vein (eg, great saphenous vein, accessory saphenous vein)
	36466	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; multiple incompetent truncal veins (eg, great saphenous vein, accessory saphenous vein), same leg
	36468	Single or multiple injections of sclerosing solutions, spider veins (telangiectasia); limb or trunk
	36470	Injection of sclerosing solution; single incompetent vein
	36471	Injection of sclerosing solution; multiple incompetent veins, same leg
	36473	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; first vein treated
	36474	;subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
	36475	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated
	36476	;subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
	36478	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated
	36479	;subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
	36482	Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous; first vein treated

Codes	Number	Description
	36483	;subsequent vein(s) treated in a single extremity, each through separate access sites (list separately in addition to code for primary procedure) Ligation and division of long saphenous vein at saphenofemoral junction, or
	37718	Ligation, division, and stripping, short saphenous vein (for bilateral procedure, use modifier 50) Ligation, division, and stripping, long (greater) saphenous veins from saphenofemoral junction to knee or below
	37735	Ligation and division and complete stripping of long or short saphenous veins with radical excision of ulcer and skin graft and/or interruption of communicating veins of lower leg, with excision of deep fascia Ligation of perforators veins, subfascial, radical (Linton type) including skin graft, when performed, open, 1 leg
	37761	Ligation of perforator vein(s), subfascial, open, including ultrasound guidance, when performed, 1 leg
	37765	Stab phlebectomy of varicose veins, one extremity; 10-20 stab incisions
	37766	Stab phlebectomy of varicose veins, one extremity; more than 20 incisions
	37780	Ligation and division of short saphenous vein at saphenopopliteal junction (separate procedure)
	37785	Ligation, division, and/or excision of varicose vein cluster(s), one leg
	37799	Unlisted procedure, vascular surgery
	93970	Duplex scan of extremity veins including responses to compression and other maneuvers; complete bilateral study
	93971	Duplex scan of extremity veins including responses to compression and other maneuvers; unilateral or limited studies
HCPCS	J3490	Unclassified drugs
	S2202	Echosclerotherapy

**Date of Origin:** October 1999

## ***Percutaneous Angioplasty and Stenting of Veins***

**Effective:** January 1, 2020

**Next Review:** September 2020

**Last Review:** November 2019

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Dilation and/or stent placement in veins is intended to restore blood flow in a narrowed or collapsed vein.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy addresses percutaneous angioplasty and stenting of **veins** only. This policy does *not* address percutaneous angioplasty and stenting of peripheral arteries, including repair of aneurysms, which may be considered medically necessary. Extracranial carotid angioplasty is addressed in a separate policy (see Cross References section).

- I. Percutaneous transluminal angioplasty, with or without stenting, may be considered **medically necessary** for the treatment of venous stenoses in the following instances:
  - A. Stenotic lesions of arteriovenous dialysis fistulas and grafts, and ipsilateral venous stenosis in the outflow of a functioning dialysis fistula and graft
  - B. Superior or inferior vena cava syndrome with significant symptoms, from either extrinsic compression or intrinsic stenosis/occlusion [when standard treatments (i.e., radiation and/or chemotherapy) have failed]

- C. Left iliac vein compression syndrome (May-Thurner Syndrome)
  - D. As an adjunct to prior or concurrent ipsilateral first rib resection for proximal upper extremity venous thrombosis due to persistent extrinsic compression (Paget-Schroetter syndrome) documented by pre-procedure imaging (i.e., ultrasound, venography, CT, or MRI)
  - E. Pulmonary vein stenosis
  - F. Thrombotic obstruction of major hepatic veins (Budd-Chiari syndrome)
  - G. Post-operative venous narrowing due to repair of sinus venosus atrial septal defect
  - H. Pulmonary artery stenosis and/or hypoplasia
  - I. Venous obstruction of an atrial baffle following Mustard or Senning repair of transposition of the great arteries
  - J. Symptomatic venous occlusion due to electrical device lead or central line placement
- II. The use of angioplasty and/or endoprotheses for creation of intrahepatic shunt connections between the portal venous system and hepatic vein may be considered **medically necessary**.
- III. Percutaneous transluminal angioplasty, with or without stenting, is considered **investigational** for all other venous indications, including but not limited to:
- A. Deep vein thrombosis that is not related to left iliac vein compression syndrome or upper extremity venous compression treated with rib resection (I.C.- D.) (e.g., inferior vena cava, iliac, lower extremity)
  - B. Chronic cerebrospinal venous insufficiency in multiple sclerosis or other conditions
  - C. Venous sinus obstruction or occlusion in idiopathic intracranial hypertension

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

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and Physical/Chart Notes
- Documentation of symptoms, associated diagnoses and treatments

## CROSS REFERENCES

1. [Extracranial Carotid Angioplasty/Stenting](#), Surgery, Policy No. 93

## BACKGROUND

### PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY OF THE VEINS

Percutaneous transluminal angioplasty (PTA) of the veins is a procedure that has been used as an alternative to open vascular surgery in order to restore blood flow through narrowed veins. Techniques may include balloon angioplasty, laser angioplasty, and stent placement.

## **INTRAVASCULAR STENTS**

Intravascular stents are used as an adjunct to angioplasty to prevent vessel wall collapse. They can be placed via transluminal catheters or placed with catheters during open vascular procedures. Drug-eluting stents are intended to prevent restenosis by reducing the growth of neointimal tissue. A number of different drugs are being evaluated for this use, including paclitaxel and sirolimus. These stents are coated with a mixture of synthetic polymers blended with the drug. A second coat of drug-free polymers is then added to serve as a diffusion barrier, thus allowing the gradual release of drug to the precise site of interest while avoiding systemic side effects.

## **ILIAC VEIN COMPRESSION SYNDROME**

Iliac vein compression syndrome (IVCS) is deep vein thrombosis (DVT) that occurs as a result of compression of the left common iliac vein between the overlying right common iliac artery and the body of the fifth lumbar vertebra. This syndrome is relatively uncommon. If DVT occurs, it is treated with anticoagulation therapy. However, the underlying mechanical compression must be treated with surgery or stent placement. Left untreated it may result in recurrent DVT or postthrombotic syndrome (PTS) characterized by chronic swelling and pain in the affected extremity. Some patients also develop varicosities and stasis ulcers. This condition may also be referred to by other terms including but not limited to May-Thurner syndrome, non-thrombotic iliac vein lesions (NIVL), and Cockett syndrome.

## **PROXIMAL UPPER EXTREMITY VENOUS THROMBOSIS**

Proximal upper extremity venous thrombosis occurs as a result of mechanical compression of the subclavian vein at the thoracic outlet. The natural history of the disorder is typically one of chronic venous obstruction with development of a painful, swollen extremity.<sup>[1,2]</sup> Thrombosis may affect the brachiocephalic, subclavian, and/or axillary veins. Typical management of this condition involves thrombolysis and surgical decompression after a variable interval of oral anticoagulation. Venous stent placement may be helpful in maintaining patency of the vein following thoracic outlet decompression surgery that includes first rib resection. This condition may also be referred to by other terms including but not limited to axillary-subclavian venous thrombosis, effort thrombosis, Paget-Schroetter syndrome, or venous thoracic outlet syndrome.

## **IDIOPATHIC INTRACRANIAL HYPERTENSION**

Idiopathic intracranial hypertension (IIH) is characterized by elevated intracranial pressure (ICP). The most common symptoms are headache and papilledema. Other symptoms include transient visual obscurations, pulsatile tinnitus, diplopia, and sustained visual loss. Initial evaluation of patients presenting with headache and papilledema consists of CT or MRI scan for possible hydrocephalus or tumor. Occlusion of the venous sinus, particularly the transverse sinus, is considered an uncommon cause of increased ICP. There has been some debate as to whether this occlusion is the cause or the effect of ICP. The hypothesis is that obstruction of venous return decreases venous outflow from the brain which also decreases cerebrospinal fluid (CSF) outflow with subsequent increase in intracranial CSF pressure.

Medical treatment includes medications that lower CSF production and/or therapeutic lumbar puncture. Since most patients with IIH are obese, weight loss is commonly recommended. If medical treatment fails to control IIH, surgical treatments include ventriculoperitoneal shunting, optic nerve sheath fenestration (optic nerve decompression), and subtemporal decompression. Angioplasty with stenting has been proposed for maintaining venous sinus patency. IIH may also be referred to as pseudotumor cerebri or benign intracranial hypertension, though these terms are considered inadequate and IIH is the preferred term.

## **CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY IN MULTIPLE SCLEROSIS**

Multiple sclerosis (MS) is generally considered a chronic inflammatory demyelinating disease of the central nervous system (brain, spinal cord, and optic nerve) believed to be triggered by an autoimmune response to myelin. However, in part due to the periventricular predilection of the lesions of MS, vascular etiologies (CCSVI) have also been considered. The core foundation of this vascular theory is that venous drainage from the brain is abnormal due to outflow obstruction in the draining jugular vein and/or azygos veins. This abnormal venous drainage, which is characterized by special ultrasound criteria, is said to cause intracerebral flow disturbance or outflow problems that lead to periventricular deposits. In the CCSVI theory, these deposits have a similarity to the iron deposits seen around the veins in the legs of patients with chronic deep vein thrombosis. Balloon dilatation, with or without stenting, has been proposed as a means to treat the outflow problems, thereby alleviating CCSVI and MS complaints.

## **REGULATORY STATUS**

While there are several types of stents that are approved by the U.S. Food and Drug Administration (FDA) for improvement of outflow for arteriovenous (A-V) access grafts in hemodialysis patients, and for the creation of intrahepatic shunt connections between the portal venous system and hepatic vein [i.e., transjugular intrahepatic portosystemic shunt (TIPS)], there are currently no stents with FDA approval for use in veins for any other indications.

In March 2017, the FDA issued a safety communication regarding the use of balloon angioplasty devices to treat autonomic dysfunction.<sup>[3]</sup> This supplemented an earlier warning from the FDA concerning the potential for adverse events following endovascular interventions to treat chronic cerebrospinal venous insufficiency (CCSVI). Reports of adverse events obtained by the FDA included death, stroke, detachment and/or migration of stents, vein damage, thrombosis, cranial nerve damage, and abdominal bleeding. This communication included the caveat that clinical trials of this procedure require FDA approval and an investigational device exemption due to potential for harms.

## **EVIDENCE SUMMARY**

The following discussion focuses on the investigational indications noted in Criterion III above.

### **DEEP VEIN THROMBOSIS (DVT)**

There are several objectives for treatment of venous thromboembolism including:<sup>[4,5]</sup>

- Prevention of pulmonary embolism;
- Restoration of unobstructed blood flow through the thrombosed vein;

- Preservation of venous valve function; and
- Prevention of recurrent thrombosis.

The current standard of treatment for achieving these goals is anticoagulant therapy (i.e., intravenous unfractionated heparin) to achieve a therapeutic partial thromboplastin time (PTT). After completion of an initial course of anticoagulation therapy, patients with venous thromboembolism (VTE) require continuing therapy to prevent recurrence. Thus, anticoagulation therapy is the standard against which percutaneous transluminal angioplasty (PTA) with or without stenting must be compared in order to evaluate the safety, efficacy, and final health outcomes. In addition, long-term follow-up is needed to determine the rates of restenosis, device failure, reoperation, and VTE recurrence.

The following literature appraisal is focused on the published evidence for DVT that is not related to left iliac vein compression syndrome or proximal upper extremity venous thrombosis.

### **Systematic Reviews**

No systematic reviews were identified.

### **Randomized Controlled Trials**

There are no randomized controlled clinical trials (RCTs) in which PTA with or without stenting was compared to standard medical management of DVT.

### **Nonrandomized Studies**

- The bulk of the current literature investigating thrombolysis followed by angioplasty and stenting is limited to small ( $n < 50$ ), non-randomized, non-comparative retrospective reviews and case series of short- to medium-term duration.<sup>[5-10]</sup>
- The majority of studies are for DVT related to extrinsic compression (e.g., May-Thurner syndrome), or have heterogeneous patient populations that include both compression-related and non-compression-related DVT.

### **IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)**

Studies for the diagnosis and treatment of IIH must answer the following questions:

1. Is venous sinus occlusion the cause or the effect of increased intracranial pressure (ICP)?
2. Is venous PTA with or without stenting safe and effective in reducing ICP compared with conventional treatment?

To assess the effectiveness and safety of intracranial venous stenting as a treatment of IIH, health outcomes must be compared with current standard treatments. The ideal clinical trial design is random allocation of similar patients to active or sham venous angioplasty, and/or conventional medical or surgical treatments.

### **Systematic Reviews**

A 2015 updated Cochrane review evaluated the evidence for IIH interventions, and included RCTs in which any intervention used to treat IIH had been compared to placebo or another form of treatment.<sup>[11]</sup> Stenting of the transverse intracerebral venous sinus was assessed as a treatment, however the reviewers found no studies that met their inclusion criteria due to the

lack of a control group for comparison. The review excluded five small case series, one retrospective review and two small clinical trials.

A 2014 systematic review of various treatments for IIH found only case series, of which 30 had extractable data.<sup>[12]</sup> Of the 332 total patients, 88 had venous sinus stenting. However, the studies only reported secondary outcomes related to symptoms of headache, papilledema, and visual acuity. The primary outcome of increased intracranial pressure was not reported. The authors concluded that the evidence was insufficient to recommend for or against any treatment modalities for IIH.

### **Randomized Controlled Trials**

There are no randomized controlled clinical trials in which PTA with or without stenting was compared to standard medical or surgical management of IIH.

### **Nonrandomized Studies**

Current evidence is limited to mainly small retrospective reviews and case series.<sup>[13-16]</sup> One of the largest studies was a retrospective review of 52 patients at a single center who underwent stenting due to IIH unresponsive to maximum acceptable medical treatment.<sup>[17]</sup> The follow-up period ranged from two months to nine years. All 52 patients were reported to have immediate elimination of the transverse sinus stenosis gradient and rapid improvement in IIH symptoms including resolution of papilledema. Six patients had relapse of symptoms (headache) and increased venous pressure with recurrent stenosis adjacent to the previous stent. In these patients, an additional stent was placed, with response similar to that following the first stent placement. Another retrospective study, published by Boddu (2019), included 70 consecutive patients who underwent venous sinus stenting for IIH and reported that 13% of the patients had impaired drainage of the vein of Labbé following treatment.<sup>[18]</sup>

## **CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY (CCSVI) IN MULTIPLE SCLEROSIS (MS)**

### **Systematic Reviews**

A Cochrane review<sup>[19]</sup> and five systematic reviews<sup>[20-24]</sup> with critical analyses of the current literature concluded that there is insufficient evidence to verify a relationship between CCSVI and MS. The authors noted the high degree of heterogeneity between study outcomes, sensitivity, and specificity, and marked variability of odds ratios.

Two meta-analyses<sup>[25,26]</sup> reported outcomes after exclusion of outlier studies (e.g., studies with a disproportionately high odds ratio (OR) and/or potential bias). Tsivgoulis (2014) reported on the association between CCSVI and MS and included 19 studies with a total of 1,250 MS patients and 899 healthy controls.<sup>[25]</sup> When data from all 19 studies were pooled, CCSVI was associated with MS with an OR of 8.35 (95% confidence interval [CI] 3.44 to 20.31,  $p < 0.001$ ). However, in additional sensitivity analyses, the OR associating CCSVI and MS decreased. In the most conservative sensitivity analysis, which excluded eight outlier studies, MS was not associated with CCSVI with an OR of 1.35 (95% CI 0.62 to 2.93,  $p = 0.453$ ). The Zwischenberger (2013) meta-analysis of 13 studies with a total of 1141 MS patients and 738 healthy controls reported CCSVI and MS was associated with MS (OR 2.57;  $p < 0.001$ ).<sup>[26]</sup> In a subsequent analysis of nine studies with four outliers (studies with disproportionately high ORs) removed, the OR decreased, but still associated CCSVI with MS.

A systematic review of the association between CCSVI and MS was published by Laupacis (2011).<sup>[23]</sup> This review included eight studies that used ultrasound to diagnose CCSVI by the Zamboni criteria and compared the rate of CCSVI in patients with MS to those without MS. These studies were mostly small, with the median number of patients with MS of 50. A large degree of heterogeneity existed across studies in the rate of CCSVI among MS patients. Two smaller studies reported a rate of 0% for CCSVI in a total of 20 and 56 patients with MS. In contrast, the original study by Zamboni (2009a) reported a 100% rate of CCSVI in 109 patients with MS.<sup>[27]</sup> A small study of 25 patients also reported a very high rate of CCSVI at 84% (21/25). There was no obvious reason identified for this large discrepancy in CCSVI rates; the authors hypothesized that the most likely reason was variability in ultrasound technique and interpretation. The analysis suggested a significant association of CCSVI with MS in combined analysis, with an OR of 13.5 (95% CI, 2.6 to 71.4). A substantial degree of heterogeneity existed in this measure as well, with a reported I<sup>2</sup> of 89%. Several sensitivity analyses showed marked variability of the OR from a low of 3.7 to more than 58,000. However, in all cases the association of CCSVI with MS remained significant.

Another systematic review published in 2011 included a smaller number of studies (n = 4) but reached conclusions similar to the other analyses.<sup>[24]</sup> The rate of CCSVI in MS patients ranged from 7% to 100%, and the rate in non-MS patients ranged from 2% to 36%. A significant association was detected between MS and CCSVI but with a high degree of heterogeneity (I<sup>2</sup>=96%) and an OR for association that varied widely, from approximately 2 to more than 26,000.

A recently updated Cochrane review evaluated the evidence for PTA to treat CCSVI in patients with MS and included three RCTs, described in greater detail below (total n=238).<sup>[28]</sup> Two of the studies were judged to be at unclear risk of bias for one item (random sequence generation in one study and blinding in the other), but otherwise at low risk of bias. The authors concluded that there was moderate-quality evidence that venous PTA did not improve health outcomes for patients with MS and that further study was not necessary.

### **Randomized Controlled Trials (RCT)**

A randomized wait list study by Napoli (2019) included 66 MS patients with a diagnosis of CCSVI who were randomized to receive venous PTA immediately (vPTA-yes) or after six months (vPTA-no).<sup>[29]</sup> A number of outcomes were assessed, including clinical-functional measures, evoked potentials and upper limb kinematic measures. While there were some statistically significant differences between groups for a composite functional outcome, there were no differences in evoked potential or upper limb kinematic measures.

The following three studies were included in the Cochrane review described above:

Traboulee (2018) published a double-blind RCT of balloon (vs. sham) venoplasty for MS patients with narrowing of the extracranial jugular and azygos veins.<sup>[30]</sup> The trial included 104 patients, 49 randomized to venoplasty and 55 to sham treatment, and 103 patients completed the trial with 48 weeks of follow-up. Narrowing of the veins >50% was confirmed by venography prior to randomization. The primary outcome of the trial was change in the MS Quality of Life-54 (MSQOL-54) questionnaire from baseline at 48 weeks. Additional clinical and MRI outcomes were also evaluated. There was no difference found between groups for any of the study's outcomes, and the authors concluded that "for patients with MS, balloon venoplasty of extracranial jugular and azygos veins is not beneficial in improving patient-reported, standardized clinical, or MRI outcomes."

Results from the Brave Dreams trial were published by Zamboni (2018).<sup>[31]</sup> This was a double-blind, sham-controlled RCT conducted at six MS centers in Italy and included a total of 115 CCSVI patients. These patients were randomized to either venous PTA (n=76) or catheter venography without angioplasty (sham, n=39). There were two primary endpoints assessed at 12 months: the number of new or expanded cerebral lesions by MRI, and a functional measure that included walking control, manual dexterity, balance, postvoid residual urine volume, and visual acuity. There were no significant differences in these endpoints between groups, and no adverse events were reported. The authors concluded that venous PTA was “a safe but largely ineffective technique; the treatment cannot be recommended in patients with MS.”

Siddiqui (2014) published results from a prospective, double-blind, sham-controlled randomized clinical trial (RCT) of venous angioplasty in MS patients with CCSVI.<sup>[32]</sup> This trial enrolled nine patients in intervention group and 10 in the sham-controlled group. All patients met the criteria for diagnosis of CCSVI.<sup>[33]</sup> The primary end points of the trial included safety at 24 hours and 30 days postangioplasty; greater than 75% restoration of venous outflow at 30 days; the presence of new MS lesions; and relapse rate over six months. Secondary end points included changes in disability scores, brain volume, cognitive test scores, and quality-of-life measures. All patients tolerated the procedures well; no operative or postoperative complications were identified. One patient in the angioplasty group experienced an episode of symptomatic bradycardia. No significant differences were observed in venous outflow characteristics between the treated and control groups, nor were any significant improvements observed in clinical disease scores among treated patients compared with controls. The results of this RCT are limited by the small number of patients. However, the failure to show a beneficial effect of venous angioplasty on MS activity supports a lack of efficacy for this treatment.

## Nonrandomized Studies

The studies that focused on the potential relationship between CCSVI and MS reported varying and contradictory outcomes. For example, while Zamboni (2009a) and other authors<sup>[27,34-36]</sup> reported a strong association between CCSVI and MS, numerous studies have reported insignificant or no difference in the prevalence of CCSVI in MS patients compared to healthy controls, or no association between CCSVI and MS occurrence or symptoms<sup>[33,35,37-43]</sup>.

The studies that focused on outcomes of PTA with or without stent placement reported few adverse events, but mixed efficacy outcomes.<sup>[44-50]</sup> For example, while Zamboni (2009b).<sup>[45]</sup> reported significant improvement in all measures for patients with relapsing-remitting MS, Kosteki (2011) reported a significant improvement only in heat intolerance and fatigue severity six months post endovascular treatment.<sup>[44]</sup> No trials were found that compared PTA with concurrent control groups. All authors noted the need for well-designed randomized clinical trials. Many authors asserted that PTA with or without stenting in these patients should not be performed outside the clinical trial setting.

## Adverse Events

Burton (2011) described five patients who had undergone venoplasty and presented with complications of the procedure.<sup>[51]</sup> The complications were internal jugular vein stent thrombosis, cerebral sinovenous thrombosis, stent migration, cranial nerve injury, and injury associated with venous catheterization. There was not a denominator in these studies to determine the rate of these events.

Petrov (2011) reported on the safety profile of 495 venoplasty procedures performed in 461 patients with MS, including 98 stent implantations.<sup>[46]</sup> There were no deaths, major bleeding events, or acute exacerbations of MS. The most common procedure-related complication was vein dissection, which occurred in 3.0% of cases. Other complications included cardiac arrhythmias (1.2%), groin hematoma (1.0%), vein rupture (0.4%), and acute stent thrombosis (1.6%).

Mandato (2012) reported adverse events within 30 days of endovascular intervention for 240 patients with MS over an 8-month period.<sup>[52]</sup> Neck pain occurred in 15.6% of patients, most commonly following stent implantation. Headache occurred in 8.2% of patients and was persistent past 30 days in 1 patient (0.4%). Intraprocedural arrhythmias occurred in 1.3%, and one patient was diagnosed with a stress-induced cardiomyopathy following the procedure.

An FDA alert issued in May 2012 reported the potential for adverse events following endovascular interventions for MS. Reports of adverse events obtained by FDA included death, stroke, detachment and/or migration of stents, vein damage, thrombosis, cranial nerve damage, and abdominal bleeding. This alert included the caveat that clinical trials of this procedure require FDA approval and an investigational device exemption because of the potential for harms.

## PRACTICE GUIDELINE SUMMARY

### DEEP VEIN THROMBOSIS

Two consensus-based clinical practice guidelines from the Society of Interventional Radiology and the American Heart Association, respectively, provided evidence appraisals and noted a benefit in venous stenting for DVT.<sup>[53,54]</sup> However, the majority of the references listed were related to May-Thurner syndrome which is caused by extrinsic compression for which stenting is considered medically necessary. Both guidelines graded the available evidence as very limited.

#### Society of Vascular Surgery / American Venous Forum

In the 2014 joint guidelines published by Society of Vascular Surgery and American Venous Forum on the management of proximal chronic total venous occlusion/severe stenosis.<sup>[55]</sup> The guideline states the following:

*In a patient with inferior vena cava or iliac vein chronic total occlusion or severe stenosis, with or without lower extremity deep venous reflux disease, that is associated with skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we recommend venous angioplasty and stent recanalization in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence.*

This was a grade 1 recommendation (strong) but the evidence was considered low/very low quality which was primarily focused on May-Thurner syndrome.

#### American College of Radiology (ACR)

The 2012 ACR Appropriateness Criteria® for radiologic management of lower extremity venous insufficiency recommendation did not address angioplasty or stenting for these indications.<sup>[56]</sup> However, they suggest that patients with venous insufficiency and associated

venous occlusion or stenosis of the common iliac vein may require venous recanalization with angioplasty and stenting as an adjunctive treatment, based on three case reports and one small retrospective analysis.

## **CHRONIC CEREBROSPINAL VENOUS INSUFFICIENCY (CCSVI) IN MULTIPLE SCLEROSIS (MS)**

### **Society of Interventional Radiology (SIR)**

In 2010 the SIR published a position statement on the association of CCSVI with MS and the efficacy of endovascular treatments.<sup>[57]</sup> Their recommendations included the following statements:

- At present, SIR considers the published literature to be inconclusive on whether CCSVI is a clinically important factor in the development and/or progression of MS, and on whether balloon angioplasty and/or stent placement are clinically effective in patients with MS.
- SIR strongly supports the urgent performance of high-quality clinical research to determine the safety and efficacy of interventional MS therapies, and is actively working to promote and expedite the completion.

## **SUMMARY**

There is enough research to show that percutaneous venous angioplasty, with or without stenting, can improve health outcomes for patients with certain types of venous stenosis. Therefore, this angioplasty may be considered medically necessary for patients that meet the policy criteria.

There is not enough research to show that percutaneous venous angioplasty, with or without stenting, can improve health outcomes for patients that do not meet the policy criteria, including patients with deep vein thrombosis that is not related to upper extremity venous compression requiring rib resection or iliac vein compression syndrome, chronic cerebrospinal venous insufficiency, or venous sinus obstruction or occlusion in idiopathic intracranial hypertension. Therefore, this procedure is considered investigational when policy criteria are not met.

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## CODES

Codes	Number	Description
		Percutaneous portal vein catheterization by any method
	36901	Introduction of needle(s) and/or catheter(s), dialysis circuit, with diagnostic angiography of the dialysis circuit, including all direct puncture(s) and catheter placement(s), injection(s) of contrast, all necessary imaging from the arterial anastomosis and adjacent artery through entire venous outflow including the inferior or superior vena cava, fluoroscopic guidance, radiological supervision and interpretation and image documentation and report
	36902	;with transluminal balloon angioplasty, peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty
	36903	;with transcatheter placement of intravascular stent(s), peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the stenting, and all angioplasty within the peripheral dialysis segment
		Percutaneous transluminal mechanical thrombectomy and/or infusion for thrombolysis, dialysis circuit, any method, including all imaging and radiological

	supervision and interpretation, diagnostic angiography, fluoroscopic guidance, catheter placement(s), and intraprocedural pharmacological thrombolytic injection(s)
36905	;with transluminal balloon angioplasty, peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty
36906	;with transcatheter placement of intravascular stent(s), peripheral dialysis segment, including all imaging and radiological supervision and interpretation necessary to perform the stenting, and all angioplasty within the peripheral dialysis circuit
36907	Transluminal balloon angioplasty, central dialysis segment, performed through dialysis circuit, including all imaging and radiological supervision and interpretation required to perform the angioplasty (List separately in addition to code for primary procedure)
36908	Transcatheter placement of intravascular stent(s), central dialysis segment, performed through dialysis circuit, including all imaging radiological supervision and interpretation required to perform the stenting, and all angioplasty in the central dialysis segment (List separately in addition to code for primary procedure)
36909	Dialysis circuit permanent vascular embolization or occlusion (including main circuit or any accessory veins), endovascular, including all imaging and radiological supervision and interpretation necessary to complete the intervention (List separately in addition to code for primary procedure)
37238	Transcatheter placement of an intravascular stent(s), open or percutaneous, including radiological supervision and interpretation and including angioplasty within the same vessel, when performed; initial vein
37239	; each additional vein (List separately in addition to code for primary procedure)
37248	Transluminal balloon angioplasty (except dialysis circuit), open or percutaneous, including all imaging and radiological supervision and interpretation necessary to perform the angioplasty within the same vein; initial vein
37249	<u>;each additional vein</u> (List separately in addition to code for primary procedure)
HCPCS C2623	Catheter, transluminal angioplasty, drug-coated, non-laser

**Date of Origin:** January 1996

## ***Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease (GERD)***

**Effective:** March 1, 2020

**Next Review:** November 2020

**Last Review:** January 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Transesophageal endoscopic therapies are a group of minimally invasive antireflux procedures being investigated as alternatives to medical management or fundoplication surgery in the treatment of GERD.

### **MEDICAL POLICY CRITERIA**

Transesophageal endoscopic therapies are considered **investigational** for the treatment of gastroesophageal reflux disease (GERD). These procedures include but are not limited to the following:

- I. Transesophageal endoscopic gastroplasty procedure (i.e., MUSE)
- II. Transoral incisionless fundoplication (TIF) procedure, (i.e., EsophyX)
- III. Transesophageal radiofrequency energy procedure (i.e., Stretta)
- IV. Endoscopic submucosal implantation of a prosthesis or injection of a bulking agent (i.e., Durasphere, polymethylmethacrylate [PMMA] beads, the Gatekeeper Reflux Repair system)

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

## CROSS REFERENCES

1. [Bariatric Surgery](#), Surgery, Policy No. 58
2. [Gastric Reflux Surgery](#), Surgery, Policy No. 186
3. [Magnetic Esophageal Ring to Treat Gastroesophageal Reflux Disease \(GERD\)](#), Surgery, Policy No. 190

## BACKGROUND

Gastroesophageal reflux disease (GERD) is a common disorder characterized by heartburn and other symptoms related to reflux of stomach acid into the esophagus. Nearly all individuals experience such symptoms at some point in their lives; a smaller number have chronic symptoms and are at risk for complications of GERD. The prevalence of GERD has been estimated to be 10% to 20% in the Western world, with a lower prevalence in Asia.<sup>[1]</sup>

The pathophysiology of GERD involves excessive exposure to stomach acid, which occurs for several reasons. There can be an incompetent barrier between the esophagus and stomach, either due to dysfunction of the lower esophageal sphincter (LES) or incompetence of the diaphragm. Another mechanism is abnormally slow clearance of stomach acid by the esophagus. In this situation, delayed clearance leads to an increased reservoir of stomach acid and a greater tendency to reflux.

In addition to troubling symptoms, some patients will have more serious disease, which results in complications such as erosive esophagitis, dysphagia, Barrett esophagus, and esophageal carcinoma. Pulmonary complications may result from aspiration of stomach acid into the lungs and can include asthma, pulmonary fibrosis and bronchitis, or symptoms of chronic hoarseness, cough, and sore throat.

Guidelines on the management of GERD emphasize initial medical management. Weight loss, smoking cessation, head of bed elevation, and elimination of food triggers are all recommended in recent practice guidelines.<sup>[1]</sup> Proton pump inhibitors (PPIs) have been shown to be the most effective medical treatment. In a Cochrane systematic review, PPIs demonstrated superiority to H<sub>2</sub>-receptor agonists and prokinetics in both network meta-analyses and direct comparisons.<sup>[2]</sup>

The most common surgical procedure used for GERD is laparoscopic Nissen fundoplication. Fundoplication involves wrapping a portion of the gastric fundus around the distal esophagus to increase LES pressure. If a hiatal hernia is present, the procedure also restores the position of the LES to the correct location. Laparoscopic fundoplication was introduced in 1991 and has been rapidly adopted because it avoids complications associated with an open procedure.

Although fundoplication results in a high proportion of patients reporting symptom relief, complications can occur, and sometimes require conversion to an open procedure. Patients who have relief of symptoms of GERD after fundoplication may have dysphagia or gas-bloat syndrome (excessive gastrointestinal gas).

Due in part to the high prevalence of gastroesophageal reflux disease, there has been interest in creating a minimally invasive transesophageal therapeutic alternative to open or laparoscopic fundoplication or chronic medical therapy. This type of procedure may be considered natural orifice transluminal surgery. Three types of procedures have been investigated.

1. Transesophageal endoscopic gastroplasty (gastroplication, transoral incisionless fundoplication) can be performed as an outpatient procedure. During this procedure, the fundus of the stomach is folded, and then held in place with staples or fasteners that are deployed by the device. The endoscopic procedure is designed to recreate a valve and barrier to reflux.
2. Radiofrequency (RF) energy has been used to produce submucosal thermal lesions at the gastroesophageal junction. (This technique has also been referred to as the Stretta procedure). Specifically, RF energy is applied through 4 electrodes inserted into the esophageal wall at multiple sites both above and below the squamocolumnar junction. The mechanism of action of the thermal lesions is not precisely known but may be related to ablation of the nerve pathways responsible for sphincter relaxation or may induce a tissue-tightening effect related to heat-induced collagen contraction and fibrosis.
3. Submucosal injection or implantation of a prosthetic or bulking agent to enhance the volume of the lower esophageal sphincter has also been investigated.

One bulking agent, pyrolytic carbon-coated zirconium oxide spheres (Durasphere®), is being evaluated.

The Gatekeeper™ Reflux Repair System (Medtronic) utilizes a soft, pliable, expandable prosthesis made of a polyacrylonitrile-based hydrogel. The prosthesis is implanted into the esophageal submucosa, and with time, the prosthesis absorbs water and expands, creating bulk in the region of implantation.

Endoscopic submucosal implantation of polymethylmethacrylate (PMMA) beads in to the lower esophageal folds has also been investigated.

## REGULATORY STATUS

In 2007, EsophyX® (EndoGastric Solutions, Redmond, WA) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for full-thickness plication. In 2016, EsophyX® Z Device with SerosaFuse Fasteners was cleared for marketing (K160960) by FDA through the 510(k) process for use in transoral tissue approximation, full thickness plication, ligation in the gastrointestinal tract, narrowing the gastroesophageal junction, and reduction of hiatal hernia of 2 cm or less in patients with symptomatic chronic gastroesophageal reflux disease (GERD).<sup>[3]</sup> In June 2017, EsophyX2 HD and the third-generation EsophyX Z Devices with SerosaFuse fasteners and accessories were cleared for marketing by FDA through the 510(k) process (K171307) for expanded indications, including patients who require and respond to pharmacologic therapy and in patients with hiatal hernias larger than 2 cm when a laparoscopic hiatal hernia repair reduces the hernia to 2 cm or less.<sup>[4]</sup> FDA product code: ODE.

The Medigus SRS Endoscopic Stapling System (MUSE, Medigus) was cleared for marketing by FDA through the 510(k) process in 2012 (K120299) and 2014 (K132151). MUSE is intended for endoscopic placement of surgical staples in the soft tissue of the esophagus and stomach to create anterior partial fundoplication for treatment of symptomatic chronic GERD in patients who require and respond to pharmacologic therapy. FDA product code: ODE.

In 2000, the CSM Stretta® System was cleared for marketing by FDA through the 510(k) process for general use in the electrosurgical coagulation of tissue and is specifically intended

for use in the treatment of GERD. Stretta® is currently manufactured by Mederi Therapeutics (Greenwich, CT). FDA product code: GEI.

Durasphere® is a bulking agent approved for treatment of urinary and fecal incontinence. Use of this product for esophageal reflux would be considered off-label use. The website of Carbon Medical Technologies states that Durasphere GR is an investigational device in the United States “intended to treat problems associated with GERD.”

## EVIDENCE SUMMARY

### MULTIPLE ENDOSCOPIC PROCEDURES

#### Systematic Reviews

A 2005 report of the Agency for Healthcare Research and Quality (AHRQ), on “Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease,” indicated additional efficacy and safety data on new endoscopic approaches were needed.<sup>[5]</sup> A 2011 update of the AHRQ report excluded Enteryx and the NDO Plicator, since they were no longer available in the U.S., and added the EsophyX procedure (endoscopic fundoplication), which was commercialized after the 2005 review.<sup>[6]</sup> The 2011 update reported the following:

The AHRQ report concluded that for the 3 available endoscopic procedures (EndoCinch, Stretta, EsophyX), effectiveness remains substantially uncertain for the long-term management of GERD. While some clinical benefits were observed in patients who had these procedures, the studies were generally small, of variable quality, and of short duration. In addition, all of these procedures have been associated with complications, including dysphagia, infection/fever, and bloating; complications which are also side effects associated with laparoscopic fundoplication<sup>[7]</sup> Higher quality studies are needed to determine the role and value of endoscopic procedures in the treatment of patients with GERD. A 2015 review of endoscopic treatment of GERD noted that EndoCinch is no longer manufactured.<sup>[8]</sup>

A systematic review was conducted in 2009 to examine 7 endoscopic treatments for GERD that included 33 studies, only 2 of which were RCTs.<sup>[9]</sup> The remainder were case series. The authors concluded, “...despite the potential benefits of these procedures, there is insufficient evidence at present to establish their safety and efficacy, particularly in the long term.”

### TRANSESOPHAGEAL ENDOSCOPIC GASTROPLASTY AND TRANSORAL INCISIONLESS FUNDOPLICATION (TIF)

#### Systematic Reviews

McCarty (2018) published a systematic review of RCTs and nonrandomized studies that showed significant improvement in a number of clinical outcomes for patients treated with TIF.<sup>[10]</sup> For example, 89% of TIF patients discontinued PPI therapy after the procedure, and the Gastroesophageal Reflux Disease Health-Related Quality of Life (GERD-HRQL) questionnaire, Gastroesophageal Reflux Symptom Score, and Reflux Symptom Index (RSI) measures showed significant improvement. The review had several limitations, including the risk of heterogeneity bias, due to the inclusion of studies of first- and second-generation TIF devices and protocols.

Richter (2018) published a network meta-analysis of RCTs comparing TIF or laparoscopic Nissen fundoplication (LNF) with sham or PPIs.<sup>[11]</sup> The meta-analysis was limited by low-quality studies (one did not report randomization method, others lacked data on allocation concealment, blinding of outcome assessors, or other aspects of study protocol). It should be noted that a reason behind for scarcity of direct comparisons between TIF and LNF is the discrepancy in populations requiring the respective treatments: consequently, TIF studies included patients with mild esophagitis and small hiatal hernias (<2 cm), while LNF studies included patients with Los Angeles grade A, B, C, or D esophagitis and all sizes of hiatal hernias.

## Randomized Controlled Trials

In 2018, Trad reported five-year outcomes on the manufacturer-sponsored TEMPO randomized controlled trial (RCT).<sup>[12]</sup> Three-year results were reported in 2016<sup>[13]</sup>, other interim results were previously reported as well.<sup>[14,15]</sup> Below are highlights from each publication:

- Participants with small or absent hiatal hernias (<2cm) and GERD symptoms while on PPI therapy for at least six months who also had abnormal esophageal acid exposure (EAE) were randomized to either EsophyX® (n=40) treatment or PPI therapy (n=23). After six months of evaluation, 21 remaining PPI therapy participants elected to crossover to EsophyX.
- At three years follow-up, 52 participants were assessed for (1) GERD symptom resolution, (2) healing of esophagitis using endoscopy, (3) EAE, and (4) discontinuation of PPI use. Two participants required revision surgery. As assessed by questionnaire (the Reflux Disease Questionnaire [RDQ], and the Reflux Symptom Index [RSI]), primary outcomes of GERD resolution and elimination of all troublesome atypical symptoms was observed in 37/40 participants, and 42/48 participants, respectively.
- At five years follow-up, data were available for 44 patients, of whom 37 (86%) showed elimination of troublesome regurgitation at 5 years. Twenty (43%) patients were completely off PPIs at the 5-year follow-up, and 31 (70%) patients expressed satisfaction with the procedure, as assessed by the GERD-HRQL scores. While data on pH normalization were available for 24 patients at the 3-year follow-up, at 5 years, 22% (n=5) of these patients could not be assessed for pH normalization.
- Although mean symptom scores were reportedly improved, standard deviations for primary (and secondary) outcomes suggest a wide range of responses and further well-designed studies may be warranted.

In 2015, four RCTs that compared the EsophyX® device to proton pump inhibitor (PPI) treatment or to a sham control were identified, 2 of which were industry sponsored. The studies differed in whether patients' symptoms were or were not controlled on PPI therapy, in the control used (i.e., sham, sham plus PPI, PPI alone), whether patients were blinded to treatment, and in outcome measures. Included in the studies were patients on daily PPI therapy for moderate-to-severe GERD symptoms. Exclusion criteria common to the RCTs are body mass index (BMI) over 35 kg/m<sup>2</sup>, hiatal hernia greater than 2 cm; esophagitis grade C or D; Barrett esophagus greater than 2 cm, and esophageal ulcer. Most studies allowed crossover to the other intervention with continued follow-up after the randomized portion of the study.

The largest RCT with the lowest risk of bias was an industry-sponsored, double-blind, sham-controlled multicenter study (RESPECT) that evaluated TIF in patients whose symptoms were not well controlled on PPIs.<sup>[16]</sup> Of 696 patients screened, 129 met inclusion and exclusion criteria and were randomized in a 2:1 ratio; 87 patients received TIF with EsophyX®-2 combined with 6 months of placebo (TIF/placebo) and 42 patients received sham surgery with 6 months of daily PPI therapy (sham/PPI). The primary outcome measure was elimination of troublesome regurgitation, defined as mild symptoms for 2 or more days per week or moderate-to-severe symptoms for more than 1 day per week. Crossover was allowed at 3 months in the case of treatment failure or at 6 months when the blind was broken. Lack of response at 3 months was observed in 36% of patients in the sham/PPI group compared with 11% in the TIF/placebo group ( $p=0.002$ ). Self-reported regurgitation was eliminated in 22% more patients following TIF compared to continued PPI therapy patients (67% vs 45%,  $p=0.023$ ), while reductions in GERD symptoms scores were similar in the 2 groups. The objective measure of control of esophageal pH was significantly reduced after TIF (mean percent time esophageal pH <4 decreased from 9.3% to 6.3%,  $p<0.001$ ), but not after sham surgery (from 8.6% to 8.9%). By the 18-month follow-up, 71% of patients in the sham/PPI group had crossed over to TIF, compared with 28% of patients in the TIF/placebo group who resumed PPI therapy ( $p<0.001$ ). There were 5 moderate-to-severe complications in the TIF group compared to one in the sham group. Strengths of this study include the use of both sham surgery and placebo control to maintain double-blinding, adequate power, objective as well as subjective outcome measures, and use of intention-to-treat analysis. A limitation is the relatively short duration of follow-up for most outcome measures.

Several other RCTs from 2015 have evaluated TIF in patients whose symptoms are at least partially controlled by PPI therapy.

Hakonsson reported a double-blind, sham-controlled randomized trial with 44 patients who had moderate-to-severe GERD symptoms without PPI therapy.<sup>[17]</sup> Controls received a sham procedure, and the primary outcome was the time in remission, which was longer following TIF than sham (197 days vs 107 days,  $p<0.0001$ ). Secondary outcomes measuring GERD symptoms showed results consistent with more favorable outcomes in the TIF group, however, no statistical between-group analysis was reported for these outcomes. Dysphagia, bloating, and flatulence were reported in twice as many patients undergoing TIF (4, 4, and 2 respectively) compared with sham (2, 2, and 1, respectively). These were reported as not statistically different, however, it is unlikely that the study was powered to detect differences in these outcomes.

Witteman reported an unplanned interim analysis of an RCT of 60 patients randomized to TIF using EsophyX®-2 or continued PPI therapy.<sup>[18]</sup> Sixty of the planned 120 patients had been recruited at the time of analysis. The patients' symptoms were adequately controlled by PPIs but they wanted to avoid lifelong PPI therapy. At 6 months, subjective GERD symptoms improved to a greater extent in the TIF group ( $p<0.001$ ), and satisfaction scores were higher (50% satisfied vs 0%), but there was no significant difference in esophageal acid exposure ( $p=0.228$ ) or pH normalization (50% vs 63%) between the TIF and PPI groups, respectively. At 12 months after TIF, normalization of pH was achieved in only 29% of patients and there was deteriorated valve appearance at endoscopy; 61% of TIF patients had resumed use of PPIs.

Trad reported 6- and 12-month results of an industry-funded, multicenter RCT (TEMPO) that compared TIF using EsophyX®-2 ( $n=40$ ) versus maximal dose PPI therapy ( $n=23$ ) in partial responders to PPI therapy.<sup>[14,15]</sup> At the 6-month follow-up, the subjective measure of

troublesome regurgitation was eliminated in 97% of TIF patients versus 50% of PPI patients (relative risk, 1.9;  $p=0.006$ ). At 6 months, 90% of patients in the TIF group had completely stopped PPI therapy. However, the objective measure of normalized esophageal acid exposure did not differ significantly between groups (TIF=54% vs PPI=52%,  $p=0.914$ ). At 12 months after TIF, 77% of patients had symptom control, 82% had stopped PPI therapy, 100% had healed esophagitis, and 45% had normalized esophageal acid exposure.

Additional controlled trials (RCTs) comparing transesophageal endoscopic gastroplasty or plication procedures to sham or other endoscopic procedures have been identified.<sup>[15,19-24]</sup> Though these studies showed a promising decrease in PPI use and symptom control at 3 to 12 months, they do not allow conclusions regarding long-term health outcomes, safety or durability of the procedure in patients with GERD for one or more of the following reasons:

**Insufficient study durations** – Only short-term follow-up of 3 to 12 months is available, which does not address the long-term safety and durability of the procedures.<sup>[15,20-25]</sup> For example, there may be suture loss over time. One study reported up to 29 % of study subjects required a second procedure at 12-month follow-up.<sup>[20]</sup> Of these patients, 72% of sutures were still present but only 19% were judged functional. A second study noted marked loss of sutures with 67% remaining at 12 months.<sup>[22]</sup>

**Small sample size** – Given the prevalence of GERD in the general population, available randomized trials include very small sample sizes. The largest study of 159 patients had an almost 10% loss in reported data with an intention to treat analysis that did not include these patients. All other studies include sample sizes of 60 or fewer patients. It is unclear if these studies are adequately powered.<sup>[15,20,22-26]</sup>

**Unreliable endpoints** – The use of subjective, point in time GERD questionnaires as a primary endpoint may give variable results depending upon symptoms present at the time the subject completes the questionnaire.<sup>[15,20,21]</sup>

Improvement over the gold standard procedures was not demonstrated. In order to establish the efficacy of transoral procedures, an improvement in symptoms of gastric reflux over the current open or laparoscopic anti-reflux procedures, must be shown.<sup>[15,24,26]</sup>

There is a single randomized trial of the TIF procedure, which compares TIF to Nissen laparoscopic fundoplication.<sup>[25]</sup> Although the authors reported comparable results at 12 months, conclusions based upon this trial are limited by the small sample size ( $n=52$ ) and the different methods used for TIF (both the Plicator® and the EsophyX).

## **Nonrandomized Studies**

Observational studies<sup>[27-58]</sup>, registry data<sup>[59,60]</sup> nonrandomized comparative studies<sup>[61]</sup> of gastroplication and fundoplication (specifically, transoral incisionless fundoplication) procedures do not allow conclusions about their long-term effectiveness and durability.

## **Harms**

Of note, although harms are not systematically reported across observational studies, Furnee reported an increased risk of gastric injury with laparoscopic Nissen fundoplication after failed EsophyX fundoplication.<sup>[62]</sup> Of 88 patients in their database who underwent EsophyX fundoplication, 11 (12.5%) subsequently underwent Nissen fundoplication for persistent or recurrent symptoms at a mean 8.1 months after the primary procedure. Endoscopy showed

partial or total disruption of fasteners in 8 of the 11 patients (72.7%). Nissen fundoplication after EsophyX resulted in gastric perforation (n=2), conversion to laparotomy (n=1), subphrenic abscess requiring surgical exploration (n=1) and symptom-worsening in 4 patients.

In 2017, Huang conducted a systematic review with meta-analysis of TIF for the treatment of GERD.<sup>[63]</sup> Authors included 5 RCTs and 13 prospective observational studies, of which 14 were performed with the TIF 2 procedure. Efficacy results from the RCTs were combined for patients whose symptoms were controlled by PPIs and for those whose symptoms were not controlled by PPIs, and are not further discussed here. Follow-up out to 6 years in prospective observational studies indicated a decrease in efficacy over time. The reported incidence of severe adverse events, consisting of gastrointestinal perforation and bleeding, was 19 (2.4%) out of 781 patients. This included 7 perforations, 5 cases of post-TIF bleeding, 4 cases of pneumothorax, 1 case requiring intravenous antibiotics, and 1 case of severe epigastric pain.

## **TRANSESOPHAGEAL RADIOFREQUENCY ENERGY (I.E., THE STRETTA PROCEDURE)**

### **Systematic Reviews**

Fass (2017) published a meta-analysis of cohort studies and RCTs evaluating the Stretta procedure for patients with GERD (N=2468 total, 9-558 per study).<sup>[64]</sup> The meta-analysis included 4 RCTs, 23 cohort studies, and 1 registry. Follow-up time varied from 3-120 months. When RCT and cohort results were pooled, there were clinically significant treatment effects for several of end points; however, the analysis was limited by the lack of control groups in many studies. Also, only 1 end point was shared between the four included RCTs.

A meta-analysis of four RCTs (total N=165 patients) was published by Lipka in 2015.<sup>[65]</sup> Three trials compared Stretta with sham, and one trial compared Stretta with PPI therapy. Results of the individual sham-controlled trials were inconsistent, generally supporting some improvement in symptoms, but not in objective measures of esophageal acid exposure. For example, Corley (2008) reported improvement in heartburn symptoms, quality of life, and general physical quality of life in the active treatment group compared with the sham group, but there were no significant differences in medication use and esophageal acid exposure.<sup>[66]</sup> Aziz (2010) found statistically significant improvements in GERD-HRQL in all treatment groups.<sup>[67]</sup> Arts (2012) reported that the symptom score and quality-of-life score for bodily pain improved, but no changes were observed in PPI use, esophageal acid exposure, or lower esophageal sphincter pressure after RF.<sup>[68]</sup> Pooled results of the meta-analysis showed no significant difference between Stretta and either sham treatment or PPI management for the measured outcomes, including the ability to stop PPI therapy. The overall quality of evidence was considered to be very low with a high risk of bias, and the meta-analysis was limited by heterogeneity in the included studies, which may be due to small sample sizes, differences in measures, and differences in follow-up time.

A 2014 systematic review and meta-analysis of four randomized trials; three reviewed previously<sup>[66-68]</sup> and one trial which compared Stretta with PPI therapy,<sup>[69]</sup> included a total of 165 patients. The overall quality of the evidence was considered to be very low with a high risk of bias. The pooled results showed no significant difference between Stretta and sham or PPI management for the measured outcomes. The meta-analysis was limited by heterogeneity in the included studies, which may be due to small sample sizes, differences in measures, and differences in follow-up time. The author also identified significant risks associated with Stretta, including pneumonia, gastroparesis, esophageal perforation, cardiac arrest, and at least 4 deaths from review of the Manufacturer and User Facility Device Experience database.

A meta-analysis completed by Perry, included 20 studies, only 2 of which were RCTs. This meta-analysis was limited by the inclusion of lower quality studies and by the analysis, which only examined within-subject differences and did not include between-subject differences, as reported in the RCTs.<sup>[70]</sup>

## **Randomized Controlled Trials**

There are 4 randomized trials comparing transesophageal radiofrequency (RF) energy with a sham procedure that involved balloon inflation but no needle deployment or RF energy delivery.<sup>[66-68]</sup>

Results of the first study failed to include 20% of the randomized patients in analysis of primary endpoints, and no intention to treat analysis was provided. Therefore, reported results of improved heartburn symptoms and GERD quality of life scores are not reliable.

Results of the second, third and fourth studies were flawed due to a small patient population and inadequate timeframe for follow up.

Other small RCT's have been published. Two compared RF to PPI therapy. One trial showed promising short-term (6 months) results but does not permit conclusions about mid- to long-term effectiveness and durability.<sup>[71]</sup> Another compared RF with PPI therapy to PPI therapy alone.<sup>[72]</sup> Results at 3 months appeared favorable to the Stretta group, however, the study sample was small (N=20) and power calculations were not conducted.

## **Nonrandomized Studies**

Other clinical studies concerning transesophageal radiofrequency are limited to observational case series that do not allow conclusions about long-term effectiveness and durability.<sup>[19,73-84]</sup> Though several case series report up to 4-10 year outcomes, there was a significant loss to follow-up in these studies such that conclusions on durability and health outcomes cannot be made.<sup>[85]</sup>

## **INJECTION OR IMPLANTATION OF BIOCOMPATIBLE POLYMERS**

### **Randomized Controlled Trials**

The available evidence for the Gatekeeper Reflux Repair System consists of one RCT. An industry-funded sham-controlled single-blind multicenter study randomized 118 patients into Gatekeeper (n=75) or sham (n=43) treatment.<sup>[86]</sup> An additional 25 patients were treated as lead-ins during the initial training of investigators and included only in the safety analysis. The patients were implanted initially with 4 Gatekeeper prostheses. At three months, 44% of implanted patients received retreatment with up to four additional prostheses due to unsatisfactory symptom control. The primary safety end point was reduction in serious device- and procedure-related adverse device effects, compared with a surgical procedure composite complication rate of 15%. Four serious adverse events were reported (2 perforations, 1 pulmonary infiltrate related to a perforation, 1 severe chest pain). The primary efficacy end point was reduction in heartburn symptoms using the GERD-HRQL questionnaire. Planned interim analysis after 143 patients were enrolled found that heartburn symptoms and esophageal acid exposure had improved significantly in both the Gatekeeper and sham groups at 6 months, but there was no significant difference between the 2 groups. The study was terminated early due to a lack of efficacy.

There is one randomized sham-controlled trial which reports results of patients randomized to receive either injection of Enteryx biopolymer or a sham procedure.<sup>[87]</sup> At 3- and 6-months follow-up, patients in the Enteryx group had greater reductions in PPI use and more improvement in GERD health-related quality of life heartburn scores. However, the small size and short duration of the study limit interpretation of findings.

### **Nonrandomized Studies**

Other data on injectable or implantable polymers consists of very small case series.<sup>[19,88]</sup> The small number of patients and lack of long-term follow-up precludes scientific analysis.

## **PRACTICE GUIDELINE SUMMARY**

Several clinical practice guidelines consider the use of transoral fundoplication or other endoscopic procedures, although none were able to recommend this treatment based upon high level evidence.

### **AMERICAN SOCIETY OF GENERAL SURGEONS**

The American Society of General Surgeons (ASGS) consensus-based position statement on transoral fundoplication states, “the ASGS supports the use of transoral fundoplication by trained General Surgeons for the treatment of symptomatic chronic gastroesophageal reflux disease (GERD) in patients who fail to achieve satisfactory response to a standard dose of Proton Pump Inhibitor (PPI) therapy or for those who wish to avoid the need for a lifetime of medication dependence.”<sup>[89]</sup>

### **AMERICAN GASTROENTEROLOGICAL ASSOCIATION**

The 2008 Medical Position Statement of the American Gastroenterological Association (AGA), makes no recommendation for or against “the use of currently commercially available endoluminal antireflux procedures in the management of patients with an esophageal syndrome” based on insufficient evidence (Grade Insufficient).<sup>[90]</sup>

### **AMERICAN COLLEGE OF GASTROENTEROLOGY**

In 2013, the ACG released updated guidelines stating that the usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy.<sup>[1]</sup>

### **SOCIETY OF AMERICAN GASTROINTESTINAL ENDOSCOPIC SURGEONS**

In 2017, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) updated its evidence-based guidelines on endoluminal treatments for GERD.<sup>[91]</sup> SAGES gave a strong recommendation based on moderate quality evidence that TIF with EsophyX can be performed with an acceptable safety risk in selected patients. SAGES concluded that EsophyX results in better control of GERD symptoms compared with proton pump inhibitor (PPI) treatment in the short term (6 months), but leads to similar improvement in objective GERD measures compared with PPIs. TIF appears to lose effectiveness during longer term follow-up and is associated with moderate patient satisfaction scores. SAGES found no comparative, controlled trials between TIF and surgical fundoplication, but preliminary evidence suggested that the surgical fundoplication can be used safely after TIF failure. SAGES gave a strong recommendation based on moderate quality evidence that Stretta is safe for adults and

significantly improves health-related quality of life score, heartburn scores, the incidence of esophagitis, and esophageal acid exposure in patients with GERD. Stretta is more effective than PPI, but less so than fundoplication.

## SUMMARY

There is not enough research to show that transesophageal endoscopic therapies for the treatment of gastroesophageal reflux disease (GERD) improves health outcomes. Although clinical guidelines based on research may recommend treating GERD with one or more of the therapies mentioned, there is not enough research to know if or how well these procedures work to treat people with GERD. This does not mean that it does not work, but more research is needed to know. Therefore, the use of any of these procedures is considered investigational for the treatment of GERD.

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## CODES

Codes	Number	Description
CPT	43192	Esophagoscopy; rigid, transoral; with directed submucosal injection(s), any substance
	43201	Esophagoscopy; flexible, transoral; with directed submucosal injection(s), any substance
	43210	Esophagogastroduodenoscopy, flexible, transoral; with esophagogastric fundoplasty, partial or complete, includes duodenoscopy when performed
	43236	Esophagogastroduodenoscopy, flexible, transoral, with direct submucosal injections, any substance
	43257	Esophagogastroduodenoscopy, flexible transoral; with deliver of thermal esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease
	43499	Unlisted procedure, esophagus
HCPCS	None	

**Date of Origin:** February 2001

## ***Gastric Electrical Stimulation***

**Effective:** July 1, 2020

**Next Review:** April 2021

**Last Review:** May 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Gastric electrical stimulation (GES) is performed using an implantable device designed to treat chronic drug-refractory nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology. Gastric electrical stimulation is also proposed as a treatment of obesity. The device may also be referred to as a gastric pacemaker or gastric pacing.

### **MEDICAL POLICY CRITERIA**

- I. Gastric electrical stimulation may be considered **medically necessary** in the treatment of chronic intractable nausea and vomiting secondary to gastroparesis of diabetic, idiopathic or post-surgical etiology when all of the following (A – C) Criteria are met:
  - A. Significantly delayed gastric emptying as documented by standard scintigraphic imaging of solid food; and
  - B. Patient is refractory or intolerant of 2 out of 3 classes of prokinetic medications and 2 out of 3 antiemetic medications. (see Appendices for classes); and
  - C. Patient's nutritional status is sufficiently low that weight has decreased to 90 percent or less of normal body weight for a patient's height and age in comparison with pre-illness weight.

- II. Gastric electrical stimulation revision(s) or replacement(s) may be considered **medically necessary** after the device has been placed.
- III. Gastric electrical stimulation for the treatment of chronic intractable nausea and vomiting secondary to gastroparesis of diabetic, idiopathic or post-surgical etiology is considered **not medically necessary** when Criterion I. is not met.
- IV. Gastric electrical stimulation is **investigational** for all other indications including but not limited to the treatment of obesity.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and Physical/Chart Notes
- Current Symptomology
- Prokinetic and Antiemetic Medications given and response

## CROSS REFERENCES

1. [Bariatric Surgery](#); Surgery, Policy No. 58
2. [Vagus Nerve Stimulation](#); Surgery, Policy No. 74
3. [Vagus Nerve Blocking Therapy for Obesity](#); Surgery, Policy No. 200

## BACKGROUND

A subcutaneously implanted pulse generator delivers electrical stimulation to the stomach via intramuscular leads that are implanted on the outer surface of the greater curvature of the stomach either laparoscopically or during a laparotomy. Stimulation parameters are typically programmed at an “on time” (ON) (e.g., 0.1 second) alternating with an “off time” (OFF) (e.g., 5.0 seconds).

### GASTRIC STIMULATION FOR THE TREATMENT OF INTRACTABLE NAUSEA AND VOMITING DUE TO GASTROPARESIS

Gastroparesis is a chronic disorder of gastric motility characterized by delayed emptying of a solid meal. Symptoms include bloating, distension, nausea, and vomiting. When severe and chronic, gastroparesis can be associated with dehydration, poor nutritional status, and poor glycemic control in diabetics. While most commonly associated with diabetes, gastroparesis is also found in chronic pseudo-obstruction, connective tissue disorders, Parkinson disease, and psychological pathology. Idiopathic gastroparesis refers to symptoms of gastroparesis which are not associated with an identifiable cause. Treatment of gastroparesis includes prokinetic agents such as metoclopramide, and antiemetic agents such as metoclopramide, granisetron, or ondansetron. Severe cases may require enteral or total parenteral nutrition.

### GASTRIC STIMULATION FOR THE TREATMENT OF OBESITY

GES has also been investigated as a treatment of obesity as a technique to increase a feeling

of satiety with subsequent reduced food intake and weight loss. The exact mechanisms resulting in changes in eating behavior are uncertain but may be related to neurohormonal modulation and/or stomach muscle stimulation.

## REGULATORY STATUS

The Enterra™ Therapy System (formerly named Gastric Electrical Stimulation [GES] System; manufactured by Medtronic) is the only device approved for treatment of chronic refractory gastroparesis. It received approval for marketing from the U.S. Food and Drug Administration (FDA) in 2000 through the humanitarian device exemption (HDE) process.<sup>[1]</sup> This process requires the manufacturer to provide adequate information for the FDA to determine that the device has “probable” benefit but does not pose an unreasonable or significant risk; it does not require data confirming the efficacy of the device. The HDE process is available for devices treating conditions that affect fewer than 4,000 Americans per year.

## EVIDENCE SUMMARY

### GASTRIC STIMULATION FOR THE TREATMENT OF INTRACTABLE NAUSEA AND VOMITING DUE TO GASTROPARESIS

#### Systematic Reviews

Several systematic reviews of studies of gastric electrical stimulation (GES) for gastroparesis have been published, the most recent and comprehensive of which was conducted by Levinthal in 2017.<sup>[2-4]</sup>

To be included in the Levinthal review, studies had to include adults with established gastroparesis, report patient symptom scores and administer treatment for at least one week. Five randomized controlled trials (RCTs) and 13 non-RCTs meeting criteria were identified. Pooled analysis of data from the five RCTs (n=185 patients) did not find a statistically significant difference in symptom severity when the GES was turned on versus off (standardized mean difference [SMD], 0.17; 95% confidence interval [CI], -0.06 to 0.40; p=0.15). Another pooled analysis did not find a statistically significant difference in nausea severity scores when the GES was on or off (SMD = -0.143; 95% CI, -0.50 to 0.22; p=0.45). In a pooled analysis of 13 open-label single-arm studies and data from open-label extensions of three RCTs, mean total symptom severity score decreased 2.68 (95% CI, 2.04 to 3.32) at follow-up from a mean of 6.85 (95% CI, 6.28 to 7.42) at baseline. The rate of adverse events in the immediate postoperative period (reported in seven studies) was 8.7% (95% CI, 4.3% to 17.1%). The in-hospital mortality rate within 30 days of surgery was 1.4% (95% CI, 0.8% to 2.5%), the rate of reoperations (up to 10 years of follow-up) was 11.1% (95% CI, 8.7% to 14.1%), and the rate of device removal was 8.4% (95% CI, 5.7% to 12.2%).

#### Randomized Controlled Trials

The data presented to the FDA documenting the “probable benefit” of the GES (Enterra™) system was based on a multicenter double-blind cross-over study referred to as the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS).<sup>[1]</sup> The study included 33 patients with intractable idiopathic or diabetic gastroparesis. The primary endpoint of the study was a reduction in vomiting frequency, as measured by patient diaries. In the initial phase of the study, all patients underwent implantation of the stimulator and were randomly and blindly assigned to stimulation ON or stimulation OFF for the first month, with crossover to OFF and

ON during the second month. The baseline vomiting frequency was 47 episodes per month, which significantly declined in both ON and OFF groups to 23 and 29 episodes, respectively. However, there were no significant differences in the number of vomiting episodes between the two groups, suggesting a placebo effect.

After the first two months of therapy, patients were asked which month of the cross-over stimulation they preferred. Twenty-one of the 33 patients selected the ON mode as their preferred month, compared to 7 who preferred the OFF mode, and 5 who had no preference. The greater preference for ON stimulation suggested some short-term effect that was not placebo.

In a continuing open phase of the trial, the patients then received the stimulation consistent with their preference. However, by four months all patients had the device turned ON (it was not clear whether this phase was by preference or design). At 6 and 12 months follow-up, the mean number of vomiting episodes continued to decline, although only 15 patients were followed for a period of 12 months. Data regarding quality of life were also obtained at 6 and 12 months and showed improvement. At 6 months, there was a significant improvement in 2-hour gastric retention (from 80% retention to 60% retention), but not in 4-hour gastric retention. (Fifty percent gastric retention at two hours was considered the upper limits of normal.)

The results of the randomized portion of the study suggest a placebo effect. Therefore, long-term results of GES must be validated in a longer-term randomized trial. It is interesting to note that GES did not return gastric emptying to normal in the majority of the patients tested. In as much as the device is intended to improve gastric emptying, as a proof of principle, it would be interesting to investigate the correlation between the degree of gastric emptying and symptom improvement.

In a 2003 update to WAVESS, Abell reported 12-month outcomes for all of the patients.<sup>[5]</sup> Statistically significant improvements were found for weekly vomiting frequency, total abdominal symptom score, and scintigraphic solid food emptying. At baseline the median vomiting frequency was 17.3 episodes per week with gastroparetic symptoms over a mean of 6.2 years. All patients had scintigraphic evidence of delayed gastric emptying at 2 and 4 hours, all patients were refractory to prokinetic and antiemetic medications, and 14 required some form of parenteral or enteral feedings. Results at the end of phase 1 (the blinded phase) showed a 50% decreased vomiting frequency for patients whose devices were ON compared to patients whose devices were OFF ( $p=0.05$ ).

Symptom severity trended toward improvement in the ON versus OFF period, although these changes did not reach statistical significance in phase 1. In a second phase of the study all patients were switched to the ON position with 6- and 12- months follow-up. Vomiting at 12 months was compared to baseline; 72% for the combined group, 63% for diabetics with gastroparesis, and 83% for patients with idiopathic gastroparesis. Total symptom score improved significantly ( $p<0.05$ ) at 6 and 12 months. Physical and mental quality of life scores improved significantly compared to baseline ( $p=$  less than 0.025). Baseline gastric retention was 78% at 2 hours. This decreased significantly with electrical stimulation to 65% at 6 months and 56% at 12 months for the combined group. The changes in 2-hour gastric emptying were not significant for the diabetic and idiopathic groups separately. Four-hour gastric emptying improved from 34% retention at baseline to 22% retention at 12 months. The difference was statistically significant for the combined group as well as the diabetic and idiopathic groups separately.

McCallum (2010) performed a multicenter prospective study to evaluate Enterra™ therapy in patients with chronic intractable nausea and vomiting from diabetic gastroparesis (DGP).<sup>[6]</sup> In this study, 55 patients with refractory DGP (5.9 years of DGP) were implanted with the Enterra™ system. After surgery, all patients had the stimulator turned ON for 6 weeks and then were randomly assigned to groups that had consecutive 3-month cross-over periods with the device ON or OFF. After this period, the device was turned ON in all patients and they were followed up unblinded for 4.5 months. During the initial 6-week phase with the stimulator turned ON, the median reduction in weekly vomiting frequency (WVF) compared with baseline was 57%. There was no difference in WVF between patients who had the device turned ON or OFF during the 3-month cross-over period. At 1 year, the WVF of all patients was significantly lower than baseline values (median reduction, 68%;  $P < 0.001$ ). One of the patients had the device removed due to infection; 2 patients required surgical intervention due to lead-related problems.

In a later study, McCallum (2013) evaluated GES (Enterra™ system) in patients with chronic vomiting due to idiopathic gastroparesis in a randomized, double-blind crossover trial.<sup>[7]</sup> In this study, 32 patients with nausea and vomiting associated with idiopathic gastroparesis, which was unresponsive or intolerant to prokinetic and antiemetic drugs, received Enterra™ implants and had the device turned on for 6 weeks. Subsequently, 27 of these patients were randomized to have the device turned on or off for 2 consecutive 3 month periods. Twenty five of these subjects completed the randomized phase; of note, 2 subjects had the device turned on early, 2 subjects had randomization assignment errors, and 1 subject had missing diaries. During the initial 6-week on period, all subjects demonstrated improvements in their WVF, demonstrating a median reduction of 61.2% compared with baseline (17.3 episodes/week at baseline vs 5.5 episodes/week at 6 week postimplant,  $p < 0.001$ ). During the on-off crossover phase, subjects demonstrated no significant differences between the on and off phase in the study's primary end point, median WVF (median 6.4 in the on phase vs 9.8 in the off phase;  $p = 1.0$ ). Among the 19 subjects who completed 12 months of follow up, there was an 87.1% reduction in median WVF compared with baseline (17.3 episodes/week at baseline vs 2 episodes/week at 12-month follow-up,  $p < 0.001$ ). Two subjects required surgical intervention for lead migration/dislodgement or neurostimulator migration.

## Nonrandomized Studies

Laine (2018) published a retrospective, multicenter analysis of patients with severe, medically refractory gastroparesis who received GES.<sup>[8]</sup> Fourteen patients (11 diabetic, 1 idiopathic, and 2 postoperative) treated in Finland between 2007 and 2015 were included; median follow-up was 3 years. Eight (57.1%) patients experience marked relief of gastroparesis symptoms, while 3 (21.4%) patients experience partial relief. There was a median weight gain of 5.1 kg in 11 (78.6%) patients after GES implantation, and, at last possible follow-up, 5 out of 10 (50%) patients were without medication for gastroparesis. The study was limited by its retrospective nature, small population size, and relatively short follow-up time.

Shada (2018) published a prospective study of patients with medically refractory gastroparesis who underwent implantation of GES between 2005 and 2016.<sup>[8]</sup> One hundred nineteen patients (64 diabetic, 55 idiopathic), with mean follow-up of  $39.0 \pm 32.0$  months, were included in the analysis. Before GES placement, operatively placed feeding tubes were present in 22% of diabetic and 17% of idiopathic patients, however, after GES placement, 67% of feeding tubes were removed. Due to a perceived lack of benefit, 8 patients decided to have their GES device removed after a mean time of  $36 \pm 29$  months. Also, there was significant improvement in

GCSI scores for both diabetic ( $p=0.01$ ) and idiopathic ( $p=0.003$ ) subgroups at  $\geq 2$  years after implantation. The study was limited by its not all patients being administered the GCSI before GES, and a number of patients being lost to follow-up.

In 2016, Heckert reported on GES as a treatment for refractory symptoms of gastroparesis in 138 patients (65 diabetic, 68 idiopathic, and 5 other) with delayed gastric emptying at one-year follow-up ( $1.4 \pm 1.0$  years).<sup>[9]</sup> Patients reported their response to GES using the Clinical Patient Grading Assessment Scale (CPGAS), of which, 75% of patients felt their symptoms had improved, and 25% felt their symptoms were the same or worsened (diabetics had a greater response than idiopathic patients). Symptom severity was assessed by analyzing Patient Assessment of GI Symptoms (PAGI-SYM) questionnaires, before insertion of GES and at the last follow-up visit. PAGI-SYM scores were improved for all symptoms, though the authors report nausea, early satiety and loss of appetite to have been most improved; and constipation, diarrhea, and abdominal distension to have been least improved. In this selected group of patients, the authors concluded GES to be beneficial in the majority of patients.

In 2013, Keller reported complication rates and need for a second surgery in 233 patients who had GES implantation surgery over a ten year period at a single institution.<sup>[10]</sup> Additional surgery was required in 58% of patients. The majority of reoperations were due to the following complications: nutritional access (45 patients, requiring 77 procedures), subcutaneous pocket issues ( $n = 21$ ), gastroparetic symptoms ( $n = 11$ ), mechanical issues ( $n = 9$ ) and infection ( $n = 4$ ). The study reported that patient BMI was predictive of additional surgeries, with 4.45 overall increased risk of pocket revision surgery. Although 70% of patients reported improved symptoms of pain, bloating and nausea, GES had a significantly high reoperation rate due to complications associated with the initial procedure.

In 2007, Anand reported on a study of 214 consecutive drug-refractory patients with the symptoms of gastroparesis (146 idiopathic, 45 diabetic, 23 after surgery).<sup>[11]</sup> A GES device was implanted in 156 patients. The remaining 58 patients, designated as the control group, were either on the waiting list for permanent implantation or consented to not receive a permanent implant. At last follow-up (median 4 years), most patients who received implants (135 of 156) were alive with intact devices, significantly reduced gastrointestinal symptoms, and improved health-related quality of life, with evidence of improved gastric emptying. Also, 90% of the patients had a response in at least 1 of 3 main symptoms. Most patients that explanted, usually for pocket infections, were later successfully reimplanted.

GES placement using minimally invasive surgical approaches has also been evaluated in several publications. Laparoscopy has been reported in at least two studies as a feasible approach in placement of GES for patients with medically refractory diabetic or idiopathic gastroparesis.<sup>[12,13]</sup>

Several small case series and retrospective reviews have been reported, some with long-term outcomes up to 5 years.<sup>[12,14-30]</sup> The data indicate that GES may be associated with improvements in gastrointestinal symptom scores, nutrition and quality-of-life for patients; these improvements were sustained over time. However, gastric emptying rates were mixed.

## Adverse Events

In 2017, Bielefeldt analyzed the number, severity and type of voluntarily reported adverse events related to Enterra™ in the Manufacturer and User Device Experience (MAUDE) databank of the FDA.<sup>[31]</sup> Data were retrieved for 2001 through October 31, 2015, of which 1472 reports were

abstracted. Thirty-six perioperative complication reports were reviewed; six were serious events, including three deaths (one due to cardiac arrest, two due to septic complications with resulting multi organ failure), one stroke, and one myocardial infarction complicated further by a pulmonary embolism. Overall, most of the reports were regarding patient concerns, local complications, or system failure. Limitations of these findings include reporting bias (the MAUDE data are voluntarily submitted), and report misclassification bias (MAUDE data sources vary from patient reports to published articles and inconsistencies in reporting have been found). Risk-benefit could not directly be assessed given the nature of the MAUDE database, though the author cites other studies for outcomes measurement, most of which are included in the other sections of this evidence review. Overall, 35% of the reported adverse events prompted an additional surgery.

## Section Summary

The evidence regarding the clinical utility of GES for gastroparesis due to intractable nausea and vomiting is limited to three small crossover RCTs. However, longer-term data suggest improvements in gastrointestinal symptom scores, nutrition, and quality-of-life scores, suggesting some benefit with GES treatment. Given the lack of alternative treatment options in this specific patient population, GES may be considered reasonable treatment of symptoms of gastroparesis.

## GASTRIC STIMULATION FOR THE TREATMENT OF OBESITY

### Systematic Review

In 2014, Cha published a review of 33 studies evaluating various methods of gastric stimulation as a treatment of obesity, including implantable GES.<sup>[32]</sup> The majority of included studies were small in nature with 24 studies evaluating 30 or fewer patients. In addition, many of the studies reported high dropout rates of more than 50% of patients at the end of the study follow-up period. A major limitation of the review was the inclusion of studies which did not include the treatment of obesity (i.e., BMI or weight loss) as a primary outcome measure. Furthermore, there were methodological difference in the patient inclusion criteria and most of the studies included in the review were limited by short-term follow-up of less than one year. The authors concluded that the level of evidence regarding GES as a treatment of obesity was low. Long-term RCTs which compare GES to other treatments of obesity and sham are needed in order to assess the safety and efficacy of GES in this population.

### Randomized Controlled Trials

There is one published RCT on GES for the treatment of obesity. In 2009, Shikora reported on a randomized controlled, double-blind study (SHAPE trial) to evaluate GES for the treatment of obesity.<sup>[33]</sup> All 190 patients participating in the study received an implantable gastric stimulator and were randomized to have the stimulator turned on or off. All patients were evaluated monthly, participated in support groups and reduced their diet by 500-kcal/day. At 12-month follow-up, there was no difference in excess weight loss between the treatment group (weight loss of 11.8% +/- 17.6%) and the control group (weight loss of 11.7% +/- 16.9%) using intention-to-treat analysis ( $p=0.717$ ).

### Nonrandomized Studies

Additional, small studies – including one patient population with comorbidities of gastroparesis and morbid obesity – have reported positive outcomes in weight loss and maintenance of

weight loss along with minimal complications.<sup>[34-39]</sup> However, due to lack of long-term outcomes from well-designed randomized clinical trials, conclusions cannot be made concerning the safety and efficacy of chronic gastric stimulation as a treatment for morbid obesity.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN COLLEGE OF GASTROENTEROLOGY<sup>[40]</sup>

The American College of Gastroenterology (ACG) published a clinical practice guideline on management of gastroparesis in 2013. The recommendations for this guideline were based on review of the evidence-base through 2011. The ACG concluded that GES treatment does not adequately address the clinical needs of these patients, but that, “GES may be considered for compassionate treatment in patients with refractory symptoms, particularly nausea and vomiting. Symptom severity and gastric emptying have been shown to improve in patients with diabetic gastroparesis (DG), but not in patients with idiopathic gastroparesis (IG) or postsurgical gastroparesis (PSG). (Conditional recommendation, moderate level of evidence.)”

## SUMMARY

It appears that gastric electrical stimulation (GES) may improve intractable nausea and vomiting for patients with gastroparesis. Clinical guidelines based on research state GES may be considered for compassionate treatment in patients with refractory symptoms, particularly nausea and vomiting. Therefore, given the lack of treatment options in this very specific patient population, GES may be medically necessary in carefully selected patients with gastroparesis when policy Criteria are met. GES for the treatment of chronic intractable nausea and vomiting secondary to gastroparesis of diabetic, idiopathic or post-surgical etiology is considered not medically necessary when policy Criteria are not met.

Due to limited evidence on the efficacy and safety GES, all other indications including treatment for obesity are considered investigational.

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## CODES

### NOTES:

- The CPT coding manual indicates that procedures related to laparoscopic gastric stimulation electrodes for morbid obesity should be reported using code 43659 - Unlisted laparoscopy procedure, stomach
- HCPCS code C1823 is NOT the correct code to use for reporting these services. Please refer to the codes listed below for guidance.

Codes	Number	Description
CPT	43647	Laparoscopy, surgical; implantation or replacement of gastric neurostimulator electrodes, antrum
	43648	Laparoscopy, surgical; revision or removal of gastric neurostimulator electrodes, antrum
	43659	Unlisted laparoscopy procedure, stomach
	43881	Implantation or replacement of gastric neurostimulator electrodes, antrum, open
	43882	Revision or removal of gastric neurostimulator electrodes, antrum, open
	43999	Unlisted procedure, stomach
	64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling.
	64595	Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver
	95980	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude and duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient measurements) gastric neurostimulator pulse generator/transmitter; intraoperative, with programming
		95981
	95982	;subsequent, with reprogramming
HCPCS	C1767	Generator, neurostimulator (implantable), nonrechargeable
	C1778	Lead neurostimulator
	C1883	Adaptor/Extension, pacing lead or neurostimular lead (implantable)
	C1897	Lead neurostimulator test kit (implantable)
	E0765	FDA approved nerve stimulator, with replaceable batteries, for treatment of nausea and vomiting
	L8679	Implantable neurostimulator, pulse generator, any type

Codes	Number	Description
	L8680	Implantable neurostimulator electrode, each
	L8686	;non-rechargeable, includes extension
	L8688	;non-rechargeable, includes extension

### Appendix 1: Prokinetic Medications

Class	Common Examples
Cholinergic Agonists	dexpanthenol (Ilopan®), bethanechol (Urecholine®)
Motolin receptor agonists	erythromycin
Dopamine receptor antagonists	metoclopramide (Reglan®)

### Appendix 2: Antiemetic Medications

Class	Common Examples
Antihistamines	diphenhydramine (Benadryl®), dimenhydrinate (Dramamine®), meclizine (Antivert®), hydroxyzine (Vistaril®), trimethobenzamide (Tigan®)
Serotonin (5HT <sub>3</sub> ) receptor antagonists	ondansetron (Zofran®), granisetron (Kytril®), dolasetron (Anzemet®)
Dopamine receptor antagonists	Metoclopramide (Reglan®), perphenazine (Trilafon®), prochlorperazine (Compazine®), promethazine (Phenergan®), thiethylperazine (Torecan®), cyclizine (Marezine®)

**Date of Origin:** February 2001

## ***Transcutaneous Bone-Conduction and Bone-Anchored Hearing Aids***

**Effective:** July 1, 2020

**Next Review:** March 2021

**Last Review:** May 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

External bone-conduction hearing aids function by transmitting sound waves through the bone of the skull to the inner ear.

### **MEDICAL POLICY CRITERIA**

#### **Notes:**

- This policy applies *only* to bone-conduction hearing aid systems that are bone anchored (also called bone-anchored hearing aids (BAHAs) or osseointegrated implants) or transcutaneous (non-surgical, secured by a Softband or other method). It does *not* apply to cochlear implants, which are addressed in a separate medical policy (see Cross References), or to intraoral bone-conduction hearing aids.
- Both bone-anchored and transcutaneous bone-conduction systems are hearing aids. There may be specific member benefit language addressing coverage of hearing aids. Any specific contract language supersedes medical policy. Unless otherwise specified, the contract language addressing coverage of hearing aids applies to both bone-conduction hearing aids and externally worn air-conduction hearing aids.

- Oregon HB 4104 Coverage of Hearing Loss Treatments (Oregon Hearing Mandate), effective January 1, 2019, requires coverage of medically necessary hearing aids, including specified replacement supplies, for Oregon members meeting age and educational enrollment requirements. This coverage is detailed in applicable contracts. Note that contract language rather than Criterion IV. may apply for Oregon members meeting the parameters of the Oregon Hearing Mandate.

I. **Unilateral or bilateral transcutaneous bone-conduction or bone-anchored hearing aid(s)** may be considered **medically necessary** as an alternative to air-conduction hearing aid(s) for conductive or mixed hearing loss when all of the following criteria (A-D) are met:

A. Patients who meet any of the following criteria:

1. Congenital or surgically induced malformations (e.g., atresia) of the external ear canal or middle ear; or
2. Chronic external otitis or otitis media; or
3. Tumors of the external canal and/or tympanic cavity; or
4. Dermatitis of the external canal.

B. A bone-conduction pure tone average threshold at 0.5, 1, 2, and 3 kHz no poorer than (i.e. threshold average of 0.5, 1, 2, and 3 kHz no higher than) one of the following:

1. 25 dB for ADHEAR; or
2. 45 dB for OBC, Ponto 3, Ponto 4, BONEBRIDGE, Baha4 and Baha5 devices; or
3. 55 dB for Ponto 3 Power, BAHA 5 Power, Osia, and Osia 2 devices; or
4. 65 dB for Ponto 3 SuperPower and BAHA 5 SuperPower devices (see Policy Guidelines below); or
5. For a device not listed above, average threshold consistent with the device-specific FDA indication (See Policy Guidelines).

C. Meet one of the following age requirements:

1. 12 years or older for BONEBRIDGE, Osia, or Osia 2; or
2. 5 years or older for all other surgically implanted devices; or
3. Any age for non-surgically implanted devices; or
4. For a device not listed above, age consistent with the device-specific FDA indication (See Policy Guidelines).

D. Patients are to receive either:

1. A unilateral bone-conduction hearing aid; or
2. Bilateral bone-conduction hearing aids and have symmetrically conductive or mixed hearing loss (measured without augmentation) as defined by a difference between left- and right-side bone-conduction threshold of less than 10 dB on average measured at 0.5, 1, 2 and 3 kHz (and also 4 kHz for OBC,

Ponto Pro 3, and Otomag Alpha 1 [M]), or less than 15 dB at individual frequencies.

- II. **A transcutaneous bone-conduction or bone-anchored hearing aid** may be considered **medically necessary** as an alternative to an air-conduction contralateral routing of signals (CROS) hearing aid in patients five years of age and older with single-sided sensorineural deafness and normal hearing in the other ear.
- III. Other uses of transcutaneous bone-conduction or bone-anchored hearing aids, including but not limited to when Criterion I. is not met and use in patients with bilateral sensorineural hearing loss, are considered **investigational**.
- IV. **Implant replacement**, including **replacement parts or upgrades** to existing bone-anchored hearing aids and/or components, may be considered **medically necessary** when components are no longer functional, or for functional devices only in the small subset of patients whose response to existing components is inadequate to the point of interfering with activities of daily living, which would include school and work,.
- V. **Implant replacement**, including **replacement parts or upgrades** to existing bone-anchored hearing aids and/or components are considered **not medically necessary** when Criterion IV. is not met, including but not limited to when requested for convenience or technology upgrade. Replacement parts or upgrades include, but are not limited to batteries, processors, headbands or Softbands. This criterion may not apply to Oregon members who meet the parameters of the Oregon Hearing Mandate (see applicable contracts for details).

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

## POLICY GUIDELINES

### HEARING TESTS

Pure tone hearing tests measure the faintest level (hearing threshold) at which a tone can be heard at selected frequencies approximately 50% of the time. Lower thresholds represent better hearing.

Each ear is tested separately. The pure tone average threshold hearing level is calculated separately for each ear by averaging the hearing levels at each frequency. For example, if a patient's bone-conduction hearing threshold in the right ear at frequencies 0.5, 1, 2, and 3 kHz is 20, 20, 30, and 40 dB, respectively, the pure tone average for that ear is  $(20 + 20 + 30 + 40) \div 4 = 27.5$  dB.

### FDA APPROVAL

FDA-approved indications can be found by searching by device name in the FDA [510\(k\) Premarket Notification Database](#) or the [De Novo Database](#) and viewing the Summary. Product codes for these devices include LXB, MAH, and PFO.

## LIST OF INFORMATION NEEDED FOR REVIEW

### SUBMISSION OF DOCUMENTATION

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

- History and physical/chart notes
- Audiology test results

## CROSS REFERENCES

1. [Cochlear Implant](#), Surgery Policy No. 8

## BACKGROUND

Conventional external hearing aids can be generally subdivided into air-conduction hearing aids and bone-conduction hearing aids. Air-conduction hearing aids require the use of ear molds, which may be problematic in patients with chronic middle ear and ear canal infections, atresia of the external canal, or an ear canal that cannot accommodate an ear mold. In these patients, bone-conduction hearing aids may be an alternative.

External bone-conduction hearing aids historically were closely applied to the temporal bone with either a steel spring over the top of the head or with the use of a spring-loaded arm on a pair of spectacles. These devices may be associated with either pressure headaches or soreness. Partially implantable bone-conduction hearing aids have been investigated as an alternative, and external bone-conduction hearing aids applied with less or no pressure have also become available.

The bone-anchored hearing aid (BAHA) implant systems, also called osseointegrated devices, work by combining a vibrational transducer coupled directly to the skull via a percutaneous abutment that permanently protrudes through the skin from a small titanium implant anchored in the temporal bone. The system is based on the process of “osseointegration” through which living tissue integrates with titanium in the implant over a period of three to six months, allowing amplified and processed sound to be conducted via the skull bone directly to the cochlea. The lack of intervening skin permits the transmission of vibrations at a lower energy level than required for external bone-conduction hearing aids.

The BAHA device has been used successfully in children younger than five years in Europe and the United Kingdom. (The most recent [1999] update of the U.S. Food and Drug Administration [FDA] notification lists age less than five years as a contraindication.) A number of reports describe experience with preschool children or children with developmental issues that might interfere with maintenance of the device and skin integrity. A two-stage procedure is used in young children with the fixture placed into the bone at the first stage and, after three to six months to allow for osseointegration, a second procedure to connect the abutment through the skin to the fixture.

Baha sound processors can also be used with the Baha® Softband™. With this application there is no implantation surgery. The sound processor is attached to the head using either a hard or soft headband. The band can be adjusted to the individual's head size. The amplified sound is transmitted transcutaneously to the bones of the skull for transmission to the cochlea. These devices have been suggested as a bridge to bone anchor implantation in young children who are not eligible for the implant due to young age and/or bone strength/thickness not yet adequate. The recently approved ADHEAR device attaches with an adhesive and no

headband is required.

Partially implantable magnetic bone conduction hearing systems, also referred to as transcutaneous bone-anchored systems, are an alternative to bone conduction hearing systems connected percutaneously via an abutment. With this technique, acoustic transmission occurs transcutaneously via magnetic coupling of the external sound processor and the internally implanted device components. The bone conduction hearing processor contains a magnet that adheres externally to magnets implanted in shallow bone beds with the bone conduction hearing implant. Since the processor adheres magnetically to the implant, there is no need for a percutaneous abutment. To facilitate greater transmission of acoustics between magnets, skin thickness may be reduced to 4-5 mm over the implant when it is surgically placed.

## REGULATORY STATUS

The following \*Baha® sound processors, currently marketed by Cochlear™ (formerly called Cochlear™ Americas), have received 510(k) clearance from the U.S. Food and Drug Administration (FDA) for use with the Baha auditory osseointegrated implant (hearing aid) systems (such as the Baha® Connect and Attract systems):

- Baha® 5 Sound Processor
- Baha® 5 SuperPower Sound Processor
- Baha® 5 Power Sound Processor

The above devices are currently available from Cochlear™. However, predicate devices include the Baha®4, Cordelle II, Divino®, Intenso™ and BP100™.

\*Note: These devices may be referred to as Cochlear™ Baha® systems or Cochlear osseointegrated implants, reflecting the manufacturer's name. These devices are bone conduction hearing aids and *should not* be confused with cochlear implants which are prostheses that replace a damaged or absent cochlea in the inner ear. Cochlear implants are addressed in a separate medical policy (see Cross References).

The FDA approved the Cochlear™ Baha® system (initially approved under the trade name Branemark Bone-Anchored Hearing Aid [BAHA™] by Entific Medical Systems, Inc.) for use in children aged five years and older, and in adults, for the following indications:

- Patients who have conductive or mixed hearing loss and can still benefit from sound amplification;
- Patients with bilaterally symmetric conductive or mixed hearing loss, may be implanted bilaterally;
- Patients with sensorineural deafness in one ear and normal hearing in the other (i.e., single-sided deafness, SSD);
- Patients who are candidates for an air-conduction contralateral routing of signals (AC CROS) hearing aid but who cannot or will not wear an AC CROS device.

Baha sound processors can also be used with the Baha® Softband and Baha® SoundArc. The Baha® Softband received FDA clearance in 2002 for use in children under the age of five years. The Baha® SoundArc received FDA clearance in 2017 for use in people of any age.

Subsequent bone conduction hearing systems (listed below) share similar indications as the Cochlear™ Baha® devices:

- OBC Bone Anchored Hearing Aid System (Oticon Medical)
- Sophono® (S) (Cochlear) (predicate device was Otomag [Sophono])
- Ponto Pro, Ponto Plus, Ponto Plus Power, Ponto 3, Ponto 3 Power, Ponto 3 SuperPower, and Ponto 4 processors (Oticon Medical), to be used with the Oticon or BAHA osseointegrated implant.

The MedEl ADHEAR device, which has no implantable components, received FDA 510(k) clearance with the Contact Mini (audiofon) and BAHA 5 (Cochlear) as predicate devices.

The following partially implantable magnetic bone conduction devices have received FDA 510(k) clearance:

- Sophono® (M) (Cochlear) (predicate device was Otomag Alpha [Sophono])
- Sophono™ Alpha 2 MPO™ (Medtronic)
- Baha® Attract (Cochlear®)

The BoneBridge™ (MedEl) partially implantable bone-conduction hearing aid received FDA approval via the de novo pathway in 2018.

The Osia™ (Cochlear) bone-conduction hearing aid received FDA 510(k) approval with BoneBridge™ as the predicate device in July 2019. The Osia™ 2 received FDA 510(k) approval with Osia™ as the predicate device in November 2019.

## EVIDENCE SUMMARY

Hearing results of semi-implantable bone-conduction hearing aids may be compared either to 1) external bone-conduction hearing aids in patients with atresias who are unable to use external air-conduction hearing aids, or 2) external air-conduction hearing aids in patients who are unable to tolerate air-conduction hearing aids due to chronic infection. Reported studies have suggested that the bone-anchored hearing aid (BAHA) is associated with improved hearing outcomes compared to external bone-conduction hearing aids and equivalent outcomes compared to conventional air-conduction hearing aids.<sup>[1-4]</sup> However, given the objectively measured outcomes and the largely invariable natural history of hearing loss in individuals who would be eligible for an implantable bone-conduction device, a within-subjects comparison of hearing before and after device placement may be a reasonable study design.

### UNILATERAL DEVICES

#### Systematic Review

In 2017 Kim conducted a systematic review on the efficacy of BAHAs in single-sided deafness, including 14 studies (N=296 patients). The reviewers reported that in the six studies that dealt with sound localization, no significant difference was found after the implantation. However, twelve studies showed the benefits of BAHAs for speech discrimination in noise. Regarding subjective outcomes of using the prosthesis in patients with SSD (abbreviated profile of hearing aid benefit [APHAB] and the Glasgow hearing aid benefit profile [GHABP], etc.), improvements in quality of life were reported in the majority of studies.

This systematic review has indicated that BAHAs may successfully rehabilitate patients with SSD by alleviating the hearing handicap to a certain degree, which could improve patients' quality of life. This report has presented additional evidence of effective auditory rehabilitation

for SSD and will be helpful to clinicians counseling patients regarding treatment options for SSD

In a 2015 Peters published a systematic review of the literature through April 7, 2014 on the use of BAHA devices with contralateral routing of sound systems for single-sided deafness (SSD).<sup>[5]</sup> Five<sup>[6-10]</sup> of the six studies that met inclusion criteria were rated as moderate to high directness of evidence and low to moderate risk of bias and, thus, were included in the review. Significant heterogeneity was found in the 91 total patients included. For speech perception in noise there was not consistent improvement with aided hearing over unaided hearing in all environments. All studies reported equal sound localization in the aided and unaided conditions, and quality of life measures were similar for the aided and unaided conditions. Interpretation of these outcomes was limited by the methodological limitations of the included studies, including the lack of RCTs, unclear inclusion criteria, small sample sizes, use in some studies of headband devices which have different bone conduction thresholds in the higher frequencies than implanted devices, clinical heterogeneity of included populations (e.g., duration of deafness, grade of hearing loss), unexplained missing data, and lack of long-term audiometric follow-up. The authors also noted that the lack of recent studies was surprising considering the recent advances in these devices and recommended high-quality studies on the clinical outcome of current devices.

### **Randomized Controlled Trials**

No RCTs of unilateral BAHAs have been published.

### **Nonrandomized Studies**

Since publication of the Peters systematic review, three prospective, interventional studies compared patient satisfaction with transcutaneous BAHA devices to CROS hearing aids for SSD.

den Besten (2019) assessed 54 adults with SSD, each of whom underwent a trial with the Baha Softband before a trial of the percutaneous, partially implantable Baha Attract device.<sup>[11]</sup> No statistically significant difference in audiological outcomes was seen between the two devices ( $p>0.05$ ). At a six-month follow-up after implantation, patients reported numbness (20%) and slight pain/discomfort (38%) associated with the device.

Choi (2019) compared the performance of contralateral routing of signal (CROS)/bilateral routing of signal (BiCROS) and soft-band bone-anchored hearing aid (BAHA) devices in 21 patients with unilateral sensorineural hearing loss.<sup>[12]</sup> All participants were naïve to hearing devices. Sound localization, speech perception, psychoacoustic performance, and subjective assessments were analyzed. The subjects were assessed with each device and in the unaided condition. Sound localization was not improved in the soft-band BAHA condition and was significantly impaired with the CROS/BiCROS. Both devices significantly improved speech-in-noise perception when targeted to the impaired ear side. With regard to psychoacoustic performance, temporal resolution was significantly decreased with the BAHA compared to the unaided condition and CROS/BiCROS. There were no significant differences reported for preference between devices or subjective assessments of background noise or sound quality.

In 2017, Snapp reported a prospective single-center study of 27 patients with unilateral severe-profound sensorineural hearing loss who had either a CROS ( $n=13$ ) or transcutaneous BAHA ( $n=14$ ) device.<sup>[13]</sup> Mean device use was 66 months for the BAHAs and 34 months for CROS

devices. Both BAHA and CROS groups had significant improvement in speech-in-noise performance, but neither showed improvement in localization ability. There were no differences between the devices for subjective measures of posttreatment residual disability or satisfaction as measured by the Glasgow Hearing Aid Benefit Profile (GHABP).

Leterme (2015) assessed 24 adults with SSD, 18 of whom were evaluated with trials of both hearing aids with CROS and bone conduction–assisted hearing using the Baha Softband.<sup>[14]</sup> Most patients (72%), after completing trials of both devices, preferred the BAHA device to hearing aid with CROS. Glasgow Benefit Index and Abbreviated Profile of Hearing Aid Benefit (APHAB) scores did not differ significantly between devices. Sixteen of the 18 subjects elected to undergo implantation of a percutaneous BAHA device. In general, hearing improvement with the Baha Softband trial correlated with hearing improvements following device implantation.

## **BILATERAL DEVICES**

Use of bilateral devices has been evaluated in nonrandomized studies of patients with conductive or mixed hearing losses. A number of studies, published over several years, have demonstrated a consistent improvement in speech recognition in noise and in sound localization with bilateral devices.

### **Systematic Reviews**

A systematic review by the Health Technology Assessment Program was published in 2011 on the use of bone-anchored hearing aids (BAHAs) for bilateral hearing impairment.<sup>[15,16]</sup> The authors noted that the quality of available studies on the use of BAHAs is weak. No studies with control groups were identified for the review. Cohort pre-post studies and cross-sectional comparative studies demonstrated improvements in hearing with use of BAHAs over conventional bone-conduction hearing aids or unaided hearing. However, whether improvements in hearing with BAHAs are greater than air-conduction hearing aids is uncertain. Additionally, bilateral use of BAHAs improved hearing outcomes in some patients over unilateral use, but the evidence was uncertain. Implant loss was noted to be between 6.1% and 19.4%. The authors noted hearing-specific quality of life improved, but overall quality of life did not differ.

In 2012 Janssen reported similar findings in a systematic review that assessed the outcomes of bilateral versus unilateral BAHA for individuals with bilateral permanent conductive hearing loss (CHL).<sup>[17]</sup> Their search strategy included studies of all languages published between 1977 and July 2011. Studies were included if subjects of any age had permanent bilateral CHL and bilateral implanted BAHAs. Outcome measures of interest were any subjective or objective audiologic measures, quality of life indicators, or reports of adverse events. Eleven studies met their inclusion criteria. All 11 studies were observational. There were a total of 168 patients in the 11 studies, 155 of whom had BAHAs and 146 of whom had bilateral BAHAs. In most studies, comparisons between unilateral and bilateral BAHA were intra-subject. Patients ranged from 5 to 83 years of age; 46% were male, and 54% were female. Heterogeneity of the methodologies between studies precluded meta-analysis, therefore a qualitative review was performed. Results from three studies were excluded from synthesis because their patients had been included in multiple publications. Adverse events were not an outcome measure of any of the included studies. In general, bilateral BAHA was observed to provide additional objective and subjective benefit compared to unilateral BAHA. For example, the improvement in tone thresholds associated with bilateral BAHA ranged from 2-15dB, the improvement in speech recognition patterns ranged from 4-5.4dB, and the improvement in the Word

Recognition Score ranged from 1 to 8%. However, these results were based on a limited number of small observational studies consisting of heterogeneous patient groups that varied in age, severity of hearing loss, etiology of hearing loss, and previous amplification experience.

### **Randomized Controlled Trials**

No RCTs of bilateral BAHAs have been published.

### **Nonrandomized Studies**

No new studies have been published since the most recent systematic review.

## **BAHA IN CHILDREN UNDER AGE FIVE YEARS**

### **Nonrandomized Studies**

The literature on the use of these devices in children consists of a review article and several nonrandomized studies.

The largest series in children under five years identified for this review, described by Amonoo-Kuofi in 2015, which included 24 children identified from a single center's prospectively maintained database.<sup>[18]</sup> Most patients underwent a 2-stage surgical approach. The largest proportion of patients (52%) received the implant for isolated microtia, followed by Goldenhar syndrome (16%). Following implantation, 13 patients (54%) had grade 2 or 3 local reactions on the Holgers Scale (redness, moistness, and/or granulation tissue) and 7 (29%) had grade 4 local reactions on the Holgers Scale (extensive soft-tissue reaction requiring removal of the abutment). Quality of life scores (Glasgow Children's Benefit Inventory [GCBI]; scoring range, -100 to 100) were obtained in 18 subjects/parents with a finale mean score change of +40 points. Audiologic testing indicated that the average performance of the device fell within the range of normal auditory perception in noisy and quiet environments.

Marsella (2012) reported on their center's experience with pediatric BAHA in all 47 children implanted, seven of which were younger than five years of age.<sup>[19]</sup> The functional gain was significantly better with BAHA than with conventional bone-conduction hearing aids. There was no significant difference in terms of functional outcome between the seven patients younger than age five and the rest of the patient cohort. Based on these findings, the study authors suggested that implantation of children at an age younger than five years can be conducted safely and effectively in such settings. However, the conclusions from this study were limited by the small number of children younger than five years of age and the limited power to detect a difference between younger and older children.

A 2008 review article noted that for children younger than age five years, other solutions (such as a bone conductor with transcutaneous coupling) should be utilized.<sup>[20]</sup> This recommendation is in agreement with the FDA clearance of the osseointegration implant only for children five years of age and older, and adults.

McDermott (2008) reported on the role of BAHAs in children with Down syndrome in a retrospective case analysis and postal survey of complication rates and quality of life outcomes for 15 children aged 2 to 15 years.<sup>[21]</sup> All patients were using their BAHA devices after a follow-up of 14 months. No fixtures were lost, and skin problems were encountered in three patients. All 15 patients had improved social and physical functioning as a result of better hearing.

Dauids (2007) at the University of Toronto provided BAHA devices to children less than five

years of age for auditory and speech-language development and retrospectively compared surgical outcomes for a study group of 20 children five years or younger and a control group of 20 older children.<sup>[22]</sup> Children with cortical bone thickness greater than 4 mm underwent a single-stage procedure. The interstage interval for children having 2-stage procedures was significantly longer in the study group to allow implantation in younger patients without increasing surgical or postoperative morbidity. Two traumatic fractures occurred in the study group versus four in the older children. Three younger children required skin site revision. All children were wearing their BAHA devices at the time of writing.

## **BAHA SOFTBAND USE IN CHILDREN**

### **Nonrandomized Studies**

The current evidence consists of small retrospective studies and comparative studies. Externally worn AOD sound processors appears to consistently be beneficial for children under age five years with bilateral aural atresia who are too young to receive an implantable device.<sup>[23-25]</sup>

A 2014 report compared use of the Softband in 16 children (ages ranging from three months to six years) with bilateral aural atresia to 29 normal-hearing children (ages ranging from eight months to six years).<sup>[26]</sup> Auditory development was assessed at baseline, six months, and 12 months. The full text of the article was not available and the abstract did not provide data from the normal-hearing children for comparison. The authors concluded that the Softband was a suitable bridge to surgical implantation in infants and young children with bilateral atresia.

Ramakrishnan used the Glasgow Benefit Inventory (GBI) and Listening Situation Questionnaire to report quality of life findings in a retrospective cross-sectional survey administered to parents of 22 children (n=109 total participants), some with skull and congenital/chromosomal abnormalities from inherited syndromes that involve unilateral (hemifocal microsomia) or bilateral hearing impairment (Treacher-Collins Syndrome, n=4 of 22) due to microtia or aural atresia.<sup>[27]</sup> The youngest child utilizing an externally worn BAHA with Softband was six months of age. Overall, parents reported short-term satisfaction in the mean GBI scores for the children after three months of implanted BAHA or externally worn BAHA with Softband use. Despite the heterogeneous etiology of children in the study population, the authors suggest that the utility of BAHAs for children with syndromes and craniofacial anomalies is poorly recognized, resulting in delays in aid fitting and therefore in early hearing rehabilitation. In such cases, surgical reconstruction of the ear canal and middle-ear defects is not only technically challenging but also plagued by poor results (with a high rate of ear canal restenosis and limited functional hearing benefit). Hence, alternative treatment options such as Softband and BAHA may be of considerable benefit.

In 2010 Christensen reported on a retrospective chart review of 10 children (ages 6 months to 16 years) with bilateral conductive hearing loss.<sup>[28]</sup> Participants had been initially fit with a traditional bone-conduction hearing aid, then progressed first to the externally worn AOS with the Softband, then to the implanted BAHA. Functional gain was measured at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz for each device. Both the external AOS and the implanted BAHA provided statistically significantly higher functional gain than the conventional BCHAs.

A number of the same authors for the Christensen study also reported the results of a retrospective chart review of 25 children aged 6 months to 18 years with craniofacial disorders and bilateral conductive hearing loss.

It is unknown whether some of the children in the 2010 study were also included in these results. The focus of this study was on functional as measure by comparison of aided (using the Baha Softband) and unaided soundfield audiometric thresholds. Soundfield thresholds were improved with the Baha amplification, with over 80% of the thresholds meeting significant target levels. The authors concluded that this demonstrated the benefit of the Baha for children with bilateral congenital conductive hearing loss.

Hol (2008) evaluated the validity of a BAHA with Softband (fitted unilaterally and bilaterally) in two young children with severe bilateral conductive hearing loss due to CAA.<sup>[29]</sup> In a small multicenter comparative study, 12 children (including the two children in the Hol, 2005 study) with bilateral CAA with a pure conductive hearing loss of around 60 dB HL were fitted with the BAHA with Softband.<sup>[30]</sup> These children were retrospectively compared to a reference group of eight children selected from a database of those who had a conventional bone conduction hearing aid for bilateral CAA. The authors reported the mean aided hearing threshold of the children with the BAHA with Softband compared to the reference group was 27 dB HL,  $\pm$  6 dB HL to 25 dB HL  $\pm$  6 dB HL, respectively. Further results compared psychological and language development in 5 of the 12 children available from the BAHA with Softband group.

## ADVERSE EFFECTS OF BAHAS

### Systematic Reviews

In 2016, Verheij published a systematic review on complications of tissue preservation surgical techniques with percutaneous BAHA devices including 18 studies with 381 devices.<sup>[31]</sup> The implantation techniques reported in the studies were as follows: punch method, four studies (81 implants); linear incision technique without soft tissue reduction, 13 studies (288 implants); and Weber technique, one study (12 implants). Indications for surgery were SSD (n=68), sensorineural hearing loss (n=4), mixed hearing loss (n=65), or CHL (n=66). The Holgers classification was used to grade soft tissue reactions (grade 0, no reaction; grade 2, red and moist tissue; grade 3, granulation tissue; grade 4, removal of skin-penetrating implant necessary due to infection). The incidence of Holgers 3 was 2.5% with the punch technique, 5.9% with the linear incision technique, and 0% with the Weber technique. Holgers 4 was reported in one patient implanted with the linear incision technique.

In 2014 Mohamad performed a systematic review focusing on the association between surgical technique and skin complications following BAHA implantation. Thirty randomized controlled trials and retrospective studies were included, which highlighted that the most common surgical techniques identified were full-thickness skin graft, dermatome and linear incision. The investigators reported that dermatome technique is associated with higher rate of skin complications and the use of a linear incision technique is associated with lower skin complications. However, the investigators concluded that the data to support these conclusions in limited and that higher quality studies are needed.<sup>[32]</sup>

In 2103 Kiringoda reported on a meta-analysis of complications related to BAHA devices. Included in the meta-analysis were 20 studies that evaluated complication in 2134 adult and pediatric patients who received a total of 2310 BAHA devices.<sup>[33]</sup> The quality of available studies was considered poor and lacking in uniformity. The most common complications related to BAHA devices were minor skin reactions. Holgers Grade 2 to 4 skin reactions were reported to occur from 2.4% to 38.1% in all studies. Zero to 18% of implants failed osseointegration in adult and mixed population studies while 0% to 14.3% failed osseointegration in pediatric population studies. Adult and mixed population studies reported

revision surgery was required in 1.7% to 34.5% of cases while pediatric population studies reported required revision surgery in 0.0% to 44.4% of cases. Implant loss occurred in 1.6% to 17.4% in adult and mixed population studies and from 0.0% to 25% in pediatric studies.

## **Nonrandomized Studies**

In 2016, Roplekar compared skin-related complications of the traditional skin flap method to the linear incision method performed by a single surgeon in 117 patients with at least one year of follow-up.<sup>[34]</sup> Twenty-one (24%) patients experienced skin-related complications in the skin flap group (12 skin overgrowths, eight wound infections, one numbness) and three (10%) patients experienced complications in the linear incision group (three wound infections).

Four 2014 retrospective studies reported specific complication rates related to BAHA implants. The rate of skin reaction (e.g., skin overgrowth, inflammation) ranged from 6% to 22%. Implant loss was 10-18% and were spontaneous while others required removal; the primary reasons for implant loss were loss of osseointegration, trauma, and soft tissue reactions or discomfort. In addition, a number of small studies reported the safety outcomes of various techniques for surgically implanting BAHA devices. These included skin flap versus full-thickness skin graft implantation<sup>[35]</sup>, non-skin-thinning technique versus either flap or dermatome implantation<sup>[36]</sup>, and techniques related to implant size<sup>[37,38]</sup>.

## **Section Summary: Safety and Adverse Events Related to BAHA Devices**

The quality of available data for adverse events is generally poor with high heterogeneity. The most frequently reported complication from surgical procedures for BAHA insertion are adverse skin reactions, with an incidence of Holgers grade 2 to 4 reactions ranging from less than 2% to more than 34%, and implant loss ranging from less than 2% to more than 17%. There is some evidence of improvement in complication rates and severity with newer surgical techniques such as linear incision.

## **PARTIALLY IMPLANTABLE MAGNETIC BONE CONDUCTION HEARING AIDS**

A small body of literature addresses outcomes associated with transcutaneous, partially implantable bone-anchored devices. The majority of studies use a within-subjects comparison of hearing thresholds with and without the device. The indications for partially implantable systems are the same as those for transcutaneous bone-anchored devices.

## **Systematic Reviews**

Bezdjian (2017) published a systematic review of noncomparative studies that assessed outcomes and adverse events in patients with Sophono implants.<sup>[39]</sup> Thirteen articles were assessed for directness of evidence (DoE) and risk of bias (RoB) using predetermined criteria. Of these, eight studies (including 86 patients; 79.1% children) were considered to have high enough quality for data extraction. These studies all had medium or low risk of bias and high directness of evidence. A pooled analysis of all studies showed an average unaided pure tone average of 63.70 dB and an aided pure tone average of 31.60 dB. Four studies reported unaided and aided sound reception thresholds in raw dB scores. A pooled analysis of these studies showed a mean unaided score of 66.90 dB and a mean aided score of 33.34. No intra-operative complications were reported and 29% of patients reported post-operative complications. Of these, three were serious adverse events. No implant loss occurred, except

in one patient who requested explanation due to severe headaches. While there were improvements in auditory functions, no statistical analyses were reported.

In 2016, Dimitriadis reported on a systematic review of observational studies of the BAHA Attract device including 10 studies (total n=89 patients; range, 1 to 27 patients).<sup>[40]</sup> Seventeen (19%) of the patients were children, of whom five had unilateral sensorineural hearing loss and 4 had CHL. Of the 27 (45%) adults, 22 had unilateral sensorineural hearing loss and 11 (18%) had bilateral mixed hearing loss. Audiologic and functional outcome measures and the timing of testing varied greatly in the studies. Summary measures were not reported. In general, audiologic and functional outcomes measured pre- and postimplantation showed improvement, although statistical comparisons were lacking in some studies.

## Nonrandomized Studies

Iseri (2015) described a retrospective, single-center study from Turkey comparing 21 patients treated with a transcutaneous, fully implantable BAHA with 16 patients treated with a percutaneous device (the BAHA Attract).<sup>[41]</sup> Groups were generally similar at baseline, with most individuals undergoing BAHA placement for chronic otitis media. Operating time was longer in patients treated with the transcutaneous partially implantable devices (46 minutes vs 26 minutes,  $p < 0.05$ ). Three patients treated with percutaneous devices had Holger grade 2 skin reactions, and two had stopped using their devices. Mean thresholds for frequencies 0.5 to 4.0 kHz were 64.4 dB without the BAHA and 31.6 dB with the BAHA in the percutaneous device group, and 58.3 dB without the BAHA and 27.2 dB with the BAHA in the transcutaneous device group. Frequency-specific threshold hearing gains did not differ significantly between groups. Mean hearing gain measured by speech reception threshold was statistically significantly smaller in the percutaneous group (24 dB vs 36.7 dB,  $p = 0.02$ ).

There have been other, small nonrandomized studies that have assessed the outcomes of the BAHA Attract device, in comparison with other devices, or in single-center observational studies.<sup>[42-44]</sup> In addition, one case series of 34 patients has reported on complications of the BAHA attract device, where only three patients reported moderate to severe complications, two of which required removal of the magnet.<sup>[45]</sup>

In 2015, Denoyelle reported on a prospective trial of the Sophono device in children ages 5 to 18 years with uni- or bilateral congenital aural atresia with complete absence of the external auditory canal with pure CHL.<sup>[46]</sup> The study included a within-subject comparison of hearing results with the Sophono devices to those obtained with the Baha Softband preoperatively. All 15 patients enrolled were implanted (median age, 97 months). At 6-month follow-up, mean aided AC pure-tone audiometry was 33.49 (mean gain, 35.53 dB), with a mean aided sound reception threshold of 38.2 (mean gain, 33.47 dB). The difference in AC PTA between the Baha Softband and the Sophono device was 0.6 dB (confidence interval upper limit, 4.42 dB), which met the study's prespecified noninferiority margin. Adverse effects were generally mild, including skin erythema in two patients, which improved by using a weaker magnet, and brief episodes of pain or tingling in three patients.

The Otomag Sophono system has been studied in a number of very small (n=5 to 12) nonrandomized studies in pediatric patients.<sup>[42,43,47-53]</sup>

Similarly, the Bonebridge partially implantable system has also been studied in a number of small (n=5 to 44) case series, summarized in table 1.<sup>[54-60]</sup>

**Table 1. Case Series Evaluating the Bonebridge Implant**

Study	N	Patient Population	Main Hearing Results	Safety Outcomes
Bravo-Torres (2018) <sup>[61]</sup>	15	<ul style="list-style-type: none"> <li>Pediatric patients with bilateral CHL (microtia associated with external auditory canal atresia)</li> </ul>	<ul style="list-style-type: none"> <li>Aided sound-field threshold improvement: 25.2 dB</li> </ul>	Minor feedback (4), broken processors (4), mild skin redness (2) with one-month follow-up
Schmerber (2017) <sup>[62]</sup>	25	<ul style="list-style-type: none"> <li>SSD (n=12)</li> <li>Bilateral CHL (n=7)</li> <li>Bilateral mixed HL (n=6)</li> </ul>	<ul style="list-style-type: none"> <li>SSD, in 5/7 patients speech reception threshold in noise lower with Bonebridge activated</li> <li>CHL and mixed, average functional gain: 26 dB HL; mean % of speech recognition in quiet improved from 74% unaided to 95% aided</li> </ul>	No complications, device failures, revision surgery, or skin injury reported with one year follow-up
Rahne (2015) <sup>[59]</sup>	11	<ul style="list-style-type: none"> <li>SSD (n=6; 1 sensorineural, 3 mixed, 2 conductive)</li> <li>Bilateral CHL (n=2)</li> <li>Bilateral mixed HL or mixed/sensorineural (n=3)</li> </ul>	<ul style="list-style-type: none"> <li>Aided sound-field threshold improvement: 33.4 dB</li> <li>WRS improved from mean of 10% unaided to 87.5% aided</li> </ul>	One case of chronic fibrosing mastoiditis requiring mastoidectomy and antrotomy; no other complications
Laske (2015) <sup>[60]</sup>	9	<ul style="list-style-type: none"> <li>Adults with SSD and normal contralateral hearing</li> </ul>	<ul style="list-style-type: none"> <li>Speech discrimination signal-to-noise improvement for aided vs unaided condition, sound presented to aided ear: 1.7 dB</li> <li>Positive improvements on quality-of life questions</li> </ul>	Not reported
Riss (2014) <sup>[54]</sup>	24	<ul style="list-style-type: none"> <li>Combined HL (n=9)</li> <li>EAC atresia (n=12)</li> <li>SSD (n=3)</li> </ul>	<ul style="list-style-type: none"> <li>Average functional gain: 28.8 dB</li> <li>Monosyllabic word scores at 65-dB sound pressure increased from 4.6 to 53.7 percentage points</li> </ul>	Not reported
Manrique (2014) <sup>[55]</sup>	5	<ul style="list-style-type: none"> <li>Mixed HL (n=4)</li> <li>SSD (n=1)</li> </ul>	<ul style="list-style-type: none"> <li>PTA improvement: 35.62 dB (p=0.01)</li> <li>Disyllabic word discrimination improvement: 20% (p=0.016)</li> </ul>	No perioperative complications reported
Ihler (2014) <sup>[56]</sup>	6	<ul style="list-style-type: none"> <li>Mixed HL (n=4)</li> <li>CHL (n=2)</li> </ul>	<ul style="list-style-type: none"> <li>PTA functional gain (average, 0.5-4.0 kHz): 34.5 dB</li> <li>Speech discrimination at 65 dB improvement:                             <ul style="list-style-type: none"> <li>In quiet: 63.3</li> </ul> </li> </ul>	Prolonged wound healing in one case

Study	N	Patient Population	Main Hearing Results	Safety Outcomes
			<ul style="list-style-type: none"> <li>○ percentage points</li> <li>○ In noise: 37.5 percentage points</li> </ul>	
Desmet (2014) <sup>[57]</sup>	44	<ul style="list-style-type: none"> <li>● All unilaterally deaf adults</li> </ul>	<ul style="list-style-type: none"> <li>● Statistically significant improvement on APHAB and SHHIA</li> </ul>	Not reported

APHAB: Abbreviated Profile of Hearing Aid Benefit; CHL: conductive hearing loss; EAC: external auditory canal; HL: hearing loss; PTA: pure-tone average; SHHIA: Short Hearing Handicap Inventory for Adults; SSD: single-sided deafness; WRS: Word Recognition Score.

## Section Summary: Partially Implantable Magnetic BAHA Devices

Studies of transcutaneous, partially implantable BAHAs have typically used a retrospective within-subjects comparison of hearing thresholds with and without the device, although there have been two small (27 and 15 participants) prospective studies. There was heterogeneity in the audiologic and functional outcome measures used in the studies and the timing of testing. Studies of partially implantable BAHAs have generally demonstrated within-subjects improvements in hearing.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY (AAO-HNS)

In 2016, the American Academy of Otolaryngology – Head and Neck Surgery updated its consensus-based position statement on the use of bone conduction hearing devices.<sup>[63]</sup> It specifies that bone conduction hearing devices are “acceptable, and in many cases preferred, procedures in the treatment of conductive or mixed hearing loss and single-sided deafness”. The statement indicates that the procedure should be performed by a qualified otolaryngologist-head and neck surgeon with devices which have been Food and Drug Administration (FDA)-approved, and “should adhere to the restrictions and guidelines specified by the appropriate governing agency, such as the Food and Drug Administration in the United States”.

## SUMMARY

There is enough research to show that unilateral or bilateral transcutaneous bone-conduction or bone-anchored hearing aid(s) improve net health outcomes when used as an alternative to air-conduction hearing aids in select patients. Clinical guidelines based on research recommend bone conduction hearing devices for the treatment of conductive or mixed hearing loss and single-sided deafness. In addition, a binaural hearing benefit may be provided for patients with single-sided sensorineural deafness by the routing of signals to the hearing ear. Therefore, use of these devices is considered medically necessary for patients who meet the policy criteria.

There is not enough research to show that unilateral or bilateral transcutaneous bone-conduction or bone-anchored hearing aid(s) improve health outcomes for patients who do not meet the policy criteria due to a lack of, including but not limited to patients not meeting

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the age requirements and patients with bilateral sensorineural hearing loss. In addition, there are no evidence-based clinical practice guidelines that recommend these devices for patients who do not meet the criteria. Therefore, these devices are considered investigational for patients who do not meet the policy criteria.

Implant replacement, including replacement parts or upgrades, may be considered medically necessary only in the small subset of patients whose response to existing components is inadequate to the point of interfering with activities of daily living, which would include school and work; or when components are no longer functional.

Implant replacement, including replacement parts or upgrades to existing bone-anchored hearing aid components (for example, batteries, processor, headband or Softband) are considered not medically necessary when criteria are not met, including when requested for convenience or to upgrade to newer technology when the current components remain functional.

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## CODES

### Codes Number Description

**NOTE:** The following CPT codes describe semi-implantable electromagnetic bone conduction hearing aids:

CPT	69710	Implantation or replacement of electromagnetic bone conduction hearing device in temporal bone*
	69711	Removal or repair of electromagnetic bone conduction hearing device in temporal bone

\*The Audiant™ bone conductor is a type of electromagnetic bone conduction hearing device. While this product is no longer actively marketed, patients with existing Audiant devices may require replacement, removal, or repair.

	69714	Implantation, osseointegrated implant, temporal bone, with percutaneous attachment to external speech processor/cochlear stimulator; without mastoidectomy**
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	69715	;with mastoidectomy**
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	69717	Replacement (including removal of existing device), osseointegrated implant, temporal bone, with percutaneous attachment to external speech processor/cochlear stimulator; without mastoidectomy
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	69718	;with mastoidectomy
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\*\*These codes describe implantation of the Baha®, Ponto™, and similar devices.

HCPCS	L8621	Zinc air battery for use with cochlear implant device and auditory osseointegrated sound processors, replacement, each
	L8624	Lithium ion battery for use with cochlear implant device or auditory osseointegrated device speech processor, ear level, replacement each
	L8625	External recharging system for battery for use with cochlear implant or auditory osseointegrated device, replacement only, each
	L8690	Auditory osseointegrated device, includes all internal and external components***
	L8691	Auditory osseointegrated device, external sound processor, excludes transducer/actuator, replacement only, each
	L8692	Auditory osseointegrated device, external sound processor, used without osseointegration, body worn, includes headband or other means of external attachment
	L8693	Auditory osseointegrated device abutment, any length, replacement only
	L8694	Auditory osseointegrated device, transducer/actuator, replacement only, each

\*\*\*These codes describe the Baha®, Ponto™, and similar devices.

**Date of Origin:** July 2003

## ***Cryosurgical Ablation of Miscellaneous Solid Organ, Pulmonary, and Breast Tumors***

**Effective:** March 1, 2020

**Next Review:** November 2020

**Last Review:** January 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Cryoablation kills cells freezing the tissue using a coolant that is circulated via a probe inserted into the tumor.

### **MEDICAL POLICY CRITERIA**

#### **Notes:**

- This policy is limited to cryosurgery for the treatment of solid organ tumors, as well as breast and pulmonary tumors.
- This policy does not address liver tumors (primary or metastatic). See Cross References.

- I. Cryosurgical ablation may be considered **medically necessary** for the treatment of any of the following indications:
  - A. Kidney tumors

- B. Prostate tumors
- C. Lung cancer when either of the following criteria is met:
  1. For non-small cell lung cancer when the patient has early-stage (Stage I, and selected node negative Stage IIA) non-small cell lung cancer; or
  2. The patient requires palliation for a central airway obstructing lesion.
- II. Cryosurgical ablation is considered **investigational** as a treatment of malignant or benign (fibroadenoma) breast tumors, pulmonary tumors not meeting Criterion I., and all other solid organ tumors including but not limited to bone and pancreatic cancer.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and Physical
- Treatment plan including treatment area.

## CROSS REFERENCES

1. [Radioembolization, Transarterial Embolization \(TAE\), and Transarterial Chemoembolization \(TACE\)](#), Medicine, Policy No. 140
2. [Radiofrequency Ablation \(RFA\) of Tumors Other than Liver](#), Surgery, Policy No. 92
3. [Magnetic Resonance \(MR\) Guided Focused Ultrasound \(MRgFUS\) and High Intensity Focused Ultrasound \(HIFU\) Ablation, Surgery](#), Policy No. 139
4. [Microwave Tumor Ablation](#), Surgery, Policy No. 189
5. [Ablation of Primary and Metastatic Liver Tumors](#), Surgery, Policy No. 204

## BACKGROUND

Cryosurgical ablation (also called cryosurgery, cryotherapy, or cryoablation) kills cells (cancerous and normal) by freezing target tissues, most often by inserting a probe into the tumor through which coolant is circulated. Cryosurgery may be performed as an open surgical technique or as a closed procedure under laparoscopic or ultrasound guidance.

The goals of cryosurgery may include the following:

- Destruction or shrinkage of tumor tissue
- Controlling local tumor growth and preventing recurrence
- Palliating symptoms
- Extending survival duration for patients with certain tumors.

Potential complications associated with cryosurgery in any organ include the following:

- Hypothermic damage to normal tissue adjacent to the tumor (e.g., nerve damage)
- Structural damage along the probe track
- Secondary tumors if cancerous cells are seeded during probe removal.

## REGULATORY STATUS

There are several cryoablation devices cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for use in open, minimally invasive or endoscopic surgical procedures in the areas of general surgery, urology, gynecology, oncology, neurology, dermatology, proctology, thoracic surgery and ear, nose and throat. Examples include:

- Cryocare® Surgical System by Endocare;
- CryoGen Cryosurgical System by Cryosurgical, Inc.;
- CryoHit® by Galil Medical;
- IceRod® CX, IcePearl® 2.1 CX and IceFORCE® 2.1 CX Cryoablation Needles by Galil Medical;
- SeedNet™ System by Galil Medical;
- Visica® System by Sanarus Medical;
- Visual-ICE® Cryoablation System by Galil;
- ERBECRYO 2® Cryosurgical Unit, ERBE USA Incorporated

## EVIDENCE SUMMARY

In order to understand the impact of cryosurgical ablation on local or distant tumor recurrence and disease-free and overall survival in patients with solid tumors, randomized trials are needed that compare this technique with current standard treatments. The standard treatment for most solid tumors is surgical resection. For unresectable solid tumors, alternatives to resection depend on the tumor type and location, and may include thermal ablation, percutaneous ethanol injection, chemoembolization, chemotherapy, and radiation therapy.

Despite the weaknesses in the published clinical evidence, cryosurgical ablation has become a recognized standard of care for tumors of the kidney, liver (addressed in Ablation of Primary and Metastatic Liver Tumors, Surgery, Policy No. 204), prostate, and carefully selected patients with tumors of the lung.<sup>[1-51]</sup>

The following literature appraisal focuses on the investigational indications noted in medical policy criteria above.

## BREAST TUMORS

The standard treatment for breast cancer is surgical excision by lumpectomy or mastectomy, with or without adjuvant radiation therapy, chemotherapy, and/or hormone therapy. Fibroadenomas, benign tumors of the breast, generally do not require treatment. If treated, they are typically surgically excised.

## SYSTEMATIC REVIEWS

One systematic review (Zhao 2010) was found that included cryoablation along with other minimally-invasive thermal ablation techniques (i.e., radiofrequency, microwave, cryoablation and high-intensity focused ultrasound) for treatment of early-stage breast cancer.<sup>[52]</sup> Zhao reported that studies on cryoablation for breast cancer were primarily limited to pilot and feasibility studies conducted in the research setting. A wide range of 36-83% was reported for complete ablation of tumors. The authors concluded that, while promising, large randomized controlled trials are needed to further evaluate patient selection criteria, techniques to ensure

complete tumor ablation, and long-term outcomes compared with surgical excision of breast tumors.

## **RANDOMIZED CONTROLLED TRIALS**

There are no prospective, randomized controlled trials comparing survival and recurrence rates following cryoablation of breast tumors with surgical excision or, for unresectable tumors, with nonoperative therapies.

## **NONRANDOMIZED STUDIES**

The remaining nonrandomized evidence does not permit reliable conclusions concerning the impact of cryosurgical ablation on breast cancer survival or recurrence due to a number of methodological limitations, including: heterogeneous or unreported patient selection criteria, the use of varied cryoablation techniques, nonrandomized allocation of treatment, lack of an appropriate surgical excision control group for comparison, small subject population, and limited data on long-term outcomes.<sup>[53-66]</sup>

## **PULMONARY TUMORS**

### **SYSTEMATIC REVIEWS**

Lee (2011) conducted a systematic review of endoscopic cryoablation of lung and bronchial tumors.<sup>[67]</sup> Included in the review were 15 case studies and one comparative observational study. Cryoablation was performed for inoperable, advanced lung and bronchial cancers in most studies. Some studies included patients with comorbid conditions and poor general health who would not be considered surgical candidates. Complications occurred in 11.1% of patients (10 studies) and consisted of hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea. Within 30 days of the procedure, death from hemoptysis and respiratory failure, considered to be most likely related to disease progression, occurred in 7.1% of patients. Improvements in pulmonary function and clinical symptoms occurred in studies reporting these outcomes. One published review reported the outcomes of 15 case series and one comparative observational study for endoscopic cryotherapy of endobronchial tumors. Most studies were for inoperable, advanced lung and bronchial cancers. A critical analysis of the studies was not provided. However, the authors noted the significant limitations in the available evidence due to lack of control groups, lack of random treatment allocation, and heterogeneity in study methodologies, participants' characteristics (e.g., comorbid conditions, general health, cancer grade), treatment protocols, operative techniques, and outcome measures. Complications occurred in 11.1% of patients from ten studies and consisted of hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea. Within 30 days of the procedure, death from hemoptysis and respiratory failure, considered to be most likely related to disease progression, occurred in 7.1% of patients. Improvements in pulmonary function and clinical symptoms occurred in studies reporting these outcomes. Because the studies in the review did not include control groups or compare outcomes of cryosurgery to alternative strategies for managing similar patients, no conclusions can be made on the net health outcomes of cryosurgery for lung cancer.

### **RANDOMIZED CONTROLLED TRIALS**

One preliminary randomized trial studied 36 female patients with NSCLC who also had epidermal growth factor receptor gene mutations.<sup>[68]</sup> All patients received six months treatment

with molecular target therapy gefitinib, an epidermal growth factor receptor-tyrosine kinase inhibitor. Patients were randomized to either an experimental group and underwent cryoablation prior to receiving gefitinib, or to a control group in which cryoablation was not performed. At one-year follow-up, the survival rate in the cryoablation group was significantly higher than that of the control group. The findings of this preliminary study suggest that cryoablation may improve the effects of gefitinib in this patient population. Additional larger, long-term randomized trials are needed to validate these findings.

## NONRANDOMIZED STUDIES

The ECLIPSE trial is prospective, multicenter trial of cryoablation for metastatic disease in the lungs, interim results at one-year follow-up were published in 2015.<sup>[69]</sup> The trial enrolled 40 patients with 60 metastatic lung lesions who were treated with cryoablation and had at least 12 months of follow-up. Outcomes included survival, local tumor control, quality of life, and complications. Local tumor control was achieved in 94.2% (49/52) of treated lesions, and one-year OS was 97.5% (39/40). There were no significant changes in quality of life over the 12-month study. The most common adverse event was pneumothorax requiring chest tube insertion in 18.8% (9/48 procedures).

## OTHER TUMORS

Cryoablation for the treatment of other solid tumors has not been well-studied.

## SYSTEMATIC REVIEWS

In 2014, Keane reported on a systematic review of ablation therapies, including cryoablation, for locally advanced pancreatic cancer.<sup>[70]</sup> The review noted studies have demonstrated ablative therapies, including cryoablation, are feasible but larger studies are needed. No conclusions could be made on whether ablation resulted in better oncologic outcomes than best supportive care.

In 2012, Tao reported on a systematic review of cryoablation for pancreatic cancer.<sup>[71]</sup> The authors identified 29 studies from the literature search and included five of these studies in the review. The five studies were all case series and considered to be of low quality. Adverse events, when mentioned in the studies, included delayed gastric emptying (0% to 40.9% in three studies), pancreatic leak (0% to 6.8% in four studies), biliary leak (0% to 6.8% in three studies), and one instance of upper gastrointestinal hemorrhage. Pain relief was reported in three studies and ranged from 66.7% to 100%. Median survival times reported in three studies ranged from 13.4 to 16 months. One-year total survival rates reported in two studies were 57.5% and 63.6%.

## NONRANDOMIZED STUDIES

The remaining published literature is limited to case series and retrospective reviews.<sup>[72-81]</sup> As discussed above, these studies do not permit reliable conclusions concerning the impact of cryoablation on health outcomes.

## PRACTICE GUIDELINE SUMMARY

Clinical practice guidelines from U.S. professional associations consistently list cryoablation as a treatment option for tumors of the kidney or prostate.<sup>[82-87]</sup>

No clinical practice guidelines or position statements based on research from U.S. professional societies were identified that recommend cryoablation for the treatment of solid tumors other than kidney and prostate tumors.

## SUMMARY

Cryosurgical ablation has become a recognized standard of care in the management of tumors of the kidney and prostate, and carefully selected patients with lung tumors. Therefore, this technique may be considered medically necessary in the treatment of these tumors when criteria are met.

There is not enough research to show that cryosurgical ablation for the treatment of bone, breast, and solid organ tumors other than tumors of the kidney or prostate, or lung tumors meeting criteria improves health outcomes. In addition, there are no clinical practice guidelines based on research that recommend the use of cryosurgical ablation of those tumors. Therefore, cryosurgical ablation as a treatment for bone, breast, and solid organ tumors other than those of the kidney, prostate, or lung tumors meeting criteria is considered investigational.

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88. BlueCross BlueShield Association Medical Policy Reference Manual "Cryosurgical Ablation of Miscellaneous Solid Tumors Other Than Liver, Prostate, or Dermatologic Tumors." 7.01.92
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## CODES

Codes	Number	Description
CPT	0581T	Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral
	19105	Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma
	20983	Ablation therapy for reduction or eradication of 1 or more bone tumors (eg, metastasis) including adjacent soft tissue when involved by tumor extension, percutaneous, including imaging guidance when performed; cryoablation
	31641	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with destruction of tumor or relief of stenosis by any method other than excision (eg, laser therapy, cryotherapy)
	32994	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation
	50250	Ablation, open, 1 or more renal mass lesion(s), cryosurgical, including intraoperative ultrasound guidance and monitoring, if performed
	50542	Laparoscopy, surgical; ablation of renal mass lesion(s), including intraoperative ultrasound guidance and monitoring, when performed
	50593	Ablation, renal tumor(s), unilateral, percutaneous, cryotherapy
	55873	Cryosurgical ablation of the prostate (includes ultrasonic guidance and monitoring)
	HCPCS	None

**Date of Origin:** March 2004

## ***Sacral Nerve Neuromodulation (Stimulation) for Pelvic Floor Dysfunction***

**Effective:** April 1, 2020

**Next Review:** December 2020

**Last Review:** February 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Sacral nerve neuromodulation involves the implantation of a permanent electrical stimulation device that modulates the neural pathways controlling bladder or rectal function.

### **MEDICAL POLICY CRITERIA**

**Note:** Sacral nerve neuromodulation should be initiated with a *trial period* of sacral nerve neuromodulation (peripheral nerve stimulation test) with a *temporarily implanted* lead and may be followed by *permanent implantation*. This policy addresses these services as one combined episode beginning with the temporary placement.

- I. Sacral nerve neuromodulation (including a *trial period* of sacral nerve neuromodulation [peripheral nerve stimulation test] with a *temporarily implanted* lead and, when used, the *permanent implantation*) may be considered **medically necessary** when one or more of the following criteria are met:
  - A. For the treatment of urinary incontinence and non-obstructive retention in patients who meet **all** of the following criteria (1.– 3.):

1. There is a diagnosis of at least one of the following:
    - a. Urge incontinence
    - b. Urgency-frequency syndrome
    - c. Non-obstructive urinary retention
    - d. Overactive bladder
  2. There is documented failure or intolerance to at least 2 conventional conservative therapies (e.g., behavioral training such as bladder training, prompted voiding, or pelvic muscle exercise training, pharmacologic treatment for at least a sufficient duration to fully assess its efficacy, and/or surgical corrective therapy); and
  3. Incontinence is not related to a neurologic condition.
- B. For the treatment of fecal incontinence in patients who meet **all** of the following criteria (1.- 5.):
1. There is a diagnosis of chronic fecal incontinence of greater than 2 incontinent episodes on average per week with duration greater than 6 months or for more than 12 months after vaginal childbirth;
  2. There is documented failure or intolerance to conventional conservative therapy (e.g., dietary modification, the addition of bulking and pharmacologic treatment for at least a sufficient duration to fully assess its efficacy);
  3. The condition is not related to an anorectal malformation (e.g., congenital anorectal malformation; defects of the external anal sphincter over 60 degrees; visible sequelae of pelvic radiation; active anal abscesses and fistulae) or chronic inflammatory bowel disease;
  4. Incontinence is not related to another neurologic condition; and
  5. The patient has not had rectal surgery in the previous 12 months, or in the case of rectal cancer, the patient has not had rectal surgery in the past 24 months.
- II. Sacral nerve neuromodulation device revision(s) or replacement(s) may be considered **medically necessary** after the device has been placed.
- III. Sacral nerve neuromodulation for the treatment of urinary incontinence, non-obstructive retention, and fecal incontinence is considered **not medically necessary** when Criterion I. is not met, including but not limited to stress incontinence and urge incontinence due to a neurologic condition (e.g. detrusor hyperreflexia, multiple sclerosis, spinal cord injury, or diabetes with peripheral nerve involvement).
- IV. Sacral nerve neuromodulation for the treatment of all other indications is considered **investigational**, including but not limited to chronic pelvic pain and constipation.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine whether the

policy criteria are met. If these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Documented applicable Diagnosis/Diagnoses and any neurological diagnoses present
- Documented failure or intolerance to conventional conservative therapies attempted as detailed in criteria I.A.2. and I.B.2.
- Documentation of surgical history within the last 24 months as applicable to fecal incontinence

## CROSS REFERENCES

1. [Pelvic Floor Stimulation as a Treatment of Urinary Incontinence](#), Allied Health, Policy No. 4
2. [Transanal Radiofrequency Treatment of Fecal Incontinence](#), Surgery, Policy No. 129

## BACKGROUND

Sacral nerve neuromodulation (SNM), previously known as sacral nerve stimulation is defined as the implantation of a permanent device that modulates the neural pathways controlling bladder or rectal function. The SNM device consists of an implantable pulse generator that delivers controlled electrical impulses. This pulse generator is attached to wire leads that connect to the sacral nerves, most commonly the S3 nerve root. Two external components of the system help control the electrical stimulation. A control magnet is kept by the patient and can be used to turn the device on or off. A console programmer is kept by the physician and used to adjust the settings of the pulse generator.

Treatment using SNM is one of several alternative modalities for patients with fecal or urinary incontinence who have failed behavioral (e.g., prompted voiding) and/or pharmacologic therapies.

Prior to implantation of the permanent device, patients undergo a peripheral nerve stimulation test to estimate potential response to SNM. This procedure is done under local anesthesia, using a test needle to identify the appropriate sacral nerve(s). Once identified, a temporary wire lead is inserted through the test needle and left in place for several days. This lead is connected to an external stimulator which is carried by patients in their pocket or on their belt. Patients then keep track of voiding symptoms while the temporary device is functioning. The results of this test phase are used to determine whether patients are appropriate candidates for the permanent device. If patients show a 50% or greater reduction in incontinence frequency, they are deemed eligible for the permanent device. According to data from the manufacturer, approximately 63% of patients have a successful peripheral nerve evaluation and are thus candidates for the permanent SNM.

The permanent device is implanted with the patient under general anesthesia. An incision is made over the lower back and the electrical leads are placed in contact with the sacral nerve root(s). The wire leads are extended through a second incision underneath the skin across the flank to the lower abdomen. Finally, a third incision is made in the lower abdomen where the pulse generator is inserted and connected to the wire leads. Following implantation, the physician programs the pulse generator to the optimal settings for that patient. The patient can switch the pulse generator between on and off by placing the control magnet over the area of the pulse generator for one to two seconds.

## REGULATORY STATUS

In 1997, the Medtronic Interstim® Sacral Nerve Stimulation™ system received U.S. Food and Drug Administration (FDA) approval for marketing for the indication of urinary urge incontinence in patients who have failed or could not tolerate more conservative treatments. In 1999 the device received FDA approval for the additional indications of urgency-frequency and urinary retention in patients without mechanical obstruction.

In 2006, the Medtronic Interstim® II System received FDA approval for treatment of intractable cases of overactive bladder and urinary retention. The new device is smaller and lighter than the original system and is reported to be suited for those with lower energy requirements or small stature. The device also includes updated software and programming options.

In 2011, the Medtronic InterStim System received FDA approval for the indication of chronic fecal incontinence in patients who have failed or could not tolerate more conservative treatments.

The Interstim device has not been specifically approved by FDA for treatment of chronic pelvic pain.

**Note:** Sacral nerve neuromodulation should be distinguished from pelvic floor stimulation. Pelvic floor stimulation refers to electrical stimulation of the pudendal nerve. This therapy is addressed in a separate medical policy (see Cross References).

## EVIDENCE SUMMARY

Assessment of the safety and efficacy of sacral nerve modulation (SNM) as a treatment for urinary or fecal incontinence requires large, blinded, long-term randomized controlled trials to determine whether 1) the benefits of SNM outweigh any risks, and 2) whether SNM offers advantages over conventional conservative treatments. The appropriate control group(s) against which SNM should be compared is sham stimulation, on- versus off-phases in which patients act as their own controls, or conventional conservative therapies.

### URINARY DYSFUNCTION

#### Urge Incontinence

##### Systematic Reviews

Initially, the policy for SNM as a treatment of urge incontinence was based on a 1998 BlueCross BlueShield Association Technology Evaluation Center (TEC) assessment.<sup>[1]</sup> Based on a multicenter RCT<sup>[2]</sup> conducted as part of the FDA approval process, the TEC Assessment concluded that SNM reduced urge incontinence compared with control patients.

Brazzelli performed a review of articles published between 1966 and 2003 which included four randomized controlled trials and 30 case series.<sup>[3]</sup> The authors reported that about 80% of patients in the randomized trials achieved continence or greater than 50% improvement in their main incontinence symptoms after SNM compared with about 3% of controls receiving conservative treatments. The case series, which were larger but methodically less reliable, showed similar results. Benefits were reported to persist three to five years after implantation. The authors noted that technical changes over time were associated with decreased complication rates.

## Randomized Controlled Trials

No new RCTs for urge incontinence were identified since the above systematic reviews were published.

## Nonrandomized Studies

A 2011 series by Groen in reported the longest follow-up.<sup>[4]</sup> A total of 60 patients had at least five years of follow-up after SNM for refractory idiopathic urge urinary incontinence. Success was defined as at least a 50% decrease in the number of incontinent episodes or pads used per day. The success rate was 52 of 60 (87%) at one month and gradually decreased to 37 (62%) at five years. The number of women who were completely continent was 15 (25%) at one month and 9 (15%) at five years. At the five-year follow-up, SNM was still used by 48/60 (80%) women. A total of 57 adverse events were reported in 32 of 60 (53%) patients. The most frequent adverse events were hardware-related or pain or discomfort. There were a total of 23 reoperations in 15 patients. In most cases, pain problems were managed conservatively.

## **Urinary Urgency/Frequency**

### Systematic Reviews

No recent systematic reviews were identified.

### Randomized Controlled Trials

In the multicenter randomized clinical study of 581 patients with a variety of urinary dysfunctions, 220 had significant urgency-frequency symptoms.<sup>[5]</sup> After six months of SNM therapy, 83% of patients with urgency-frequency symptoms reported increased voiding volumes with the same or reduced degree of frequency. At 12 months, 81% of patients had reached normal voiding frequency. Compared to a control group, patients with implants reported significant improvements in quality of life, as evaluated by the SF-36 health survey.

In 2016, Amundsen reported on a RCT comparing intradetrusor injection of onabotulinumtoxinA (n=192) with SNM (n=189) in women with refractory urgency urinary incontinence, defined as at least one supervised behavioral or physical therapy intervention and the use of a minimum of two anticholinergics (or inability to tolerate or contraindications to the medication).<sup>[6]</sup> In intention-to-treat analysis, onabotulinumtoxinA-treated patients had greater reductions in urge incontinence per day than SNM-treated patients: 3.9 vs 3.3/ day (mean difference: 0.63; 95% CI 0.13 to 1.14, P=0.01). OnabotulinumtoxinA-treated patients had greater reductions in some overactive bladder-related quality of life questionnaire-related measures, although the clinical meaningfulness of the changes was uncertain. Patients in the onabotulinumtoxinA-treated group were more likely to have urinary tract infections (UTIs, 35% vs 11%; risk difference -23%, 95% CI -33% to -13%, p<0.001).

In 2014 Siegel published an industry-sponsored FDA-mandated postapproval randomized study and is known as the Insite trial.<sup>[7]</sup> This study compared SNM using a two-stage surgical procedure with standard medical therapy. Study inclusion criteria included a diagnosis of overactive bladder (OAB) (at least eight voids per day and/or at least two involuntary leaking episodes in 72 hours) and a failed trial of at least one anticholinergic or antimuscarinic medication. In addition, there needed to be at least one such medication that had not yet been attempted. Patients with neurologic diseases and with primary stress incontinence were excluded. A total of 70 patients were allocated to SNM and 77 to standard medical therapy. Of

the 70 patients in the SNM group, 11 elected not to receive test stimulation with the tined lead and eight received the lead but did not receive a full system implant due to lack of response to a 14-day test stimulation period (response was defined as at least a 50% reduction in average leaks and/or voids). Patients in the medical treatment group tried the next recommended medication or restarted a discontinued medication. Therapeutic success was defined as at least a 50% improvement in average leaks/day or at least a 50% improvement in the number of voids per day or a return to fewer than eight voids per day. In an intention-to-treat analysis, the therapeutic success rate at six months was 61% in the SNM group and 42% in the standard medical treatment group; the difference between groups was statistically significant ( $p=0.02$ ). Quality of Life (QOL) at six months was a secondary outcome. Several validated QOL scales were used, and all favored the SNM group compared with the standard medical treatment group ( $p<0.002$  for all comparisons).

In 2014, Noblett published twelve-month follow-up results of the Insite trial. The analysis included patients included in the SNM group of initial RCT plus additional patients enrolled and implanted in the interim.<sup>[8]</sup> A total of 340 patients underwent test stimulation, 272 underwent implantation, and 255 completed 12 months of follow-up. In a modified completers' analysis, the therapeutic success rate was 82%. This modified completers' analysis included patients who were implanted and had either a baseline or 12-month evaluation, or withdrew from the trial due to a device-related adverse event or lack of efficacy. In an analysis limited to study completers, the therapeutic response rate was 85%. The Noblett analysis did not include data from the control group of patients receiving only standard medical therapy.

In 2014 Tang published the results of an RCT in which 240 women with OAB were randomized to receive tolterodine with ( $n=120$ ) or without ( $n=120$ ) sacral neuromodulation.<sup>[9]</sup> Participants were also divided into subgroups based on the presence or absence of urinary incontinence. The treatment period was three months; results were measured by voiding diaries and urodynamic parameters, in addition to psychological depression and anxiety scores. The group receiving SNM reported significantly greater improvements in the conditions of first desire to void, maximum cystometric capacity, daily average volumes, and daily single maximum voided volumes compared to the group receiving medication alone ( $p=.001$ ). The SNM group also reported greater decreases in self-rated depression and anxiety scales ( $p<0.001$ ). The authors concluded that combined treatment with SNM and tolterodine could improve the quality of life in women with OAB by decreasing voiding dysfunction symptoms and related depression and anxiety.

### Nonrandomized Studies

There has also been interest in the use of sacral nerve neuromodulation as a treatment of interstitial cystitis, a condition characterized by painful urinary urgency and frequency.<sup>[10-12]</sup> These studies reported a decrease in both urgency/frequency and pain. These patients would be considered candidates for sacral nerve neuromodulation therapy based on the presence of urgency and frequency alone.

## **Urinary Retention**

### Systematic Review

A 2009 Cochrane review<sup>[13]</sup> described eight randomized studies on implanted devices for urinary storage and voiding dysfunction in adults. In spite of methodologic problems (e.g., generally poor-quality studies), the evidence "seems clear that continuous stimulation offers

benefits for carefully selected people with overactive bladder syndrome and for those with urinary retention but no structural obstruction.” The authors concluded that while some people benefit, more research is needed to improve patient selection, to carry out the implant, and to find why so many fail.

In 2014, the Agency for Healthcare Research and Quality published a comparative effectiveness review focused on chronic urinary retention treatments.<sup>[14]</sup> The authors identified the previously described Cochran review as providing “low-strength evidence that neuromodulation improves the rate at which patients with Fowler’s syndrome can be catheter free after treatment,” but noted that there were few studies overall, and most were small and had other methodologic limitations.

### Randomized Controlled Trial

In the randomized clinical study submitted to the FDA as part of the approval process, 177 of 581 patients had urinary retention.<sup>[15]</sup> Patients with urinary retention reported significant improvements in terms of volume catheterized per catheterization, a decrease in the number of catheterizations per day, and increased total voided volume per day. At 12 months post-implant, 61% of patients had eliminated the use of catheterization. Patients with implants also reported improved quality of life.

### **Complications of SNM for Urinary Dysfunctions**

A large prospective series by White focused on complications associated with SNM in 202 patients with urge incontinence, urinary urgency, or urinary retention.<sup>[15]</sup> At a mean follow-up of 37 months (range, 7-84), 67 patients (30%) had experienced adverse events that required either lead or implantable pulse generator revisions. Complications included pain (3%), device malfunction secondary to trauma (9%), infection (4%), postoperative hematoma (2%), and lead migration (6%). In addition, 5% of patients underwent elective removal, 4% had device removal due to lack of efficacy, and 2% required removal due to battery expiration. At the last follow-up, 172 patients (85%) had functional implanted units.

### **Section Summary**

Data from RCTs and case series with long-term follow-up provides sufficient evidence to conclude that sacral nerve neuromodulation is effective and safe in selected patients with urge incontinence, urgency-frequency syndrome, and non-obstructive urinary retention.

## **DEFECATION DYSFUNCTION**

### **Fecal Incontinence**

#### Systematic Reviews

In 2019, Simillis published a systematic review and meta-analysis of treatments for fecal incontinence.<sup>[16]</sup> A total of 47 RCTs were included and 37 treatments were addressed. Overall, no treatment was ranked best or worst for any outcome. With respect to SNM, significant improvements compared to placebo were reported for incontinence scores.

A 2018 SR by Dulskas evaluated the literature on treatments for lower anterior resection syndrome.<sup>[17]</sup> The authors identified a total of 21 studies that met inclusion criteria, of which eight evaluated the use of SNM. Only one of the identified studies was determined not to be of

poor quality. Therefore, the authors concluded that high quality RCTs are needed to determine the efficacy of SNM.

A 2015 Cochrane review evaluated sacral nerve stimulation for fecal incontinence and constipation in adults.<sup>[18]</sup> This review included six trials assessing the effects of SNM for fecal incontinence. Two parallel group trials found that SNM reduced the number of incontinence episodes when compared with optimal medical therapy or percutaneous tibial nerve stimulation. Three of the four included crossover trials found reductions in incontinence episodes during the SNM “on” period relative to the “off” period; in the other crossover trial, participants did not experience any episodes of fecal incontinence during either period. The primary methodological quality issue noted was related to lack of clarity around randomization techniques and allocation concealment. The review authors concluded that there was limited evidence that SNM could improve continence in some patients with fecal incontinence.

In 2016, the Agency for Healthcare Research and Quality published a comparative effectiveness review on treatments for fecal incontinence.<sup>[19]</sup> There were 63 studies that met inclusion criteria for the review, and 53 surgical case series were reviewed for adverse events. There were 38 RCTs that assessed nonsurgical treatments and 12 that reviewed surgical interventions, including five studies of SNM. Regarding SNM, the authors concluded that the evidence was “insufficient because all five studies had moderate or high risk of bias, and none assessed the same treatment-outcome combination.”

In 2013, Thin published a systematic review of randomized trials and observational studies on SNM for treating fecal incontinence.<sup>[20]</sup> A total of 61 studies met eligibility criteria; including at least 10 patients, having a clear follow-up interval and reporting the success rate of therapy based on a 50% or greater improvement in fecal incontinence episodes. Only two of the studies were RCTs.<sup>[21,22]</sup> and 50 were prospective case series. Data from two studies with long-term follow-up could be pooled to calculate median success rates using an intention-to-treat analysis. These median success rates were 63% in the short term (no more than 12 months’ follow-up), 58% in the medium term (12-36 months), and 54% in the long term (>36 months). The per-protocol short-, medium-, and long-term success rates were 79%, 80%, and 84%, respectively.

A 2009 Cochrane review reported on three cross-over studies, two for fecal incontinence (n=34 and n=2, respectively) and one for constipation (n=2).<sup>[23]</sup> This very limited evidence suggested that sacral nerve stimulation can improve continence in selected patients; however, it also reported that temporary, percutaneous stimulation for a two to three week period did not always successfully identify patients most likely to benefit from the stimulation. The authors concluded that larger, good quality randomized crossover trials are needed.

In 2011, Maeda published a systematic review of studies on complications following permanent implantation of a SNM device for fecal incontinence and constipation.<sup>[24]</sup> The authors identified 94 articles. The vast majority of studies addressed fecal incontinence. A combined analysis of data from 31 studies on SNM for fecal incontinence reported a 12% suboptimal response to therapy (149 of 1,232 patients). A review of complications reported in the studies found that the most commonly reported complication was pain around the site of implantation, with a pooled rate of 13% (81/621 patients). The most common response to this complication was repositioning the stimulator, followed by explantation of the device and reprogramming. The second most common adverse event was infection, with a pooled rate of 4% (40/1025 patients). Twenty-five of the 40 infections (63%) led to explantation of the device.

In 2011, Tan published a meta-analysis of randomized trials and observational studies published between 2000 and 2008 on SNM for treating fecal incontinence.<sup>[25]</sup> They identified a total of 34 studies that reported on at least one of their outcomes of interest and clearly documented how many patients underwent temporary and permanent SNM. Only one of these studies was an RCT; this was the study by Tjandra discussed earlier.<sup>[21]</sup> In the 34 studies, a total of 944 patients underwent temporary SNM and 665 subsequently underwent permanent SNM implantation. There were 279 patients who did not receive permanent implantation, and 154 of these were lost to follow-up. Follow-up in the studies ranged from 2 weeks to 35 weeks. In a pooled analysis of findings of 28 studies, there was a statistically significant decrease in incontinence episodes per week with SNM compared to maximal conservative therapy (weighted mean difference: -6.83; 95% confidence interval [CI]:-8.05 to -5.60, p<0.001). Fourteen studies reported incontinence scores, and when these results were pooled, there was also a significantly greater improvement in scores with SNM compared to conservative therapy (weighted mean difference: -10.57, 95% CI-11.89 to -9.24, p<0.001).

A 2016 systematic review focused on the adverse events associated with SNM treatment of fecal incontinence.<sup>[26]</sup> A literature search of PubMed and Embase was performed for studies that included at least five patients with fecal incontinence treated with SNM. The researchers additionally searched the FDA's Manufacturer and User Device Experience (MAUDE) database for reports from 2005 to October 2015. There were 45 articles included in the review that described distinct patient cohorts and provided information about adverse events. These included a total of 1,953 patients and a median follow-up time of 27 months. There were two studies with a total of 201 that provided the most detailed information.<sup>[27,28]</sup> In these two studies, approximately 20% of the patients had their devices explanted by the end of follow-up and a substantial number required additional surgeries. There were five more studies that reported adverse events with less detail, and these reported a significantly lower incidence of such events. Information on infectious complications was reported in 44 studies with 1,953 patients, and the pooled rate of these was 5.1%. There were 39 studies with 1,810 patients that reported explant rates, with an average rate of 10.0%. Increases in explant rates were seen with increased follow-up duration. An overall re-operation rate of 18.6% was seen, based on data from 1,784 patients. According to the MAUDE database, there was an average of ten incidents per month related to the Interstim device in 2005. This rose to approximately 100 incidents per month within the next three years and stabilized until the year prior to FDA approval of the device as a treatment for fecal incontinence, and have since tripled. From August 1 - October 31, there were 1,684 problem reports received by the FDA, with 652 reports mentioning gastrointestinal issues as indications for SNM treatment and 278 reports specifically referring to fecal incontinence or bowel dysfunction. Most adverse events were reported within two years after device implantation.

In 2015, a systematic review was published that evaluated the impact of SNM on clinical symptoms and gastrointestinal physiology in patients with fecal incontinence.<sup>[29]</sup> There were 81 studies included in the review, and the clinical outcomes assessed included frequency of fecal incontinence episodes, fecal incontinence severity score, and treatment success rates. A meta-analysis of the data from these studies was not possible, as most lacked a comparison group. Following SNM device implantation, 'perfect' continence was reported in 13%-88% of patients. The majority of studies found a reduction in incontinence episodes per week (mean, -7.0; range, -24.8 to -2.7) and Wexner scores. The studies did not demonstrate any consistent, statistically significant effects of SNM on physiological parameters or identify any clinicophysiological factors that predicted success.

## Randomized Controlled Trials

No new RCTs for fecal incontinence were identified since the above systematic review was published.

## Nonrandomized studies

In 2017, Koh reported on outcomes following SNM at a single Scottish center.<sup>[30]</sup> Of a total of 83 patients undergoing temporary SNM testing, 52 patients were permanently implanted. There were four failures, one removal due to cancer, seven infections, one lead migration, and three reports of post-operative pain or numbness.

Irwin (2017) assessed morbidity following SNM implantation for fecal incontinence. Seventy-five patients were evaluated, 61 received insertion of a temporary SNM, and 40 received a permanent SNM.<sup>[31]</sup> Significant reduction in the Cleveland Clinic Incontinence Scores (14 pre-SNM to 9 post-SNM) and improvements in Role Physical, General Health, Vitality, Social Functioning, Role Emotional, Mental Health, and Mental Health Summary measures were reported.

A 2016 study by Rice compared the commonly used staging procedure for evaluating candidacy for implantation of SNM to an office-based evaluation.<sup>[32]</sup> In this retrospective study, a total of 86 patients were evaluated, with 45 in the office-based evaluation group and 41 in the staged group. The primary outcome was >50% improvement in Wexner score, resulting in patients progressing to permanent implantation. There was no significant difference in the primary outcome between groups or in the mean three-month Wexner score. Infection was significantly more likely in the staged group.

In 2016, Patton evaluated medium-term outcomes from SNM patients at a single institution.<sup>[33]</sup> Of the 166 patients that underwent preliminary nerve stimulation testing, 112 had a permanent device implanted, and an additional 15 patients received a device without an initial testing phase for a total of 127 patients with SNM devices. The mean follow-up was 2.7 years (range, two months – 8.5 years), and 14 patients had the device removed and four had died, leaving 109 patients. Of these, 91 (83%) responded to the follow-up survey. There were significant improvements from baseline in St Mark's continence score (from 10.3 to 14.4,  $p < 0.01$ ), bowel control score, and fecal incontinence quality of life measures. Complications from the device included 12 infections, five of which required surgery, 17 lead dislodgements, and five rotated SNM devices that required repositioning.

In 2016, Duelund published the results of a two-center prospective registry study that included 164 fecal incontinence patients treated with SNM between 2009 and 2013.<sup>[34]</sup> The median follow-up in the study was 22 months (range, 1-50 months). There were improvements in Wexner incontinence scores and VAS impact on daily life. During follow-up, additional surgeries were required in 19.5% of patients. The most common complication was repositioning of the device due to pain or migration in 12.1% of patients, and infections leading to explantation were reported for 3% of patients. The same group also evaluated the effects of bilateral versus unilateral SNM for fecal incontinence treatment, and found no significant differences between groups.<sup>[35]</sup>

A 2014, study by Altomare reported long-term outcomes (minimum of 60-month follow-up, median of 84-month follow-up) in patients implanted with a sacral nerve stimulator for fecal incontinence.<sup>[36]</sup> Patients were identified in a European registry and surveyed. Long-term

success was defined as maintaining the temporary stimulation success criteria, i.e., at least 50% improvement in the number of fecal incontinence episodes (or fecal incontinence symptom score) at last follow-up, compared with baseline. A total of 272 patients underwent permanent implantation of an SNM device and 228 were available for follow-up. A total of 194 of the 272 (71.3%) implanted patients maintained improvement in the long term.

In 2013, Hull reported outcomes in 72 patients (60% of the 120 implanted patients) who had completed a five-year follow-up visit.<sup>[27]</sup> Sixty-four (89%) of the patients who contributed bowel diary data at five years had at least a 50% improvement from baseline in weekly incontinent episodes and 26 of the 72 patients (36%) had achieved total continence. It is uncertain whether outcomes differed in the 40% of patients who were missing from the five-year analysis.

Mellgren (2011) reported on the long-term effectiveness and safety of sacral nerve stimulation for fecal incontinence in a large prospective multicenter study.<sup>[37]</sup> One hundred thirty-three patients underwent test stimulation with a 90% success rate. Mean length of follow-up was 3.1 (range, 0.2-6.1) years, with 83 patients completing all or part of the 3-year follow-up assessment. At three years follow-up, 86% of patients ( $P < .0001$ ) reported  $\geq 50\%$  reduction in the number of incontinent episodes per week compared with baseline and the number of incontinent episodes per week decreased from a mean of 9.4 at baseline to 1.7. Perfect continence was achieved in 40% of subjects. Sacral nerve stimulation had a positive impact on the quality of life. There were no reported unanticipated adverse device effects associated with sacral nerve stimulation therapy.

In 2011, Maeda in Denmark published a retrospective review of prospectively collected data from 176 patients who underwent permanent SNM for fecal incontinence.<sup>[38]</sup> A total of 245 patients had initially undergone temporary stimulation. The review focused on reportable events, defined as suboptimal outcomes (lack of or loss of efficacy) or adverse events. At the time of data collection, a median of 47 months had elapsed since implantation of InterStim ( $n=106$ ) and 21 months in patients implanted with InterStim II ( $n=70$ ). A total of 592 reportable events were identified in 150 of the 176 (85.2%) patients after a median of 11 months using the implantable devices. Overall, interventions were able to successfully resolve 63 of 212 events (30%). The five-year follow-up results from this study was published in 2014.<sup>[28]</sup> At this point, 60 of the 101 patients reported a favorable outcome and 41 reported an unfavorable outcome, with 24 of these patients having had their devices removed or permanently switched off. There were 521 reportable events recorded from 94 of the patients (93.1%)

Michelsen reported on the outcome of percutaneous nerve evaluation tests and sacral nerve stimulation for the treatment of fecal incontinence from a single center covering a period of six years.<sup>[39]</sup> A total of 177 patients with fecal incontinence underwent a percutaneous nerve evaluation test. Of these patients, 142 (80%) had a positive test, including 21 of 25 (84%) patients who required a repeat percutaneous nerve evaluation test. Because of a functional failure, 16 patients underwent a revision of the permanent electrode. Of 126 patients, 15 (12%) have undergone an explantation, with an infection rate of only 1.6%. Overall, after a median follow-up of 24 (range, 3-72) months, the median Wexner incontinence score decreased from 16 (range, 6-20) to 10 (range, 0-20) ( $P < .0001$ ).

In 2010, Wexner and others determined the safety and efficacy of sacral nerve stimulation.<sup>[40]</sup> A total of 133 patients underwent test stimulation with a 90% success rate, and 120 (110 females) of a mean age of 60.5 years and a mean duration of FI of 6.8 years received chronic

implantation. Mean follow-up was 28 (range, 2.2-69.5) months. At 12 months, 83% of subjects achieved therapeutic success (95% confidence interval: 74%-90%;  $P < 0.0001$ ), and 41% achieved 100% continence. Therapeutic success was 85% at 24 months. Incontinent episodes decreased from a mean of 9.4 per week at baseline to 1.9 at 12 months and 2.9 at two years. There were no reported unanticipated adverse device effects associated with InterStim Therapy.

Other case series have reported the experiences of patients with fecal incontinence who were treated with sacral neuromodulation. These series are not summarized in depth here because methodological limitations do not permit conclusions on the safety and effectiveness of SNM for fecal incontinence. These limitations included patients with a variety of etiologies of fecal incontinence, including obstetric injury, spinal cord injury, prior surgery, sacral malformation, or idiopathic incontinence, lack of a comparator, and a wide range of follow-up periods (e.g., two months– 9.5 years). Thus, it is difficult to determine the complication rates or the durability of any benefits initially reported.

### Section Summary

With longer term results from two randomized controlled trials, prospective case series, and a pooled analysis of data from the RCTs and observational studies, evidence is considered sufficient to conclude that sacral nerve neuromodulation/stimulation improves outcomes when used for the treatment for chronic fecal incontinence in well-selected patients who have failed conservative therapy.

## **Constipation**

### Systematic Review

A 2017 systematic review by Pilkington on behalf of the NIHR CapaCiTY working group, Pelvic floor Society assessed outcomes of sacral nerve stimulation in adults with chronic constipation.<sup>[41]</sup> They identified seven articles, reporting on 375 patients. Morbidity rates were heterogeneous and varied from 13 to 34%. Device removal rates were also heterogeneous and ranged from 8 to 23%. Harms were inconsistently reported. Treatment success was reported between 57 and 87%. Reviewers concluded that the quality of studies was poor and therefore although the results were positive in favor of sacral nerve stimulation for chronic constipation, they urged caution.

The 2015 Cochrane review of SNM for fecal incontinence and constipation, described earlier, included two studies assessing SNM as a constipation treatment.<sup>[18]</sup> One trial, which included only two participants, found that the participants experienced a greater number of bowel movements per week when the device was on. The other trial, a larger randomized trial by Dinning et al., found that SNM did not affect the frequency of bowel movements.<sup>[42]</sup> The study included patients aged 18 to 75 years with slow transit constipation. Potentially eligible patients completed a three-week stool diary and, in order to continue participating, they needed to indicate in the diary that they had complete bowel movements less than three days per week for at least two of the three weeks. Patients with metabolic, neurogenic or endocrine disorders known to cause constipation were excluded. There were 57 patients that met eligibility criteria and had temporary percutaneous nerve evaluation (PNE), and 55 underwent permanent implantation. In random order, patients received active stimulation or sham stimulation. The primary outcome measure, determined by stool diaries, was a bowel movement with feelings of complete evacuation more than two days per week for at least two of three weeks; it was

only assessed in phase 2. Compared with sham stimulation, 16 of 54 patients (29.6%) met the primary outcome during stimulation and 11 of 53 patients (20.8%) met it during sham stimulation; the difference was not statistically significant ( $p=0.23$ ). Other outcomes did not differ significantly by group. The review authors concluded that SMN did not improve constipation symptoms and there were some adverse events associated with its use.

In 2013, Thomas published a systematic review of controlled and uncontrolled studies evaluating sacral nerve stimulation for treatment of chronic constipation.<sup>[43]</sup> The authors identified 11 case series and two blinded cross-over studies. Sample sizes in the case series ranged from 4 to 68 patients implanted with a permanent SNM device; in 7 of the 11 studies, fewer than 25 patients underwent SNM implantation. Among the two cross-over studies, one included two patients implanted with an SNM device. The other, a 2012 study by Knowles and colleagues, temporary stimulation was evaluated in 14 patients.<sup>[44]</sup> Patients were included if they were diagnosed with evacuatory dysfunction and rectal hyposensitivity and had failed maximal conservative treatment. Patients were randomized to two weeks of stimulation with the SNM device turned on and two weeks with the SNM device turned off, in random order. There was no wash-out period between treatments. The primary efficacy outcome was change in rectal sensitivity and was assessed using three measures of rectal sensory thresholds. The study found a statistically significantly greater increase in rectal sensitivity with the device turned on in two of the three measures. Among the secondary outcome measures, there was a significantly greater benefit of active treatment on the percentage of successful bowel movements per week and the percentage of episodes with a sense of complete evacuation. In addition to its small sample size, the study was limited by the lack of a wash-out period between treatments i.e., there could have been a carry-over effect when the device was used first in the “on” position. Moreover, the authors noted that the patients were highly selected; only 14 of the approximately 1800 patients approached met the eligibility criteria and agreed to participate in the study.

### Randomized Controlled Trials

One RCT has been published since the 2015 Cochrane review. This double-blind crossover trial, by Zerbib, included 36 patients (34 women) with refractory constipation, defined as at least two of the following criteria: fewer than three bowel movements per week, sensation of incomplete evacuation on more than a quarter of attempts, or straining to evacuate on more than a quarter of attempts.<sup>[45]</sup> This study defined a positive response to therapy as a more than 50% improvement in symptoms and/or at least three bowel movements per week. Of the 36 patients, 20 responded to the initial peripheral nerve evaluation and had a permanent stimulator implanted. Positive responses were seen in 12 of the patients during the active stimulation period and 11 of the patients during the sham stimulation period. Adverse events noted by the researchers included device-related pain in five patients and wound infection or hematoma in three patients, leading to device removal in two patients. SNM did not have a significant effect on colonic transit time. The authors concluded that the results of the study did not support the placement of SNM devices in patients with refractory constipation. The improvements seen with sham stimulation highlight the importance of control groups for comparison in studies of this technology.

Additionally, longer-term follow-up results to the study by Dinning<sup>[42]</sup> were published in 2016.<sup>[46]</sup> There were 53 patients that entered long-term follow-up, with one patient death. Adverse events or patient dissatisfaction lead to 44 patients withdrawing from the study by the end of the second year. Because of this, only ten patients met the primary outcome measure after

one year, and only three patients met this measure after two years. There was no difference in colonic isotope retention at 72 hours at one-year follow-up.

### Nonrandomized Studies

A 2019 report by Widmann analyzed a prospective database of fecal incontinence and constipation patients treated with SNM therapy. A total of 101 patients underwent test stimulation, 79 received permanent implantation, and 57 were still receiving SNM at the end of follow-up. The five-year success rate was 88.2% (95% CI 80.1 to 97.0%) for fecal incontinence and 31.2% (95% CI, 10.2 to 95.5%) in patients with isolated constipation. Complications necessitating reinterventions were reported in 24 patients. Battery replacement was reported in 23 patients, and the median battery life was 6.2 years.

In 2017, Maeda published a prospective multicenter study.<sup>[47]</sup> Of the 62 patients who underwent test stimulation, 45 proceeded to permanent implantation and 18 were followed up through 60 months. Fourteen patients reported improved Cleveland Clinic constipation score, which was sustained at 60 months. Ten patients submitted a bowel diary. Analysis of these showed significantly increased defecations per week and reduced sensation of incomplete emptying. Device-related adverse events were reported in 61% of patients.

In 2010, Maeda published a retrospective review of 38 patients with constipation who received permanent SNM after a successful trial period.<sup>[48]</sup> The study focused on reportable events, defined as suboptimal outcomes (lack of or loss of efficacy) or adverse events. The authors did not report detailed criteria for temporary or permanent placement of an SNM device. At the time of chart review, a mean of 25.7 months had elapsed since implantation. A total of 58 reportable events were identified in 22 of the 38 (58%) patients. A median of two (range 1-9) events per patient were reported; 26 of 58 events (45%) were reported in the first six months after device implantation. The most common reportable events were lack or loss of efficacy (26 of 58 events, 45%), and pain (16 events, 28%). Twenty-eight (48%) of the events were resolved by reprogramming. Surgical interventions were required for 19 (33%) of the events, most commonly permanent electrode replacement (14 events). Three of 38 (8%) patients discontinued use of the device due to reportable events.

In 2010, Kamm published findings on a prospective study that included patients who failed conservative treatment for intractable idiopathic constipation and underwent 21 days of test stimulation.<sup>[49]</sup> Sixty-two patients who had idiopathic chronic constipation lasting at least one year and had failed medical and behavioral treatments were included. Forty-five of the 62 (73%) met criteria for permanent implantation during the three-week trial period. After a median follow-up of 28 months (range 1-55 months) after permanent implantation, 39 of 45 (87%) patients were classified as treatment successes (i.e., met same improvement criteria as were used to evaluate temporary stimulation). There was a significant increase in the frequency of bowel movements from a median of 2.3 per week at baseline to 6.6 per week at latest follow-up ( $p < 0.001$ ). The frequency of spontaneous bowel movements (i.e., without use of laxatives or other stimulation) increased from a median of 1.7 per week at baseline to 4.3 per week at last follow-up;  $p = 0.0004$ . A total of 101 adverse events were reported; 40 (40%) of these were attributed to the underlying constipation or an unrelated diagnosis. Eleven serious adverse events related to treatment were reported (the authors did not specify whether any patients experienced more than one serious event). The study has been criticized for including a large number of patients who had more than two bowel movements per week at study entry.

A prospective registry study published in 2016 evaluated the effects of SNM on antigrade continence enema use in pediatric patients with severe constipation.<sup>[50]</sup> There were 22 patients below age 21 included; 55% were male and the median age was 12 years. The median frequency of antigrade continence enema use dropped from seven per week to one per week at 12 months. The Fecal Incontinence Severity index improved after six months, while other outcomes, including laxative use, Gastrointestinal Symptom Scale, and Fecal Incontinence Quality of Life Scale did not change. Ten children received cecostomy/appendicostomy closure within two years.

Several small case series were identified that focused on patients with slow transit constipation.<sup>[51-54]</sup> While promising results were reported, these case series are inadequate to permit scientific conclusions due to methodological limitations such as lack of randomization and blinding, and lack of an adequate comparison group.

### Section Summary

Only three controlled cross-over studies are available; one study was very small and had only two patients, the second study had methodological limitations, and the third and largest study showed no statistical difference between sham and stimulation. In addition, there are several, mainly small, case series. This represents insufficient evidence to permit scientific conclusions about the efficacy and safety of sacral nerve neuromodulation/stimulation for patients with constipation.

## **Chronic Pelvic Pain**

### Systematic Review

Tirlapur assessed the effectiveness of tibial and sacral nerve stimulation in the treatment of bladder pain syndrome (BPS) and chronic pelvic pain (CPP).<sup>[55]</sup> Authors included randomized and prospective quasi-randomized controlled studies vs. sham nerve stimulation treatment or usual care of patients with CPP and BPS who underwent sacral or tibial nerve stimulation were included. Three studies with 169 patients treated with tibial nerve stimulation were included; two for CPP and one for BPS. There were improvements in pain, urinary and quality of life scores. There were no reported data for sacral nerve stimulation. Authors concluded that due to the quality of the literature, a large multi-centered clinical trial investigating the effectiveness of electrical nerve stimulation to treat BPS and CPP is recommended.

### Nonrandomized studies

Several case series have evaluated sacral neuromodulation for treating chronic pelvic pain. For example, in 2012 Martelluci reported on 27 patients with chronic pelvic pain (at least six months) who underwent testing for SNM implantation<sup>[56]</sup>. After a four-week temporary stimulation phase, 16 of 27 patients (59%) underwent implantation of an Interstim device. In the 16 implanted patients, mean pain on a visual analogue scale (VAS) was 8.1 prior to implantation and 2.1 at the 6- and 12-month follow-ups. An earlier study by Siegel reported on 10 patients and stated that 9 of the 10 experienced a decrease in pain with SNM.<sup>[57]</sup>

### Section Summary

Data from several small case series with heterogenous patients represents insufficient evidence that sacral nerve neuromodulation/stimulation is safe and effective for treating

chronic pelvic pain. RCTs are needed, with sham control groups, to assess the efficacy of neuromodulation/stimulation as a treatment of chronic pelvic pain.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN UROLOGICAL ASSOCIATION AND THE SOCIETY OF URODYNAMICS, FEMALE PELVIC MEDICINE & UROGENITAL RECONSTRUCTION

The (updated in 2019) joint American Urological Association (AUA) and The Society of Urodynamics (SUFU) guidelines for non-neurogenic OAB in adults considers SNM an option for third-line treatment in carefully selected patients who failed conservative therapies and are characterized by severe OAB symptoms or those not considered candidates for pharmacologic therapy.<sup>[58]</sup> The strength of evidence was given a Grade C defined as low quality/low certainty based on observational studies that are inconsistent, small, or have other limitations that potentially confound interpretation of the data.

### AMERICAN COLLEGE OF GASTROENTEROLOGY

The 2014 clinical guideline on the management of benign anorectal disorders, including fecal incontinence, from the American College of Gastroenterology found that "sacral nerve stimulation should be considered in [fecal incontinence] who do not respond to conservative therapy (strong recommendation, moderate quality of evidence)."<sup>[59]</sup>

## SUMMARY

There is enough research to show that sacral nerve neuromodulation/stimulation (SNM) can improve health outcomes and quality of life in some patients with urinary incontinence, non-obstructive urinary retention, or fecal incontinence. Therefore, SNM, including temporary and the potential permanent implantation, as well as revision(s) and replacement(s) after the device has been placed may be considered medically necessary for these conditions when the policy criteria are met.

Sacral nerve neuromodulation/stimulation (SNM) is considered not medically necessary for the treatment of urinary incontinence, non-obstructive urinary retention, and fecal incontinence in patients who do not meet criteria, including for individuals with urinary stress incontinence, or urge incontinence due to neurologic conditions such as multiple sclerosis, spinal cord injury, diabetes-related peripheral nerve conditions, and detrusor hyperreflexia because the procedure is not considered clinically effective or appropriate for these individuals.

There is not enough research to show that sacral nerve neuromodulation/stimulation (SNM) improves health outcomes for people with conditions other than urge incontinence, non-obstructive urinary retention, and fecal incontinence. Therefore, SNM is considered investigational for other conditions, including but not limited to chronic constipation and chronic pelvic pain.

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## CODES

**NOTE:** HCPCS code C1823 is NOT the correct code to use for reporting these services. Please refer to the codes listed below for guidance.

Codes	Number	Description
		Percutaneous implantation of neurostimulator electrode array; sacral nerve
	64581	Incision for implantation of neurostimulator electrode array; sacral nerve (transforaminal placement)
	64585	Revision or removal of peripheral neurostimulator electrode array

Codes	Number	Description
	64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling.
	64595	Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter, programming by physician or other qualified health care professional
	95972	;with complex spinal cord, or peripheral (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
HCPCS	C1767	Generator, neurostimulator (implantable), nonrechargeable
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8684	Radiofrequency transmitter (external) for use with implantable sacral root neurostimulator receiver for bowel and bladder management, replacement
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator

**Date of Origin:** February 1999

## Orthognathic Surgery

**Effective:** June 1, 2020

**Next Review:** December 2020

**Last Review:** April 2020

### IMPORTANT REMINDER

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

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

### DESCRIPTION

Orthognathic surgery involves the surgical manipulation of the facial skeleton, particularly the maxilla and mandible, to restore the proper anatomic and functional relationship in patients with dentofacial skeletal anomalies.<sup>[1]</sup>

### MEDICAL POLICY CRITERIA

#### Notes:

- This policy does not address the surgical management of sleep apnea, which is addressed in a separate medical policy (see Cross References). Also, this policy does not address temporomandibular joint (TMJ) surgical interventions, which may require pre-authorization.
- Member contracts for covered services vary. Member contracts may have specific language defining congenital and developmental anomalies. Member contract language takes precedence over medical policy. A congenital anomaly is defined as an anomaly that is present at birth (e.g., cleft palate). Developmental anomalies are conditions that develop some time after birth.

- I. Orthognathic surgery for the treatment of obstructive sleep apnea in adults may be considered **medically necessary** when the criteria in Surgery, Policy No. 166 are met.

- II. Orthognathic surgery to treat conditions other than obstructive sleep apnea may be considered **medically necessary** to correct jaw and craniofacial deformities when all of the following Criteria (A-D) are met:
- A. Significant functional impairment that is documented to be directly attributable to jaw and craniofacial deformities and to include one or more of the following:
    - 1. Chewing-induced trauma secondary to malocclusion; or
    - 2. Significantly impaired swallowing and/or choking due to inadequate mastication secondary to malocclusion; or
    - 3. Significant speech abnormalities (e.g., sibilant distortions or velopharyngeal distortion) which have not responded to speech therapy and are secondary to malocclusion; or
    - 4. Loss of masticatory or incisive function due to malocclusion or skeletal abnormality; or
    - 5. Airway restriction; and
  - B. Significant over- or underjet as documented by one of the following:
    - 1. In mandibular excess or maxillary deficiency, a reverse overjet of 3mm or greater; or
    - 2. In mandibular deficiency, an overjet of 5mm or greater; or
    - 3. Open bite of 4mm or greater; or
    - 4. Deep bite of 7mm or greater and/or palatal impingement of the mandibular teeth on the palatal tissue; or
    - 5. Less than six posterior teeth in functional opposition to other teeth secondary to a developmental or congenital growth abnormality (as opposed to a consequence of the loss of teeth); and
  - C. The functional impairment and over- or underjet are not correctable with non-surgical treatment modalities (e.g. orthodontics) and;
  - D. The following documentation is required to determine medical necessity for orthognathic surgery:
    - 1. Clinical record of history and physical performed demonstrating medical necessity of orthognathic surgery and when appropriate, any other pertinent diagnostic findings; and
    - 2. Intra-oral and extra-oral photographs; and
    - 3. Cephalometric and panoramic radiographs with either a written report or a summary of radiographic findings in the clinical record (e.g. cephalometric tracings).
- III. Reduction of the masseter muscle and bone may be considered **medically necessary** as a component of orthognathic surgery only when there is clinical documentation of the presence of masseteric hypertrophy.
- IV. Orthognathic surgery is considered **cosmetic** when Criteria are not met, including but not limited to when used for improvement of appearance.

- V. Genioplasty is considered **cosmetic** when performed in conjunction with orthognathic surgery for the sole purpose of improving appearance and/or profile.

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

## CROSS REFERENCES

1. [Administrative Guidelines to Determine Dental vs Medical Services](#), Allied Health, Policy No. 35
2. [Prefabricated Oral Appliances for Obstructive Sleep Apnea](#), Allied Health, Policy No. 36
3. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12
4. [Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome](#), Surgery, Policy No. 166
5. [Hypoglossal Nerve Stimulation](#), Surgery, Policy No. 215

## SUMMARY

Orthognathic surgery improves health outcomes including functional impairments for some people with dentofacial skeletal anomalies that are not correctable with non-surgical treatment modalities. Therefore, orthognathic surgery may be considered medically necessary when policy Criteria are met.

The reduction of the masseter muscle and bone improves health outcomes for some people with masseteric hypertrophy when performed as a component of orthognathic surgery. Therefore, reduction of the masseter muscle and bone may be considered medically necessary when policy Criteria are met.

In all other situations, it is unclear how orthognathic surgery improves health outcomes or corrects functional impairments. Therefore, orthognathic surgery is considered cosmetic when policy Criteria are not met including but not limited to for the sole purpose of improving appearance.

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## CODES

Codes	Number	Description
CPT	21085	Impression and custom preparation; oral surgical splint
	21110	Application of interdental fixation device for conditions other than fracture or dislocation, includes removal
	21120	Genioplasty; augmentation (autograft, allograft, prosthetic material)
	21121	Genioplasty; sliding osteotomy, single piece

<b>Codes</b>	<b>Number</b>	<b>Description</b>
	21122	Genioplasty; sliding osteotomies, two or more osteotomies (e.g., wedge excision or bone wedge reversal for asymmetrical chin)
	21123	Genioplasty; sliding, augmentation with interpositional bone grafts (includes obtaining autografts)
	21125	Augmentation, mandibular body or angle; prosthetic material
	21127	Augmentation, mandibular body or angle; with bone graft, onlay or interpositional (includes obtaining autograft)
	21141	Reconstruction midface, LeFort I; single piece, segment movement in any direction (e.g., for Long Face Syndrome), without bone graft
	21142	Reconstruction midface, LeFort I; two pieces, segment movement in any direction, without bone graft
	21143	Reconstruction midface, LeFort I; three or more pieces, segment movement in any direction, without bone graft
	21145	Reconstruction midface, LeFort I; single piece, segment movement in any direction, requiring bone grafts (includes obtaining autografts)
	21146	Reconstruction midface, LeFort I; two pieces, segment movement in any direction, requiring bone grafts (includes obtaining autografts) (e.g., ungrafted unilateral alveolar cleft)
	21147	Reconstruction midface, LeFort I; three or more pieces, segment movement in any direction, requiring bone grafts (includes obtaining autografts) (e.g., ungrafted bilateral alveolar cleft or multiple osteotomies)
	21150	Reconstruction midface, LeFort II; anterior intrusion (e.g., Treacher-Collins Syndrome)
	21151	Reconstruction midface, LeFort II; any direction, requiring bone grafts (includes obtaining autografts)
	21154	Reconstruction midface, LeFort III (extracranial), any type, requiring bone grafts (includes obtaining autografts); without LeFort I
	21155	Reconstruction midface, LeFort III (extracranial), any type, requiring bone grafts (includes obtaining autografts); with LeFort I
	21159	Reconstruction midface, LeFort III (extra and intracranial) with forehead advancement (e.g., mono bloc), requiring bone grafts (includes obtaining autografts); without LeFort I
	21160	Reconstruction midface, LeFort III (extra and intracranial) with forehead advancement (e.g., mono bloc), requiring bone grafts (includes obtaining autografts); with LeFort I
	21188	Reconstruction midface, osteotomies (other than LeFort type) and bone grafts (includes obtaining autografts)
	21193	Reconstruction of mandibular rami, horizontal, vertical C, or L osteotomy; without bone graft
	21194	Reconstruction of mandibular rami, horizontal, vertical C, or L osteotomy; with bone graft
	21195	Reconstruction of mandibular rami and/or body, sagittal split; without internal rigid fixation
	21196	Reconstruction of mandibular rami and/or body, sagittal split; with internal rigid fixation
	21198	Osteotomy, mandible, segmental;
	21206	Osteotomy, maxilla, segmental (e.g., Wassmund or Schuchard)
	21208	Osteoplasty, facial bones; augmentation (autograft, allograft, or prosthetic implant)
	21209	Osteoplasty, facial bones; reduction
	21210	Graft, bone; nasal, maxillary or malar areas (includes obtaining graft)
	21215	Graft, bone; mandible (includes obtaining graft)

<b>Codes</b>	<b>Number</b>	<b>Description</b>
	21230	Graft; rib cartilage, autogenous, to face, chin, nose or ear (includes obtaining graft)
	21295	Reduction of masseter muscle and bone (eg, for treatment of benign masseteric hypertrophy); extraoral approach
	21296	Reduction of masseter muscle and bone (eg, for treatment of benign masseteric hypertrophy); intraoral approach
CDT	D7940	Osteoplasty – for orthognathic deformities
	D7941	Osteotomy; mandibular rami
	D7943	Osteotomy; mandibular rami with bone graft; includes obtaining the graft
	D7944	Osteotomy; segmented of subapical – per sextant or quadrant
	D7945	Osteotomy; body of mandible
	D7946	LeFort I (maxilla – total)
	D7947	LeFort I (maxilla – segmented)
	D7948	LeFort II or LeFort III (osteoplasty of facial bones for midface hypoplasia or retrusion); without bone graft
	D7949	LeFort II or LeFort III; with bone graft
	D7950	Osseous, osteoperiosteal, or cartilage graft of the mandible or facial bones – autogenous or nonautogenous, by report
	D7995	Synthetic graft – mandible or facial bones, by report
	D7996	Implant – mandible for augmentation purposes (excluding alveolar ridge), by report

**Date of Origin:** October 2004

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

**Effective:** November 1, 2019

**Next Review:** August 2020

**Last Review:** September 2019

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Magnetic resonance (MR) guided focused ultrasound (MRgFUS) and high-intensity focused ultrasound (HIFU) concentrate high-energy ultrasound waves via probe on a single location to cause coagulative necrosis.

### **MEDICAL POLICY CRITERIA**

- I. High-intensity focused ultrasound (HIFU) may be considered be considered **medically necessary** as a local treatment for prostate cancer when all of the following (A.-D.) criteria are met:
  - A. For the treatment of radiation recurrence (see Policy Guidelines); and
  - B. The patient is a candidate for local therapy (see Policy Guidelines); and
  - C. Transrectal ultrasound guided (TRUS) biopsy positive; and
  - D. In the absence of metastatic disease.

- II. HIFU is considered **investigational** for all other indications not meeting policy criteria, above.
- III. Magnetic resonance (MR) guided focused ultrasound (MRgFUS) may be considered **medically necessary** for medicine-refractory essential tremors.
- IV. Magnetic resonance (MR) guided focused ultrasound (MRgFUS) is considered **investigational** for all indications, including but not limited to treatment of the following:
  - A. Uterine fibroids
  - B. All tumors, including but not limited to brain, breast, prostate and renal
  - C. Bone metastases for palliation of pain

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

## POLICY GUIDELINES

### CANDIDATE FOR LOCAL THERAPY

According to National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 3.2018), in the presence of radiation therapy recurrence (see below), a candidate for local therapy includes:

- Original clinical stage T1-T2, NX or N0
- Life expectancy > 10y
- PSA now < 10 ng/mL

### RADIATION RECURRENCE

NCCN guidelines for prostate cancer (version 3.2018) cite radiation therapy recurrence as either 1) a positive digital rectal exam (DRE), or 2) Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology (RTOG-ASTRO) Phoenix Consensus biochemical failure.

RTOG-ASTRO Phoenix Consensus biochemical failure is further defined as:

- 1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; and
- 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy.

Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and Physical
- Treatment plan including treatment area
- For essential tremors, clinical documentation must demonstrate medicine-refractory symptoms
- For prostate cancer treatment, clinical documentation must also demonstrate results from transrectal ultrasound guided (TRUS) biopsy

## CROSS REFERENCES

1. [Radioembolization, Transarterial Embolization \(TAE\), and Transarterial Chemoembolization \(TACE\)](#), Medicine, Policy No. 140
2. [Radiofrequency Ablation \(RFA\) of Tumors Other than Liver](#), Surgery, Policy No. 92
3. [Cryosurgical Ablation of Miscellaneous Solid Tumors](#), Surgery, Policy No. 132
4. [Microwave Tumor Ablation](#), Surgery, Policy No. 189
5. [Ablation of Primary and Metastatic Liver Tumors](#), Surgery, Policy No. 204

## BACKGROUND

Magnetic resonance (MR) guided focused ultrasound (MRgFUS) and high-intensity focused ultrasound (HIFU) are proposed as less invasive approaches than surgery for treatment of localized prostate cancer, uterine fibroids, and pain palliation of bone metastases. Broadly, these devices use an integrated imaging system to take measurements, confirm the treatment area, and monitor thermal destruction in real time.

MRgFUS is a noninvasive treatment that combines focused ultrasound and magnetic resonance imaging (MRI). The ultrasound beam penetrates through the soft tissues and, using MRI for guidance and monitoring, the beam can be focused on targeted sites. Ultrasound causes a local increase in temperature in the target tissue, resulting in coagulation necrosis while sparing the surrounding normal structures. Ultrasound waves from each sonication are focused at a focal point that has a maximum focal volume of 20 nm in diameter and 15 nm in height/length. This causes a rapid rise in temperature (to approximately 65°C-85°C), which is sufficient to achieve tissue ablation at the focal point. In addition to providing guidance, the associated MRI can provide online thermometric imaging that provides a temperature “map” to confirm the therapeutic effect of the ablation treatment and allow for real-time adjustment of the treatment parameters.

HIFU focuses high-energy ultrasound waves on a single location, which increase the local tissue temperature to over 80°C. This causes a discrete locus of coagulative necrosis of approximately 3×3×10 mm. In the treatment of prostate cancer, HIFU is a minimally invasive localized option. The surgeon uses a transrectal probe to plan, carry out, and monitor ablative treatment in a real-time sequence with a combination of ultrasound and MRI imaging.

## REGULATORY STATUS

Devices have received U.S. Food and Drug Administration (FDA) approval via the De Novo and Premarket Application (PMA) processes:

### HIFU

The Sonablate® 450 (SonaCare Medical) is the first high-intensity ultrasound system for prostate tissue ablation to receive FDA approval, and therefore underwent the *de novo*

application process, obtaining clearance in 2015. Shortly thereafter, Ablatherm Integrated Imaging® (EDAP TMS) received PMA approval.

## **MRgFUS**

MRgFUS systems may also be referred to as “high-intensity” ultrasound.

The ExAblate® 2000 System (InSightec, Inc.) was approved for two indications: “ablation of uterine fibroid tissue in pre- or peri- menopausal women with symptomatic uterine fibroids who desire a uterine sparing procedure,” and for palliation of pain associated with tumors metastatic to bone.<sup>[1]</sup>

For uterine fibroids, the FDA approval letter states that patients must have a uterine gestational size of less than 24 weeks and those patients must have completed childbearing.

In the initial safety and efficacy studies, the FDA limited MRI-guided focused ultrasound to 33% of fibroid volume with a maximum treatment time of 120 minutes. Guidelines were later modified to allow up to 50% treatment volume, 180-minute maximum treatment time, and a second treatment if within a 14-day period.

The ExAblate 2000 treatment is contraindicated for use in women who have MRI-related issues, such as metallic implants, or sensitivity to MRI contrast agents; obstructions in the treatment beam path, such as a scar, skin fold, or irregularity, bowel, pubic bone, intrauterine device, surgical slips, or any hard implants; and fibroids that are close to sensitive organs such as the bowel or bladder, or are outside the image area.

The ExAblate® 2100 System also received approval through the PMA process.<sup>[2]</sup> It includes several modifications to the previous system including enhanced sonication and a detachable cradle, and only certain cradle types can be used for palliation of pain associated with metastatic bone cancer. Approval remains limited to treatment of patients with metastatic bone cancer who failed or are not candidates for radiation therapy; or, in patient with symptomatic uterine fibroids with a uterine size of less than 24 weeks and those who have completed child bearing.

In October 2012, the FDA approved the ExAblate® System, Model 2000/2100/2100 VI for pain palliation via the PMA process.<sup>[1]</sup> For pain palliation, the intended use of the device is in adult patients with metastatic bone cancer who failed or are not candidates for radiation therapy. The device was evaluated through an expedited review process. The FDA required a post-approval study with 70 patients to evaluate the effectiveness of the system under actual clinical conditions.

For treating pain associated with bone metastases, the aim of MRgFUS treatment is to destroy nerves in the bone surface surrounding the tumor. Metastatic bone disease is one of the most common causes of cancer pain. Existing treatments include conservative measures (e.g., massage, exercise), pharmacologic agents (e.g., analgesics, bisphosphates, corticosteroids) and radiotherapy, especially conventional external beam radiotherapy (EBRT) for tumors that do not involve the nervous system.

MRgFUS is also being studied for the treatment of other tumors, including breast, prostate, renal, and for brain tumors. However, the FDA has only approved MRI-guided ultrasound ablation devices for the treatment of uterine fibroids and for the treatment of tumors metastatic to bone for the palliation of pain.

## HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU)

### Prostate Cancer

Given significant uncertainty in predicting the behavior of individual localized prostate cancers, and the substantial adverse effects associated with definitive treatments, investigators have sought a therapeutic middle ground. The latter seeks to minimize morbidity associated with radical treatment in those who may not actually require surgery while reducing tumor burden to an extent that reduces the chances for rapid progression to incurability. Locally directed therapies, also termed *focal treatment* includes several ablative methods, one of which is high-intensity focused ultrasound (HIFU). The overall goal of any focal treatment is to minimize the risk of tumor progression and preserve erectile, urinary, and rectal functions by reducing damage to the neurovascular bundles, external sphincter, bladder neck, and rectum.

As a salvage treatment, that is, for recurrent disease following initial therapy, Crouzet (2017) reported that HIFU is associated with cancer-specific (CSS) and metastasis-free survival (MFS) of at least 80% at seven years in a study of over 400 men.<sup>[3]</sup> Morbidity rate for grade III/IVa complications was 3.6%. Smaller studies with shorter-duration of follow-up are in general agreement<sup>[4-7]</sup>, however, patient selection criteria is an important predictor of treatment outcomes<sup>[8-11]</sup>. While this is still an area of investigation, there may be limited treatment for this population of men with recurrent disease. Current practice guidelines based on research recommend HIFU in the presence of radiation recurrence for carefully selected patients (e.g., no metastases, and good candidate for local therapy).<sup>[5]</sup>

As a primary treatment, evidence for HIFU is still accumulating. Data in the published literature are available for shorter follow-up times than in salvage treatment studies (e.g., two years)<sup>[4,12]</sup>. Treatment free survival rate has been reported as 89% at two years, with acceptable morbidity – a grade III complication rate of 13%. Larger, longer-term comparative studies are needed.

### Other Indications

HIFU has been investigated as a treatment for other indications, such as adenomyosis<sup>[13]</sup> and thyroid disorders,<sup>[14,15]</sup> but these are generally small, noncomparative studies.

## MAGNETIC RESONANCE (MR) GUIDED FOCUSED ULTRASOUND (MRGFUS)

### Essential Tremors

#### Systematic Reviews

A technology assessment was published by Health Quality Ontario (2018).<sup>[16]</sup> The literature search, conducted through April 2017, identified nine studies for inclusion: four single cohort studies, two retrospective chart reviews, two uncontrolled prospective studies, and an RCT. The RCT compared MRgFUS with sham treatment, the chart reviews compared MRgFUS with deep brain stimulation and radiofrequency thalamotomy. Study quality was evaluated using the GRADE system. The RCT was rated high quality, the uncontrolled comparative studies were rated very low quality, and the remaining studies were rated low quality. All studies reported tremor severity as an outcome. Pooling of results was not conducted due to heterogeneity in study designs, analyses, and outcomes across the studies. Reviewers determined that,

overall, MRgFUS decreased tremor severity and improved QOL. The high-quality RCT by Elias (2016) is discussed below.

Mohammed (2018) conducted a meta-analysis evaluating the use of MRgFUS to treat medicine-refractory essential tremors.<sup>[17]</sup> The literature search, conducted through August 2017 identified 9 studies (total n=160 patients) for inclusion, eight of which were also evaluated in the Ontario technology assessment. Pooled analyses found significant improvements in the mean percentage change in Clinical Rating Scale for Tremor scores (62.2%) and Quality of Life in Essential Tremor scores (46.5%). Complications included nausea, vomiting, and ataxia, which decreased during the 12-month follow-up.

### Randomized Controlled Trials

A single high-quality study, a double-blind, sham-controlled randomized trial by Elias (2016),<sup>[18]</sup> was identified by the two systematic reviews above. Trial selection criteria included patients with moderate or severe postural or intention tremor of the hand ( $\geq 2$  on the Clinical Rating Scale for Tremor) and refractory to at least two medical therapies. Patients were randomized to MRgFUS thalamotomy (n=56) or sham treatment (n=20). Outcomes were tremor severity, improvement, and QOL, measured at three months postprocedure. Patients in the treatment group were followed for an additional 12 months. Mean score for hand tremor improved significantly from baseline in the treatment group (47%) compared with the sham group (0.1%) at three months. Change in mean functional improvement score from baseline differed significantly in the MRgFUS group (62%) compared with the sham group (3%) at three months. Change in Quality of Life in Essential Tremor Questionnaire scores also differed significantly in the treatment group compared with the sham group, with the largest improvements experienced in the psychosocial domain. The improvements in hand tremor score, functional improvement, and QOL were maintained at 12 months in the MRgFUS group.

Chang (2018) published results from 67 patients who participated in the open-label extension of the RCT.<sup>[19]</sup> Because nine patients from the original trial received additional treatment during the two-year follow-up, they were excluded from the analysis. Improvements in tremor and disability scores were maintained at the two-year follow-up (tremor,  $19.8 \pm 4.9$  [baseline] to  $8.8 \pm 5.0$  [at two years]; disability,  $16.4 \pm 4.5$  [baseline] to  $6.5 \pm 5.0$  [at two years]).

### Nonrandomized Studies

A number of nonrandomized studies (n=11 to 15) reported results from trials implementing MRgFUS as a treatment for essential tremor and many were included in the systematic reviews discussed above.<sup>[20-23]</sup>

## **Uterine Fibroids**

There are several approaches that are currently available to treat symptomatic uterine fibroids: hysterectomy; abdominal myomectomy; laparoscopic and hysteroscopic myomectomy; hormone therapy; uterine artery embolization; and watchful waiting. Hysterectomy and various myomectomy procedures are considered the gold standard treatment. Comparisons to these procedures in well-designed prospective randomized clinical trials are needed to determine whether MRI-guided high-intensity focused ultrasound ablation (MRgFUS) results in the same or better health outcomes with respect to long-term treatment effects, recurrence rates and impact on future fertility and pregnancy. The focus of this review is therefore on randomized controlled trials.

## Systematic Reviews

A systematic review, published by Gizzo (2013) identified 38 uncontrolled studies with a total of 2,500 patients (mean age 43.67 years) who underwent MRgFUS for treatment of uterine fibroids.<sup>[24]</sup> All of the published studies included women older than age 18 years with symptomatic uterine fibroids, and most excluded patients who desired future pregnancies. The authors of the systematic review did not pool study findings, noting there was no uniform consensus regarding the parameters for evaluating treatment results and considerable variety in the inclusion criteria and follow-up periods. The review confirms the continued absence of published randomized controlled trials on MRgFUS for uterine fibroids.

A 2007 technology assessment published by the Agency for Healthcare Research and Quality (AHRQ) concluded that the strength of the evidence for MRgFUS was weak (defined as evidence from a limited number of studies of weaker design; studies with strong design either have not been done or are inconclusive).<sup>[25]</sup> The literature included one industry-sponsored prospective case series (n=109) that was ranked as poor for informing clinical decision-making.<sup>[26,27]</sup> This study was conducted to support the FDA approval application. The AHRQ report noted that while initial research demonstrated safety and preliminary efficacy, there is a need for comparative study and longer term follow-up.

The report also added the following caution, now that the device is available outside a clinical research setting:

Clinicians need to consider carefully the reality that, now that the systems are in use, care providers are using this new modality to treat fibroids more aggressively than had been allowed during the strict study protocol. The major change in how the systems are now being used is that a greater proportion of the total volume of the fibroid is treated. Therefore, no information exists at present that reflects *current* practice in terms of procedure-related risks and anticipated outcomes.

This report has now been archived by AHRQ, and there is a continued lack of publication of high-quality evidence from randomized controlled trials. Clark (2014) published a review of the evidence regarding the role of MRgFUS in the treatment of fibroids and its impact upon future fertility and reproductive outcomes.<sup>[28]</sup> The authors identified 35 reports of pregnancy after MRgFUS in the available literature; however, additional studies are needed to evaluate the impact of MRgFUS upon future fertility and reproductive outcomes.

## Randomized Controlled Trials (RCTs)

A pilot sham-controlled RCT with 20 patients was published by Jacoby (2015). The study was designed to determine the feasibility of a full scale randomized study evaluating MRgFUS for treatment of uterine fibroids.<sup>[29]</sup> The study included premenopausal women with symptomatic uterine fibroids. Women who were pregnant or had a desire for future fertility were excluded. Patients were randomized to MRgFUS with the ExAblate 2000 system (n=13) or a sham treatment in which no thermal energy was delivered (n=7). The investigators did not specify primary outcomes. The sample size of 20 was selected, not to have sufficient statistical power, but to assess the feasibility of a larger trial. All patients assigned to the MRgFUS group and six of seven in the placebo group received their allocated treatment and all treated patients completed three months of follow-up. Patients were unblinded at three months and given the sham group was given the option of active treatment.

QOL outcomes included the Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire (UFS-QOL), which has subscales including the Symptom Severity Score (SSS) and Health Related Quality of Life (HRQL) score. Other measure was the Medical Outcomes Study (MOS), which has a Mental Component Summary (MCS) and Physical Component Summary (PCS). At both the 4- and 12-week follow-ups, there were no statistically significant differences (at the  $p < 0.05$  level) between the MRgFUS and sham groups in the SSS, HRQL, PCS, or MCS. Change in uterine and fibroid volume, however, differed significantly between groups at 12 weeks. Uterine volume decreased by 17% in the MRgFUS group and by 3% in the sham group ( $p = 0.04$ ). Total fibroid volume decreased 18% in the MRgFUS group and did not change in the sham group ( $p = 0.03$ ). The authors concluded that women are willing to participate in a sham-controlled RCT of MRgFUS and that larger trials are feasible.

### Nonrandomized Studies

The “pivotal” study which led to FDA approval of the ExAblate® 2000 device was included in the AHRQ report discussed above.<sup>[26,27]</sup> Additional study outcomes have been subsequently reported from this same study, although interpretation of any such results is limited by the weak strength of the evidence from the original trial. For example, Taran (2009) failed to report on the original primary outcome measure and instead reported findings on a different quality of life measure.<sup>[30]</sup> The different measures were subject to a multiple comparison bias; a large number of statistical comparisons were done for secondary outcomes, and p-values were not adjusted for increased risk of chance statistical findings.

Another nonrandomized study compared two variations on the MRgFUS procedure.<sup>[31]</sup> Patients were either treated with the original protocol (33% of fibroid volume with a maximum treatment time of 120 minutes,  $n = 96$ ) or modified protocol (50% treatment volume, 180 minutes maximum treatment time, and a second treatment if within a 14-day period,  $n = 64$ ). Interpretation of these results was limited by 49% loss to follow-up; 55 patients (57%) from the original treatment protocol completed follow-up. Only 21 patients (33%) from the modified protocol group were evaluable at 12-month follow-up.

A prospective registry of pregnancies after MRgFUS was maintained by the manufacturer of the ExAblate device. A 2008 article reported that there were 54 known pregnancies a mean of eight months after treatment.<sup>[32]</sup> They included 8 pregnancies from clinical trials designed for women who did not desire pregnancy, 26 pregnancies after commercial treatment, and 20 pregnancies in 17 patients from an ongoing study of MRgFUS in women trying to conceive. Twenty-two of the 54 pregnancies (42%) resulted in deliveries, 11 were ongoing beyond 20 weeks at the time the article was written. There were 14 miscarriages (26%) and seven elective terminations (13%). Among the 22 live births, the mean birth weight of live births was 3.3 kg, and the vaginal delivery rate was 64%. The article provides initial information on the impact of MRgFUS for uterine fibroids on pregnancy; findings suggest that fertility may be maintained but that the number of cases is too small to draw definitive conclusions. Moreover, the study does not address the possible impact of MRgFUS treatment on the ability to become pregnant.

Other non-comparative, prospective and retrospective case series have been published; however, conclusions concerning health outcomes cannot be reached from these studies due to small study populations, high rate of loss to follow-up, and failure to control for bias which could impact treatment results.<sup>[33-40]</sup>

Although results from these trials contribute to the body of evidence on MRgFUS, interpretation of such results is limited by the lack of a comparative treatment group, the absence of which does not allow for the comparison of the relative treatment effect of MRgFUS with standard medical alternatives. In addition, there is insufficient evidence on the long-term treatment effects, recurrence rates, and impact on future fertility and pregnancy.

### Section Summary

There is insufficient evidence regarding the use of MRgFUS as a treatment of uterine fibroids compared to other established procedures. Evidence from randomized controlled trials is lacking and conclusions concerning the safety and efficacy of MRgFUS cannot be drawn from nonrandomized studies due to methodological limitations such as an inability to isolate treatment effects. Questions remain regarding the durability of MRgFUS treatment or the impact of this treatment upon future fertility.

### **Palliative Treatment of Bone Metastases**

The principal outcomes for treatment of pain are symptom relief and improved functional level. Relief of pain is a subjective outcome and can be influenced by nonspecific effects, placebo response, the natural history of the disease, and regression to the mean. Therefore, RCTs are important to control for nonspecific effects and to determine whether any treatment effect provides a significant advantage over the placebo/sham treatment or other treatments. Appropriate comparison groups depend on the condition being treated and may include placebo/sham stimulation, or medical or surgical management.

Therefore, the assessment of the safety and efficacy of MRgFUS treatment for bone metastases requires large, long-term, randomized controlled trials comparing this technique with the current standard of care for the condition being treated.

### Systematic Reviews

A systematic review by Gennaro (2019) evaluated multiple thermal ablation techniques for relief of bone pain due to metastatic disease, including MRgFUS, radiofrequency ablation, microwave ablation and cryoablation.<sup>[41]</sup> The review included 11 papers and reported a mean reduction in pain scores of 26% to 91% at four weeks and 16% to 95% at 12 weeks. The authors noted that MRgFUS was associated with a higher rate of adverse events than the other modalities.

### Randomized Controlled Trials

Hurwitz (2014) published results from a randomized trial that evaluated the safety and efficacy of MRgFUS on palliation of pain due to bone metastases.<sup>[42]</sup> The study included patients with at least three months of life expectancy who had bone metastases that were painful, despite radiotherapy treatment, or who were unsuitable for or declined radiotherapy. Patients included had to rate tumor pain on a numeric rating scale (NRS) at 4 or higher on a 10-point scale. They could have up to five painful lesions; however, only one lesion was treated and it had to cause at least 2 points greater pain on the NRS than any other lesion. In addition, targeted tumors needed to be device accessible.

Study participants were randomized in a 3:1 ratio to active (n=122) or sham (n=39) MRgFUS treatment. Ten patients in the treatment group and four in the sham group did not receive the allocated treatment. An additional 26 patients in the treatment group and 23 in the sham group

did not complete the three-month follow-up. A much larger proportion of the placebo group dropped out; 17 (49%) of 35 who were treated decided to have rescue MRgFUS treatment after lack of response to placebo. A modified intention-to-treat analysis was used that included patients who had at least one MRgFUS or placebo sonication. Missing values were imputed using the last observation carried forward method.

The primary efficacy end point, assessed at three months, was a composite outcome comprised of change in baseline in worst NRS score and morphine equivalent daily dose (MEDD) intake. Patients were considered responders if their worst NRS score decreased by at least 2 points and if their MEDD intake did not increase more than 25% from baseline to three months. NRS score and MEDD intake separately were reported as secondary outcomes.

Seventy-two (64%) of 112 patients in the MRgFUS group and 7 (20%) of 35 patients in the control group were considered responders, as previously defined. The difference between groups was statistically significant ( $p=0.01$ ), favoring active treatment. When the two measures comprising the primary end point were analyzed separately, there was a statistically significant difference between groups in change in worst NRS score and a nonsignificant difference in change from baseline in pain medication. The NRS score decreased by a mean (SD) of 3.6 (3.1) points in the MRgFUS group and by a mean of 0.7 (2.4) in the placebo group ( $p<0.01$ ). Change in MEDD was only reported in a figure. Fifty-one (46%) patients in the MRgFUS group and one (3%) in the placebo group experienced at least one adverse event (AE). Most AEs were transient, and the most common was sonication pain, experienced by 36 (32%) patients in the MRgFUS group. In 17 (15%) patients, sonication pain was severe; three patients did not complete treatment due to pain. The most clinically significant AEs that lasted more than a week were third-degree skin burns in one patient (associated with noncompliance with the treatment protocol) and fracture in two patients (one of which was outside the treatment location). Potential limitations of the trial included a nonconventional primary outcome measure and the small initial size of the sham group. Moreover, a large number of sham patients (66%) did not complete the three-month follow-up; the authors did state that this low completion rate was due to lack of response to placebo treatment. Additional randomized studies are required to isolate the treatment effect of MRgFUS upon pain and better characterize the benefit and length of symptom relief with MRgFUS in patients with bone metastases.

### Nonrandomized Studies

Examples of nonrandomized trials include four small ( $n=11$  to 31), nonrandomized prospective studies evaluating MRgFUS for the treatment of bone metastases, the majority of which are industry-sponsored.<sup>[43-46]</sup> Although none reported any treatment-related adverse effects, and all reported improvements in pain and two reported decreases in analgesic use, independent verification of treatment effects with larger groups of patients is needed. At present, results from these trials are not sufficient to reach conclusions regarding the impact of MRgFUS in palliation of pain related to bone metastases due to methodological limitations such as lack of an appropriate control group for comparison.

In addition, there have been several small case series published on the use of MRgFUS for treatment of bone metastases. However, these series did not compare the safety and efficacy of this treatment to other treatment options.

### **Other Tumors**

MRgFUS is also being studied for several other clinical applications, including the treatment of benign and malignant tumors. As with MRgFUS treatment for uterine fibroids and bone metastases, randomized controlled trials comparing this technique with the current standard of care for the condition being treated are required in order to assess the efficacy of this treatment approach.

## Breast Tumors

### *Nonrandomized Studies*

No controlled studies evaluating MRgFUS for treating breast cancer have been identified in the published literature. Evidence is limited to small case series, examples of which include six feasibility studies that describe preliminary results only.<sup>[47-52]</sup> Fibroadenoma, ductal carcinomas, adenocarcinomas, and lobular carcinomas were treated. The adverse effects profile includes a few second-degree skin burns, and protocols maintain a roughly 1 cm distance between the tumor margin and the skin or rib cage. Residual tumor in the treated area appears to be a problem, with authors recommending treatment of the entire tumor plus 1 cm of surrounding tissue, as is done in lumpectomy. No long-term outcome studies are available. As with uterine fibroids, interpretation of these results is limited by the lack of a comparative treatment group.

## Brain Cancer

### *Nonrandomized Studies*

Evidence on MRgFUS in brain cancer is similarly restricted to case series, which include a report of initial findings in three patients.<sup>[53]</sup> The authors reported that it was possible to focus an ultrasound beam into the brain transcranially, and they believe that thermal ablation without overheating the brain is possible; however, substantial technical barriers to using MRgFUS for treating brain tumors remain. Larger and longer comparative trials are needed to establish the use of MRgFUS for treating this indication.

## Prostate Cancer

### *Nonrandomized Studies*

Small (n=1 to 5) feasibility studies regarding the use of MRgFUS in patients with biopsy-proven prostate cancer have demonstrated that the procedure may be performed in this patient population.<sup>[54-56]</sup> At least one study was conducted using the ExAblate® 2100 System, which is not FDA approved for this indication. Larger and longer comparative trials are needed to establish the use of MRgFUS for treating prostate cancer.

## **PRACTICE GUIDELINE SUMMARY**

### **AMERICAN CONGRESS OF OBSTETRICS AND GYNECOLOGISTS**

A practice bulletin from American Congress of Obstetrics and Gynecologists (ACOG) considered MRgFUS as an alternative to hysterectomy as a treatment of uterine fibroids, but did not specifically recommend its use, stating:<sup>[57]</sup>

Whereas short-term studies show safety and efficacy, long-term studies are needed to discern whether the minimally invasive advantage of MRI-guided focused ultrasound

surgery will lead to durable results beyond 24 months. Protocols for treating larger leiomyoma volumes are being studied.

## **AMERICAN COLLEGE OF RADIOLOGY**

The 2017 American College of Radiology (ACR) Appropriateness Criteria guidelines regarding the treatment of uterine fibroids mention the use of MRgFUS indicating that, “(t)o date, there is little long-term information on the efficacy of [MRgFUS] technology.”<sup>[58]</sup> However, the MRgFUS approach is not recommended as treatment for fibroids.

## **AMERICAN UROLOGICAL ASSOCIATION**

In 2017, the American Urological Association (AUA) published a joint guideline (with the American Society for Radiation Oncology [ASTRO], and the Society of Urologic Oncology [SUO] regarding clinically localized prostate cancer.<sup>[59]</sup> Nearly all recommendations regarding HIFU as a treatment for prostate cancer were Expert Opinion, that is, the committee did not have sufficient evidence to grade the strength of the evidence. Additionally, the following recommendation was made:

*Clinicians should advise localized prostate cancer patients considering HIFU that tumor location may influence oncologic outcome. Limiting apical treatment to minimize morbidity increases the risk of cancer persistence. (Moderate Recommendation; Evidence Level: Grade C)*

Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data).

## **NATIONAL COMPREHENSIVE CANCER NETWORK**

The National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 4.2019) include high-intensity focused ultrasound ablation as a recommended treatment option in the presence of radiation recurrence in a manner that is consistent with the policy criteria.<sup>[5]</sup>

## **SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA**

In 2015, the Society of Obstetricians and Gynaecologists of Canada published a clinical practice guideline entitled “Management of Uterine Fibroids in Women with Otherwise Unexplained Fertility.”<sup>[60]</sup> The guideline states that there are no studies comparing MRgFUS with myomectomy or in women with fibroids who have infertility as their primary complaint, and thus additional data are needed before the treatment is offered to this patient population.

# **SUMMARY**

## **HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) ABLATION**

It appears that high-intensity focused ultrasound (HIFU) ablation may improve overall health outcomes for select men with localized recurrent prostate cancer. Clinical guidelines based on research recommend HIFU for specific patient populations. Therefore, high-intensity focused ultrasound may be considered medically necessary to treat localized prostate cancer when policy criteria are met. Due to a lack of research and clinical practice

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guidelines, HIFU is considered investigational for all other indications that do not meet the policy criteria.

## **MAGNETIC RESONANCE (MR) GUIDED FOCUSED ULTRASOUND (MRGFUS)**

### **Movement Disorders**

It appears that (MRI)-guided focused ultrasound (MRgFUS) may help those with medicine-refractory essential tremor. At least one high quality randomized study has demonstrated improvement in symptoms with MRgFUS treatment and may improve overall quality of life. Therefore, MRgFUS may be considered medically necessary for medicine-refractory essential tremors when policy criteria are met.

### **Uterine Fibroids**

The evidence for MRgFUS in individuals who have uterine fibroids includes a pilot RCT, nonrandomized comparative studies, and case series. The pilot RCT (N=20 patients) reported some health outcomes, but its primary purpose was to determine the feasibility of a larger trial. It did not find statistically significant differences in quality of life outcomes between active and sham treatment groups, but did find lower fibroid volumes after active treatment. The pivotal Food and Drug Administration trial was not randomized, the clinical significance of the primary outcome was unclear, and there were no follow-up data beyond one year. The limited nature of this evidence-base raises concerns about the reliability and validity of reported findings. In particular, the durability of any early treatment effect with MRgFUS given the potential for regrowth of treated fibroids, is not clearly understood. Therefore, treatment of uterine fibroids with MRgFUS is considered investigational.

### **Palliative Treatment of Bone Metastases**

To date, there are no published randomized controlled trials comparing magnetic resonance imaging (MRI)-guided focused ultrasound (MRgFUS) with a different treatment for pain palliation in patients with bone metastases. There is a single randomized trial comparing MRgFUS to placebo as well as some preliminary reports of safety and efficacy in small numbers of patients; however, this evidence is insufficient, and the impact of MRgFUS on health outcomes remains unknown. Therefore, treatment of pain palliation with bone metastases with MRgFUS is considered investigational.

### **Other Tumors and other Indications**

(MRI)-guided focused ultrasound (MRgFUS) is being investigated for use in several applications that are not currently approved by the FDA. There are some preliminary reports of safety and efficacy in small numbers of patients; however, this evidence is insufficient, and the impact of MRgFUS on health outcomes remains unknown. Due to the lack of evidence from well-designed randomized controlled trials, the use of MRgFUS for the treatment of any condition is considered investigational.

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## CODES

**NOTE:** There are no specific CPT codes for the use of magnetic resonance–guided high-intensity ultrasound ablation in certain cancers. In these situations an unlisted code would be used based on the anatomic location of the metastasis being treated (eg, 23929 for the clavicle) or perhaps one of the radiation oncology unlisted codes (eg, 77299 or 77499).

Codes	Number	Description
CPT	0071T	Focused ultrasound ablation of uterine leiomyomata, including MR guidance; total leiomyomata volume of less than 200 cc of tissue
	0072T	;total leiomyomata volume greater or equal to 200 cc of tissue
	0398T	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed
	23929	Unlisted procedure, shoulder
	58578	Unlisted laparoscopy procedure, uterus
	58579	Unlisted hysteroscopy procedure, uterus
HCPCS	C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (MR) guidance
	C9747	Ablation of prostate, transrectal, high intensity focused ultrasound (HIFU), including imaging guidance

**Date of Origin:** October 2004

## ***Ovarian, Internal Iliac, and Gonadal Vein Embolization, Ablation, and Sclerotherapy***

**Effective:** August 1, 2020

**Next Review:** April 2021

**Last Review:** June 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Embolization involves occlusion of blood flow through the ovarian, internal iliac, and gonadal veins with coils, foam, or a chemical sclerosant as a treatment of pelvic congestion syndrome or varicoceles.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy does not address surgical ligation of the spermatic vein(s) or uterine artery embolization.

- I. Embolization, ablation, and sclerotherapy of ovarian veins, internal iliac veins, or gonadal veins is considered **investigational** for the treatment of the following conditions:
  - A. Pelvic congestion syndrome
  - B. Varicoceles.

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

## CROSS REFERENCES

1. [Varicose Vein Treatment](#), Surgery, Policy No. 104

## BACKGROUND

Enlarged ovarian and internal iliac veins can lead to pelvic congestion syndrome in women, and enlarged gonadal and internal iliac veins can lead to a varicoceles in men. Each are discussed separately below.

### PELVIC CONGESTION SYNDROME

Pelvic congestion syndrome (PCS), also called pelvic venous incompetence, is a rare condition characterized by chronic pelvic pain. Although this condition is primarily found in women it can also be found in men. PCS is often aggravated by standing for long periods of time, and often manifests during or after pregnancy. The syndrome is thought to be associated with dilated and refluxing incompetent pelvic veins, similar to what happens in varicose veins of the legs. However, the cause of PCS is unclear. Furthermore, there are no definitive diagnostic criteria for PCS. Instead the diagnosis is generally based on a combination of symptoms, tenderness on physical exam, and documentation of pelvic vein dilation or incompetence after excluding all other causes for the nonspecific findings. Although imaging may show vein dilation or incompetence, these findings are common nonspecific findings and therefore no diagnostic.

There is no standard treatment approach for PCS, and the optimum treatment is unknown. Instead, therapy is individualized and based on symptoms. Medical therapy is generally the first line of treatment, as it is low risk and non-invasive. Other methods, such as embolization has been proposed as an alternative to surgical treatment for patients who fail medical therapy with analgesics. Embolization therapy involves the occlusion of blood flow through the ovarian and internal iliac veins with coils, glue, or chemical sclerosants. The internal iliac veins may be treated at the same time or a later date to prevent recurrence.

### VARICOCELES

A varicocele is the dilation of the pampiniform plexus of the gonadal veins. Varicocele's are present in 15 to 20% of post-pubertal males, and generally get larger over time. Most varicoceles occur in the left hemiscrotum because the left gonadal vein is one of the longest veins in the body and it enters the left renal vein at a perpendicular angle increasing pressure which can dilate the veins and cause incompetence of the valves, similar to what happens in varicose veins of the legs. Although varicoceles on the left are more common, bilateral varicoceles can occur; however, this could be caused by a possible underlying pathology warranting more investigation. Symptoms of a varicocele include dull, aching, left scrotal pain, which is often aggravated by standing for long periods of time, testicular atrophy, and decreased fertility. Although there are no clear guidelines regarding the established treatment for varicoceles, surgical ligation is the preferred first-line treatment.

## EVIDENCE SUMMARY

The primary beneficial outcomes of interest for treatments of pelvic pain in both men and woman are symptom reduction and improvement in the ability to function. These are subjective outcomes that are typically associated with a placebo effect. Therefore, data from adequately

powered, randomized controlled trials (RCTs) with sufficient long-term follow-up are required to control for the placebo effect, determine its magnitude, and to determine whether any treatment effect from provides a significant advantage over placebo or other treatment options.

## **TREATMENT FOR PELVIC CONGESTION SYNDROME**

### **Health Technology Assessments**

In 2016, Champaneria published a health technology assessment from the National Institute for Health Research that examined the diagnosis and treatment of pelvic vein incompetence and chronic pelvic pain in women.<sup>[1]</sup> Forty studies were included in the review; six association studies, ten studies involving ultrasound, two studies involving magnetic resonance venography, 21 case series, and one poor-quality randomized trial of embolization. The authors found that there were no consistent diagnostic criteria for pelvic congestion syndrome (PCS). Although the studies have showed associations between chronic pelvic pain (CPP) and pelvic vein incompetence (PVI), the prevalence of PVI ranged widely. The authors identified that transvaginal ultrasound with doppler and magnetic resonance venography are both useful screening methods; however, there is limited data on the accuracy of these methods for PCS. Finally, although the research showed embolization provides symptomatic relief in the majority of women, these studies were small case series. The authors concluded that more research is needed to determine what the diagnostic criteria for PCS are, and the efficacy of embolization as a treatment for PCS.

### **Systematic Reviews**

A 2016 systematic review by Mahmoud identified 20 case series (total N=1081 patients) who underwent vein embolization for pelvic congestion syndrome.<sup>[2]</sup> The authors did not require any particular diagnostic criteria for pelvic congestion syndrome. The length of follow-up in the studies ranged from one month to six years. Seventeen studies (n=648 patients) reported the proportion of patients who reported symptom relief. Overall, 571 (88.1%) patients reported short-term symptom relief and 77 (11.9%) reported little or no relief. Seventeen studies (n=721 patients) reported symptom relief at 12 months. A total of 88.6% had symptom improvement and 13.4% reported little or no relief. Only one study used a comparison group, but patients in it received conservative treatment because they were ineligible for vein embolization therapy, so outcomes after the two interventions cannot be compared.

A systematic review by Daniels (2016) assessed the effectiveness of sclerotherapy or embolization for the treatment of chronic pelvic pain.<sup>[3]</sup> The review included 21 case series and one poor-quality randomized trial. Due to the overall low quality and heterogeneity of the studies, a meta-analysis was not performed. However, the authors reported that approximately 75% of women who underwent embolization experienced early pain relief. Adverse events noted included, transient pain following foam embolization and a small (<2%) risk of coil migration.

In 2015 Hansrani published a systematic review that evaluated the effectiveness of trans-venous occlusion as a treatment of chronic pelvic pain.<sup>[4]</sup> Thirteen studies were included comprising 866 women. The authors noted that all 13 studies were of poor methodological quality, and most studies did not use objective outcome measures or have consistent follow-up of outcomes. Studies on embolization for treatment of PCS were rated as poor due to lack of randomization and control groups, unclear patient selection criteria, and heterogeneous outcome measures that did not permit between-study comparison or estimates of overall

treatment effects. There was one RCT included in the review, in which embolization resulted in significantly better pain reduction than hysterectomy, but the study also had significant limitations, including but not limited to, the randomization protocol was not described, and the hysterectomy patients (bilateral compared to unilateral salpingo-oophorectomy) were not blinded to their treatment allocation, small sample size limits the ability to rule out the role of chance as an explanation of study findings, and a discrepancy between reported outcomes in text and data tables. The authors recommended that more high quality studies are needed that compare embolization, with other treatments, including surgical treatments, hormonal therapy, and other noninvasive treatments.

## Randomized Controlled Trials

A randomized, prospective trial by Guirola (2018) compared the safety and efficacy of embolization with vascular plugs (VP) or fibered platinum coils (FPC) in women with pelvic congestion syndrome.<sup>[6]</sup> Patients were enrolled (N=100) and randomly assigned to each treatment group via block randomization (N=50). Diagnosis of pelvic congestion syndrome was accomplished through a symptom screening questionnaire followed by an ultrasound study. Patients with 3 or more positive symptom responses advanced to the ultrasound screening, and patients with pelvic veins >6 mm in diameter and/or venous reflux or dilated midline communicating veins were advanced to randomization. Follow-up screening occurred at 1, 3, 6, and 12 months. The primary outcome was clinical success assessed subjectively through patient responses regarding relief of symptoms and pain scores assessed with the visual analog scale. Clinical success was achieved in 89.7% of the FPC group and 90.6% of the VP group. Improvement in visual analog scale pain scores at the end of 12 months was 90.2% overall and improvement was seen in 95.9% of the FPC group and 96% of the VP group. A total of 11 (22%) complications were seen in the FPC group and 5 (10%) in the VP group. Minor adverse events included access site hematoma and ovarian vein extravasation. Device migrations were considered major complications. A major limitation in the study is the significant difference in age and pre-treatment visual analog scale pain score between groups, both of which were higher in the VP group despite randomization.

## Nonrandomized Studies

The remainder of the published literature regarding the clinical outcomes of embolization therapy consists of case series and retrospective reviews.<sup>[6-27]</sup> Collectively, conclusions concerning safety and effectiveness cannot be reached from these studies due to significant limitations in the data, including but not limited to:

- Lack of established diagnostic criteria for pelvic congestion syndrome. Without consistent criteria for patient selection it is unknown which patients are most likely to benefit, or not benefit, from treatment. Furthermore, it is unknown how results from the various case series can be applied to the overall population of patients with this condition.
- Lack of randomization and comparison groups. Failure to randomize patients to different treatment groups may introduce bias on the part of both the study participant and researchers in favor of the new technology. As noted above, for pain treatments, a comparator (preferably sham treatment) is necessary, in order to guard against this bias and to distinguish treatment from placebo effects.
- Retrospective design and failure to control for other treatments. Retrospective study designs do not allow for control of co-treatments or confounding factors that may influence results. This design may also introduce bias to interpretation of results. Control for

additional factors, such as other medical therapies, is necessary to isolate treatment response to embolization therapy.

- Failure to define relevant study endpoints. Bias may also be introduced by failure to define study endpoints and treatment success prior to commencement of the study.

## **Adverse Effects**

The following adverse effects associated with embolization of the uterine and internal iliac veins, though uncommon, have been reported in the literature.<sup>[6,14]</sup>

- Embolization of coils to the pulmonary circulation
- Embolization of coils to the renal circulation
- Accidental embolization of glue fragments
- Perforations of the ovarian vein with extravasation of contrast
- Transient cardiac arrhythmia

## **Treatment of Varicoceles**

### Systematic Reviews

In 2012 Kroese published results from a systematic review and meta-analysis that examined the effect of treatment, surgery or embolization, for varicoceles in subfertile men.<sup>[28]</sup> Ten studies were included in the review, which comprised 894 men. The authors concluded that there is evidence to suggest treatment improves a couple's chance of pregnancy; however, findings are inconclusive. Furthermore, the available evidence is of low quality and limited to men from couples with subfertility problems. Therefore further research is needed to determine the efficacy of treatment, surgery or embolization, for the treatment of varicoceles.

### Randomized-Controlled Trials

No randomized controlled trials have been published comparing embolization therapy for the treatment of varicoceles to an alternative or sham/placebo treatment. Randomized controlled trials are especially needed in situations such as this where the primary symptom is pain, a subjective outcome for which a placebo response to treatment is likely.

### Nonrandomized studies

The remainder of the published literature regarding the clinical outcomes of embolization therapy consists of case series and retrospective reviews.<sup>[29-46]</sup> Collectively, conclusions concerning safety and effectiveness cannot be reached from these studies due to significant limitations in the data.

## **PRACTICE GUIDELINE SUMMARY**

### **PELVIC CONGESTION SYNDROME**

#### **American Congress of Obstetricians and Gynecologists**

No relevant policy positions on embolization for treating pelvic congestion syndrome were identified on the American Congress of Obstetricians and Gynecologists (ACOG) website.<sup>[47]</sup>

#### **Society for Vascular Surgery (SVS) and the American Venous Forum**

The 2011 Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) guidelines for the care of patients with varicose veins and associated chronic venous diseases provided a Grade 2B recommendation in favor of coil embolization, plugs, or transcatheter sclerotherapy for treatment of PCS. A Grade 2B recommendation is defined as a weak recommendation based on medium quality evidence.<sup>[48]</sup>

## SUMMARY

There is not enough research to show that embolization, ablation, or sclerotherapy improves long term health outcomes for people with pelvic congestion syndrome or varicoceles, compared to other forms of therapy. Therefore, embolization, ablation, or sclerotherapy of ovarian veins, internal iliac veins, or gonadal veins are considered investigational for the treatment of pelvic congestion syndrome or varicoceles.

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## CODES

**NOTE:** There are no specific codes for ovarian and internal iliac vein embolization; however, the following codes may be used:

Codes	Number	Description
CPT	36012	Selective catheter placement, venous system: second order or more selective, branch (eg, left adrenal vein, petrosal sinus)
	37241	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; venous, other than hemorrhage (eg, congenital or acquired venous malformations, venous and capillary hemangiomas, varices, varicoceles)
	75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
HCPCS	None	

**Date of Origin:** October 2005

## ***Balloon Ostial Dilation for Treatment of Sinusitis***

**Effective:** January 1, 2020

**Next Review:** August 2020

**Last Review:** December 2019

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Balloon ostial dilation is proposed as a less invasive alternative to traditional endoscopic sinus surgery. In this procedure, a balloon catheter is placed in the opening of the sinus and inflated to widen the opening, allowing for better drainage of secretions.

### **MEDICAL POLICY CRITERIA**

- I. The use of a catheter-based inflatable device for the treatment of chronic sinusitis may be considered medically necessary when all of the following criteria are met:
  - A. Patient has chronic sinusitis that interferes with lifestyle and has persisted for at least 12 weeks.
  - B. Documentation of abnormal findings from diagnostic evaluation including at least one of the following:
    1. CT findings suggestive of obstruction or infection of the sinus including but not limited to air fluid levels, air bubbles, significant mucosal thickening of greater than 3 mm, pansinusitis, or diffuse opacification documented by a formal CT scan report from an independent radiologist; or
    2. Nasal endoscopy findings suggestive of significant disease

- C. Inadequate response to maximal medical therapy that included all of the following:
  1. Saline nasal irrigations or saline nasal spray; and
  2. Two or more antibiotic courses or one prolonged course of at least 21 days; and
  3. A trial of nasal steroids
- II. The use of a catheter-based inflatable device for the treatment of chronic sinusitis is considered investigational when criterion I is not met.
- III. The use of a catheter-based inflatable device for the treatment of recurrent acute rhinosinusitis may be considered medically necessary when all of the following criteria are met:
  - A. Four or more documented and treated episodes of acute rhinosinusitis over a period of 12 months
  - B. CT findings performed during the fourth episode should demonstrate obstruction or infection of the sinus including but not limited to air fluid levels, air bubbles, significant mucosal thickening of greater than 3 mm, pansinusitis, or diffuse opacification documented by a formal CT scan report from an independent radiologist.
- IV. The use of a catheter-based inflatable device for the treatment of recurrent acute rhinosinusitis is considered investigational when criterion III is not met.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and physical/chart notes
- Indication for the requested service
- If indication is chronic rhinosinusitis:
  - Documentation of chronic rhinosinusitis including length of time present and interference with lifestyle;
  - CT and/or nasal endoscopy report;
  - Failure of maximum medical therapy including saline nasal irrigations/nasal spray, two or more antibiotic courses or one minimum 21 day course, and nasal steroid trial.
- If indication is recurrent acute rhinosinusitis:
  - Documentation of four or more documented and treated episodes of acute rhinosinusitis over 12 months;
  - CT report.

## CROSS REFERENCES

1. [Implantable Sinus Devices for Postoperative Use Following Endoscopic Sinus Surgery and for Recurrent Sinonasal Polyposis](#), Surgery, Policy No. 198
2. [Balloon Dilatation of the Eustachian Tube](#), Surgery, Policy No. 206

## BACKGROUND

Balloon ostial dilation (BOD, also known as balloon sinuplasty, balloon catheter dilation, or sinus ostial dilation) for the treatment of sinusitis involves placement and inflation of a balloon catheter within an obstructed frontal, sphenoid, or maxillary sinus ostium. The balloon catheter is placed using transnasal endoscopy, or a transantral approach may be used for direct access to the maxillary sinus. Inflation of the balloon is intended to enlarge the sinus ostium by compressing mucosa and displacing local bony structures. This technique has been used as an alternative or adjunct to functional endoscopic sinus surgery (FESS) which involves surgical excision of the mucosa and bone. When performed in combination with FESS, it is sometimes referred to as a hybrid procedure.

### REGULATORY STATUS

In March 2008, the “Relieva Sinus Balloon Catheter” (Acclarent, Menlo Park, CA) device was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for use in dilating the sinus ostia and paranasal spaces in adults and maxillary sinus spaces in children. Subsequent devices developed by Acclarent have also been granted 510(k) approval. These include the Relieva Spin Sinus Dilation System®, approved in August 2011, and the Relieva Seeker Balloon Sinuplasty System®, approved in November 2012.

In June 2008, the FinESS™ Sinus Treatment (Entellus Medical, Inc, Maple Grove, MN) device was cleared for marketing by the FDA through the 510(k) process. The indication noted is to access and treat the maxillary ostia/ethmoid infundibulum in adults using a transantral approach. The bony sinus outflow tracts are remodeled by balloon displacement of adjacent bone and paranasal sinus structures. Two other balloon sinuplasty devices by Entellus Medical, Inc. also received 510(k) approval in August, 2012. These are the ENTrigue® Sinus Dilation System, and the XprESS® Multi-Sinus Dilation Tool.

In 2013, a sinus dilation system (Medtronic Xomed, Jacksonville, FL), later named the NuVent™ EM Balloon Sinus Dilation System, was cleared for marketing by the FDA through the 510(k) process for use in conjunction with a Medtronic computer-assisted surgery system when surgical navigation or image-guided surgery may be necessary to locate and move tissue, bone, or cartilaginous tissue surrounding the drainage pathways of the frontal, maxillary, or sphenoid sinuses.

Also in 2013, a sinus dilation system (ArthroCare, San Antonio, TX), later named the Ventera™ Sinus Dilation System, was cleared for marketing through the 510(k) process to access and treat the frontal recesses, sphenoid sinus ostia, and maxillary ostia/ethmoid infundibula in adults using a transnasal approach.

## EVIDENCE SUMMARY

To determine the benefits and harms of BOD as a stand-alone procedure for the treatment of sinusitis, it must be compared with standard functional endoscopic sinus surgery (FESS) which

involves excision of ostial tissues. Well-designed prospective comparative studies, preferably randomized controlled trials (RCTs), are needed to compare health outcomes between the two procedures and determine whether balloon dilation is as effective and durable as excision.

The most important clinical outcomes to compare for treatment of sinusitis are:

- Symptom relief
- Durability of any beneficial effects
- Adverse event rate and severity
- Rate and type of reoperations including repeat dilation procedures

The focus of this evidence review is on systematic reviews, randomized controlled trials, and nonrandomized comparative trials.

## ADULT PATIENTS

### Systematic Reviews

Levy (2016) reported on a systematic review and meta-analysis of studies of paranasal BOD for chronic rhinosinusitis.<sup>[1]</sup> The review included 17 studies, only three of which were RCTs. Two of the RCTs reported on differences in the change in 20-Item Sinonasal Outcome Test (SNOT-20) scores between patients treated with BOD or FESS (n = 110; standard mean difference [SMD] -0.42, 95% CI -1.39 to 0.55,  $I^2=76%$ ).<sup>[2,3]</sup> However, the reviewers found no significant differences in outcome in patients treated with BOD compared to those treated with conventional FESS (p=0.07). The reviewers did report improvements in SNOT-20 score and sinus opacification after BOD, but these conclusions were not drawn from comparative studies, but from five cohort studies.

A BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment was completed in 2012 titled “Balloon Ostial Dilation for Treatment of Chronic Rhinosinusitis”.<sup>[4]</sup> This Assessment reviewed evidence from one RCT, three non-randomized comparative studies, and nine case series. The following conclusions were made concerning the adequacy of this evidence for determining the effect of balloon sinuplasty on health outcomes:

“The evidence is insufficient to determine the effect of the technology on health outcomes. One randomized clinical trial comparing balloon sinuplasty to FESS was inadequately powered and did not evaluate differences in outcomes between the two treatments. While most nonrandomized comparative studies of balloon sinuplasty and FESS show no difference in health outcomes between the two treatments, confounding factors may bias the comparison of the two treatments. Several case series show improvement in symptoms of rhinosinusitis over baseline measures, and such improvement appears durable up to 2 years. Case series do not allow conclusions regarding the comparative efficacy of balloon sinuplasty to FESS.”

A 2011 Cochrane systematic review on balloon sinuplasty for chronic rhinosinusitis concentrated on RCTs.<sup>[5]</sup> One small RCT<sup>[6]</sup> met the inclusion criteria. Patients were randomized to a “hybrid approach” that included balloon sinuplasty of the affected frontal recess along with traditional FESS of other paranasal sinuses (n = 16), or to traditional FESS (n = 16). At 12-months follow-up, both groups reported improvements in symptoms, but there were no significant differences between the two groups. The authors of the Cochrane review rated this study as having a low risk for bias for most parameters, but a high risk for bias in

reporting of the outcomes. Specifically, symptom scores were not presented systematically and details of statistical testing were not reported. The overall conclusion of this review was that there is no convincing evidence supporting the use of balloon sinuplasty in chronic rhinosinusitis (CRS).

Batra (2011) performed a comprehensive review of the literature regarding balloon catheter technology (BCT) in rhinology.<sup>[7]</sup> The authors noted significant study design flaws in the studies, including lack of comparator group in most, lack of randomization in the single comparative study, unclear selection criteria, and use of patient-reported symptom improvement.

The authors reached the following conclusions:

“The accrued data attests to its safety, whereas the largest published observational cohort studies have demonstrated the ability to achieve ostia patency for up to 2 years. However, because the selection criteria for these studies were not clearly defined, it is unclear if this data can be extrapolated to the general population with chronic rhinosinusitis (CRS). Is BCT superior or equivalent to the existing devices employed in FESS for the management of CRS? Will the use of BCT translate into improvements in patient outcomes, overall health, and/or quality of life? The many unsettled questions “will be best answered by prospective randomized trials that directly compare FESS to BCT, or directly compare medical to surgical treatment.”

## **Randomized Controlled Trials (RCTs)**

### The REMODEL Study

The REMODEL (Randomized Evaluation of Maxillary antrostomy versus Ostial Dilation Efficacy through Long-term follow-up) study was an industry-sponsored RCT that compared BOD as a stand-alone procedure with FESS.<sup>[3]</sup> A total of 105 patients with recurrent acute sinusitis or chronic sinusitis and failure of medical therapy were randomized to BOD or FESS. BOD was performed with the Entellus device, which is labeled for a transantral approach. FESS consisted of maxillary antrostomy and uncinectomy with or without anterior ethmoidectomy. Thirteen patients withdrew consent prior to treatment, 11 in the FESS group (21%) and two in the BOD group (4%). The primary outcomes were the change in the SNOT-20 score at six-month follow-up, and the mean number of debridements performed postoperatively. Secondary outcomes included recovery time, complication rates, and rates of revision surgery. Both superiority and noninferiority analyses were performed on these outcomes.

A total of 91 patients were available at six-month follow-up. The improvement in the SNOT-20 score was  $1.67 \pm 1.10$  in the balloon dilation group and  $1.60 \pm 0.96$  in the FESS arm ( $p=0.001$  for noninferiority). Postoperative debridements were more common in the FESS group compared with balloon dilation ( $1.2 \pm 1.0$  vs.  $0.1 \pm 0.6$  in the FESS arm,  $p<0.001$  for superiority). Patients in the balloon dilation arm returned to normal daily activities earlier ( $1.6$  days vs.  $4.8$  days,  $p=0.002$  for superiority), and required fewer days of prescription pain medications ( $0.9$  days vs.  $2.8$  days,  $p=0.002$  for superiority). There were no major complications in either group, and one patient in each group required revision surgery. This study was likely to have adequate power to detect group differences; however, there were some methodologic limitations. The study was unblinded and did not have blinded outcome assessment for the symptom-based outcomes or the secondary clinical outcomes. There was

also evidence of differential dropout, with larger numbers of patients withdrawing from the FESS group following randomization (21% vs 4%).

Bikhazi (2014) reported one-year outcomes in the REMODEL study. A total of 92 patients (balloon dilation n = 50, FESS n = 42) were treated and 89 (96.7%) completed one-year follow-up.<sup>[8]</sup> Both groups showed clinically meaningful and statistically significant ( $p < 0.0001$ ) improvement in mean overall SNOT-20 scores and in all four SNOT-20 subscales. Ostial patency was 96.7 and 98.7% after balloon dilation and FESS, respectively, and each group reported significant reductions ( $p < 0.0001$ ) in rhinosinusitis episodes (mean decrease 4.2 for balloon dilation and 3.5 for FESS) during the follow-up period of one year. Overall work productivity and daily activity impairment due to chronic sinusitis were significantly improved ( $p < 0.001$ ) in both groups. There were no complications, and the revision surgery rate was 2% in each arm through one year. The authors concluded that stand-alone balloon dilation was as effective as FESS in the treatment of CRS in patients with maxillary sinus disease, with or without anterior ethmoid disease, who failed medical therapy, and met the criteria for medically necessary FESS. The study included the use of self-reported quality of life questionnaires, which are subject to recall bias.

Chandra (2015) published final results of the REMODEL study<sup>[9]</sup>, which indicated that patients in the balloon sinus dilation groups experienced significantly faster recovery (1.7 vs. 5.0 days,  $p < 0.0001$ ), less nasal bleeding (32% vs. 56%;  $p = 0.009$ ), and less need for prescription pain medication (1.0 vs. 2.8 days,  $p < 0.0001$ ). Study authors also reported results of a meta-analysis of several stand-alone balloon sinus dilation studies. The meta-analysis was based on five studies that included non-randomized studies and two studies were reportedly unpublished. Based on results of the meta-analysis, FESS and balloon dilation were not significantly different for mean SNOT-20 symptom scores and revisions rates assessed at 12 months.

### Other Randomized Controlled Trials

Bizaki (2014) reported results from an RCT that compared BOD to FESS among patients with symptomatic chronic or recurrent rhinosinusitis.<sup>[10]</sup> The trial enrolled 46 subjects, four of whom withdrew; the analysis included 42 patients (n = 21 in each group; statistical power calculations reported). Both groups demonstrated significant improvements in SNOT-22 scores from baseline to postprocedure. There were no differences in change in total SNOT-22 scores between groups at three months postprocedure. As a 2016 follow-up publication, trialists reported on nasal airway resistance and sinus symptoms between FESS- and BOD-treated groups.<sup>[11]</sup> For this analysis, 62 patients were included (32 from the FESS group, 30 from the balloon dilation group). Patients in the BOD group had significant improvements in nasal volume from pre- to postoperative measurements, but there were no significant differences between groups pre- or postoperatively in nasal volume.

Another RCT by Bizaki (2016) compared BOD to FESS, with a focus on mucociliary clearance.<sup>[12]</sup> It was conducted at the same institution as the previously reported Bizaki RCT; however, it was not specified whether it included the same patients. This trial enrolled 36 patients who were randomized to BOD (n=17) or FESS (n=19); seven patients dropped out (three in the FESS group, four in the balloon dilation group) and were not included in analyses. SNOT-22 scores improved in both groups from pre- to postoperative analyses. However, changes in total SNOT-22 scores did not differ significantly between groups. There was no significant change in mucociliary clearance before and after either treatment, nor was there a

significant between-group difference in mucociliary clearance.

Marzetti (2014) reported results of a small RCT that compared BOD with an unspecified device (or devices) with FESS in the treatment of sinus headache.<sup>[13]</sup> The study included 83 patients with sinus headache, based on the American Academy of Otolaryngology-Head and Neck Surgery criteria, 44 of whom were randomized to conventional FESS and 35 to BOD. In the balloon dilation group, 23 patients were “only frontal sinus balloon” patients, in which balloon catheters were the only tools used for frontal sinus sinusotomy, and 12 were “hybrid,” in which balloon catheters and traditional endoscopic sinus surgery were used concurrently. It was not specified how patients were selected for these groups. FESS treatment was administered on participants in both groups, but specific data was not reported by study authors. At six months of follow up, scores on the SNOT-22 improved from 28.6 at baseline to 7.8 in the FESS group and 27.3 at baseline to 5.3 in the BOD group, with a statistically significant reduction in both groups ( $p < 0.001$ ). At six months of follow up, headache scores based on the visual analog score (VAS) improved from 6.5 to 5.4 in the FESS group and from 7.1 at baseline to 1.2 in the BOD group ( $p < 0.001$ ). Study authors did not report other patient-relevant outcomes, such as the number of headache days or use of pain medications following treatment. Limitations of this study included the small number of patients who received BOD, which limits the generalizability of study results, and the lack of blinding of both patients and clinical assessors. In addition, there were various concurrent surgical procedures conducted in both treatment and control groups, which made it difficult to properly assess the treatment effects of BOD.

Another small RCT published by Achar (2012) enrolled 24 patients with chronic sinusitis who had failed medical therapy and were scheduled for surgery.<sup>[2]</sup> Patients were randomized to balloon dilation or FESS and followed for a total of 24 weeks. The primary outcome measures were changes in the SNOT-20 score and the saccharine clearance time test. Both groups improved significantly on both outcome measures. The degree of improvement was greater for the functional endoscopic dilatation sinus surgery group compared to the FESS group on both the SNOT-20 score ( $43.8 \pm 15.2$  vs.  $29.7 \pm 12.3$ ,  $p < 0.03$ ) and on the saccharine clearance score ( $7.5 \pm 5.1$  vs.  $3.5 \pm 4.3$ ,  $p = 0.03$ ). Adverse events were not reported.

A small RCT was published in 2011 that reported on physiologic outcomes.<sup>[14]</sup> Twenty patients were randomly assigned to removal of the uncinata process via FESS or balloon sinus ostial dilation as a stand-alone procedure. The main outcome measures were CO<sub>2</sub> concentration in the sinuses and maximum sinus pressure, both intended to be surrogate measures for sinus ventilation. The CO<sub>2</sub> concentration decreased in both study arms to a similar degree. The mean maxillary sinus pressure on inspiration decreased in the FESS group but did not change in the balloon sinus ostial dilation group.

Bozdemir (2011) published a small study of 10 patients with nasal polyposis, in which one side was treated with FESS and the other with balloon sinus ostial dilation.<sup>[15]</sup> All procedures were performed by the same surgeon, and polypectomy was performed prior to FESS or balloon sinus ostial dilation in all patients. Outcome measures included sinus patency, as measured by computed tomography (CT) scan (Lund-McKay classification) or repeat endoscopy (McKay grading). At 10 days following the procedure, there were improvements in both groups on measures of patency, but there were no differences between groups.

## Nonrandomized Studies

Gould (2014) assessed the one-year changes in sinonasal symptoms and health care use after office-based, multi-sinus balloon dilation in an industry-sponsored prospective,

multicenter study.<sup>[16]</sup> A total of 313 ostial dilations were attempted and 307 were successfully completed (98.1%) in 81 subjects. Seventy-six of the 81 patients completed the one-year follow-up. Mean procedure tolerance was  $2.8 \pm 2.2$  (0 = no pain, 10 = severe pain). SNOT-20 symptom improvement was observed at one and six months and sustained through one year. The RSI questionnaire that rates five major and seven minor rhinosinusitis symptoms measured a treatment effect for all major rhinosinusitis symptoms. Compared with the previous one-year period, patients reported an average of 2.3 fewer acute sinus infections ( $p < 0.0001$ ), 2.4 fewer antibiotic courses taken ( $p < 0.0001$ ), and 3.0 fewer sinus-related physician visits ( $p < 0.0001$ ) after balloon dilation. No serious device or procedure-related adverse events occurred. One subject underwent revision surgery. The authors reported that patients reported significant reductions in both sinonasal symptoms and health care use after balloon dilation. Methodological limitations included the implementation of self-reported SNOT-20 and RSI questionnaires, which may lead to recall bias; lack of a comparison group, which precludes the ability to isolate any reported treatment effects; and the uncertain timing between the preoperative CT scan and failure of medical management.

Brodner (2013) reported a prospective, multi-center study to evaluate outcomes for the XprESS device for the treatment of the frontal recesses, maxillary ostia, and/or sphenoid sinus ostia in 175 adults who had previously been scheduled for conventional FESS.<sup>[17]</sup> The criteria for previously-scheduled conventional FESS are not specified. There were a mean 2.7 sinuses per patient treated; of the targeted sinuses, 479/497 (96.4%) were successfully accessed and treated. One-year follow up was planned in the first 50 subjects, who only underwent dilation of frontal recesses and sphenoid ostia; at one year, in the 41 subjects with one-year follow-up available, 76/83 (91.6%) of the ostia dilated with the study device were patent. At one year, in 44 subjects who completed follow-up, the average overall SNOT-20 score was 0.8 (vs 1.9 at baseline;  $p < 0.0001$  for change), which was considered a clinically meaningful improvement (change  $\geq 0.8$ ).

Albritton (2012) reported results of a prospective, nonrandomized evaluation of the feasibility of in-office balloon sinus dilation with the Relieva device who were enrolled in the ORIOS trial.<sup>[18]</sup> The study included 37 subjects (59 sinuses) who had a diagnosis of chronic rhinosinusitis (>12 weeks of symptoms including but not restricted to nasal obstruction, sinus/facial pressure, nasal discharge, and congestion) that was unresponsive to maximal medical management. Successful access and dilation of all targeted sinuses occurred in 33/37 subjects (89%). Follow up was available for 32 (86.5%), 31 (83.8%), 26 (70.2%), and 21 (56.8%) at 1-, 4-, 24-, and 52-weeks post-procedure, respectively. Symptoms were assessed based on the change in SNOT-20 score from baseline to follow up, with a mean reduction from baseline of -0.98 (95% CI -1.27 to -0.70), -1.32 (95% CI -1.65 to -1.00), -1.25 (95% CI -1.65 to -0.85), and -1.42 (95% CI -1.87 to -0.90) at 1-, 4-, 24-, and 52-weeks post-procedure, respectively. For the 29 subjects who had CT scans available at baseline and 24 weeks of follow up, Lund-Mackay score improved from 6.62 preprocedure to 2.79 postprocedure ( $p < 0.0001$ ).

In the ORIOS2 study, Karanfilov (2013) reported results of a prospective, nonrandomized, multicenter evaluation of office-based balloon sinus dilation with the Relieva device in 203 patients who required FESS for medically refractory chronic sinusitis.<sup>[19]</sup> Three cohorts were enrolled, a lead-in cohort which consisted of each investigator's first cases where all targeted sinuses were successfully dilated ( $n = 36$ ), a standard enrollment cohort which consisted of up to approximately 15 cases ( $n = 84$ ), and an extended enrollment cohort which included subjects after the first 15 cases ( $n = 83$ ). Dilation technically successful in 552 of 592 attempted sinuses (93.2%). Matched baseline and twenty-four week follow up was available

for 112 patients, who demonstrated a mean improvement in SNOT-20 scores of -1.1 ( $p < 0.0001$ ). In the 110 patients with 24 week CT scans available, Lund-Mackay score improved by -4.3 compared with baseline ( $p < 0.0001$  for change).

Levine (2013) reported results of a prospective, nonrandomized, multicenter evaluation of office-based balloon sinus dilation with the FinESS device in 74 patients with chronic rhinosinusitis ( $n = 52$ ) or recurrent acute sinusitis ( $n = 17$ ).<sup>[20]</sup> Balloon dilation was successful in 69 patients, and analyses are reported per protocol. The overall technical success rate in patients was 91.9% (124 of 135 ostia) but it was not specified if this was in overall sample of 74 patients or in analysis sample of 69 patients. Mean SNOT-20 scores improved from a mean 2.3 at baseline to 1.1 at six months and 12 months in the 66 patients with follow up data available (mean change -1.2,  $p < 0.0001$ ). There were no significant differences in improvements reported between the chronic rhinosinusitis and recurrent acute sinusitis patients.

A number of additional nonrandomized studies have been identified, which do not allow conclusions concerning the impact of BSD on primary health outcomes compared with FESS. These studies have methodological limitations such as a limited number of patients,<sup>[18,21]</sup> a heterogeneous study population,<sup>[22]</sup> no primary health outcomes reported,<sup>[23]</sup> limited follow-up,<sup>[18,21,22,24]</sup> retrospective study design<sup>[24,25,26,27]</sup>, or implementation of self-reported questionnaires.<sup>[16,23,25]</sup> The exception is a single-arm study by Tomazic (2013), in which the authors planned to evaluate a cohort of 200 patients with BOD or a hybrid procedure, but ended the study early after 45 patients after a high technical failure rate was noted, with 44/68 sinuses in a planned BOD group and 29/44 sinuses in a planned hybrid procedure group failing.<sup>[28]</sup>

Retrospective studies are limited by the accuracy of the medical records reviewed or the recall ability of patients when filling out a study questionnaire. In addition, there is no randomization or blinding in a retrospective study design and therefore it is difficult to control for bias and confounders.

## **PEDIATRIC PATIENTS**

### **Nonrandomized Studies**

Wang (2015) reported on a perspective nonrandomized controlled study of 79 pediatric patients (age 7-12) with chronic sinusitis resistant to medical therapy, including 42 patients treated with sinus balloon catheter dilation balloon (SBCD) and 37 control patients treated conservatively (including oral antibiotics, local nasal steroid spray, and nasal saline irrigation).<sup>[29]</sup> At one-year posttreatment, the SN-5 scores were significantly better in the SBCD group (22 patients [52%] had marked improvement, 11 [26%] had moderate improvement, and six [14%] had mild improvement) than in the control group (five [14%], seven [19%], and four [11%], respectively) ( $p < 0.05$  for all comparisons).

In a retrospective comparative study, Thottam (2012) evaluated the incremental value of Relieva balloon catheter sinuplasty when combined with FESS in 31 children (mean age 9.3 years) who had persistent chronic sinusitis despite standard maximal medical therapy.<sup>[30]</sup> The authors performed a blinded chart review of 15 children who underwent balloon catheter sinuplasty with ethmoidectomy and 16 children who underwent FESS. Thirteen children had prior adenoidectomy. A total symptom score was constructed for the number of complaints presurgery, postsurgery, and at the final postsurgical examination (> four months) including

facial pain, sinus congestion, postnasal drip, rhinorrhea, headache, and low-grade fever. Success and improvement were defined as a decrease in the total complaint score of  $\geq 1$  point at the last visit, while total improvement was defined as total resolution of all complaints (i.e., symptom score of 0). Compared with baseline values, significant posttreatment reductions in overall sinusitis symptoms and needed interventions were observed in both treatment groups. In the Relieva balloon catheter sinuplasty group, 80% of the patients reported improvements in their overall sinus symptoms at an average of 37 weeks, versus 62.5% of the FESS patients. This difference between groups was not significant. No serious complications occurred.

In a prospective, nonrandomized controlled study, Ramadan (2010) compared the efficacy and safety of Relieva balloon sinuplasty combined with adenoidectomy (n=30) with that of adenoidectomy alone (n = 19) in 49 children (mean age 6.6 years, range 2-11) with chronic sinusitis that was refractory to medical therapy for at least six months.<sup>[31]</sup> The patients were followed at regular intervals for up to one year. Twenty-four of the 30 (80%) patients in the Relieva plus adenoidectomy group showed symptom improvement at one year compared with 10 of 19 (52.6%) children in the adenoidectomy alone group. Two (6%) patients with hypoplastic sinuses failed balloon sinuplasty and required revision FESS. One patient was lost to follow-up, and another had no improvement in SN-5 scores. Three (15%) children who did not improve after adenoidectomy had balloon sinuplasty. Overall, the mean SN-5 score for all participants decreased from a baseline value of 4.1 to 2.9 after surgery. In the Relieva plus adenoidectomy group, the mean SN-5 score decreased from 4.2 to 3.0, while in the adenoidectomy alone group, the score decreased from 3.8 to 2.9. No major complications occurred in either treatment group.

Prospective, multicenter single-arm studies have reported outcomes in pediatric patients with chronic sinusitis. In one study of 32 children, 24 had one-year follow-up data.<sup>[32]</sup> Of the 32 children enrolled, 24 were studied at one-year follow-up. Significant improvements in quality of life outcomes were reported using the SN-5 score ( $p < 0.0001$ ). Twelve (50%) children had a significant improvement of their SN-5 score, seven children (29%) had moderate improvement, two (8%) had mild improvement, one (4%) remained the same, and two children (8%) had worsening scores. A similar study with 50 participants and 157 total attempted dilations also reported significant improvement in SN-5 scores at six months ( $p < 0.0001$ ).<sup>[33]</sup> No adverse procedure-related events were reported in either study. However, these studies lacked a comparison group, limiting conclusions regarding the efficacy of the procedure.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY (AAO-HNS)

In 2015, the AAO-HNS published clinical practice guidelines for adult sinusitis, which included diagnostic criteria for chronic sinusitis but did not provide recommendations on treatment.<sup>[34]</sup> In addition, the AAO-HNS published a position statement in 2014 addressing sinus ostial dilation.<sup>[35]</sup>

## SUMMARY

There is enough research to show that balloon ostial dilation improves health outcomes for patients with sinusitis compared to functional endoscopic sinus surgery (FESS). In addition, there are clinical practice guidelines that address balloon ostial dilation for the treatment of

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sinusitis. Therefore, balloon ostial dilation as a treatment for sinusitis, either as a stand-alone procedure or in conjunction with FESS, may be considered medically necessary when policy criteria are met.

There is not enough research to show that balloon ostial dilation improves health outcomes for patients with chronic or acute sinusitis when policy criteria are not met. Therefore, balloon ostial dilation as a treatment for sinusitis, either as a stand-alone procedure or in conjunction with FESS, is considered investigational when policy criteria are not met.

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## CODES

Codes	Number	Description
CPT	31295	Nasal/sinus endoscopy, surgical, with dilation (eg, balloon dilation); maxillary sinus ostium, transnasal or via canine fossa
	31296	Nasal/sinus endoscopy, surgical, with dilation (eg, balloon dilation); frontal sinus ostium
	31297	;sphenoid sinus ostium
	31298	Nasal/sinus endoscopy, surgical; with dilation of frontal and sphenoid sinus ostia (eg, balloon dilation)
	31299	Unlisted procedure, accessory sinuses
HCPCS	C1726	Catheter, balloon dilatation, non-vascular

**Date of Origin:** August 2006

## ***Surgical Treatments for Hyperhidrosis***

**Effective:** May 1, 2020

**Next Review:** March 2021

**Last Review:** March 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

This policy addresses surgical treatments for hyperhidrosis, excessive sweating beyond a level required to maintain normal body temperature.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy only addresses the surgical treatment of hyperhidrosis.

- I. Surgical treatment of hyperhidrosis, including craniofacial hyperhidrosis, via endoscopic transthoracic sympathectomy or excision of axillary sweat glands may be considered **medically necessary** when there is clinical documentation that all of the following Criteria are met:
  - A. Primary medical conditions causing hyperhidrosis have been identified and treated where possible
  - B. The hyperhidrosis is persistent and severe, and has resulted in significant medical complications such as:
    1. Acrocyanosis of the hands
    2. Recurrent skin maceration

3. Recurrent secondary infections
  4. Persistent eczematous dermatitis despite medical treatments with topical dermatologics or systemic anticholinergics
- C. A trial of nonsurgical treatments has failed or is contraindicated.
- II. Tympanic neurectomy may be considered **medically necessary** for the treatment of severe gustatory hyperhidrosis if a trial of nonsurgical treatments failed or is contraindicated.
  - III. Surgical treatment of hyperhidrosis via endoscopic transthoracic sympathectomy, excision of axillary sweat glands, or tympanic neurectomy is considered **not medically necessary** when the Criteria in I. or II. above are not met.
  - IV. All other surgical treatments of hyperhidrosis are considered **investigational**, including but not limited to lumbar sympathectomy; axillary liposuction or curettage performed alone or in combination with any other procedure; subdermal laser-assisted axillary hyperhidrosis treatment; percutaneous radiofrequency sympathicolysis or sympathectomy; and radiofrequency ablation for palmar hyperhidrosis.

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

## 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
- Nonsurgical treatments trialed and documented response

## CROSS REFERENCES

1. [Botulinum toxin Type A injection](#), Medication Policy Manual, Drugs, Policy No. 006

## BACKGROUND

### HYPERHIDROSIS

Hyperhidrosis may be defined as excessive sweating, beyond a level required to maintain normal body temperature in response to heat exposure or exercise. Hyperhidrosis can be classified as either primary or secondary.

#### Primary Hyperhidrosis

Primary focal hyperhidrosis is defined as idiopathic bilateral, relatively symmetric, excessive sweating of at least six months' duration induced by sympathetic hyperactivity in selected areas that is not associated with an underlying disease process. The most common locations are underarms (axillary hyperhidrosis), palms (palmar hyperhidrosis), soles of the feet (plantar hyperhidrosis) or face and scalp (craniofacial hyperhidrosis). The second (T2) and third (T3)

thoracic ganglia are responsible for palmar hyperhidrosis, the fourth (T4) thoracic ganglia controls axillary hyperhidrosis, and the first (T1) thoracic ganglia controls facial hyperhidrosis.

## **Secondary Hyperhidrosis**

Secondary generalized hyperhidrosis is a type of excessive sweating that is caused by another medical condition or is a side effect of a medication. Secondary hyperhidrosis can result from a variety of drugs, [e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs)], olfactory stimuli, or underlying diseases/conditions, such as febrile diseases, diabetes mellitus, anxiety, menopause, neurologic lesions, intrathoracic neoplasms, and Raynaud's disease.

Secondary gustatory hyperhidrosis is excessive sweating related to ingesting or thinking about the ingesting food. This trigeminovascular reflex typically occurs symmetrically on scalp or face and predominately over forehead, lips and nose and can include flushing, redness, and general discomfort felt at the cheek level. This phenomenon is associated with conditions including encephalitis, syringomyelia, diabetic neuropathies, and, most commonly, conditions resulting from damage to the parotid gland (sometimes referred to as Frey's syndrome) including herpes zoster parotitis and parotid abscess. Other conditions and diseases also can cause hyperhidrosis, including those listed at [sweathelp.org](http://sweathelp.org).<sup>[1]</sup>

Frey's syndrome is an uncommon type of secondary gustatory hyperhidrosis that arises from injury to, or surgery near, the parotid gland resulting in damage to the secretory parasympathetic fibers of the facial nerve. After injury, these fibers regenerate and miscommunication occurs between them and the severed postganglionic sympathetic fibers that supply the cutaneous sweat glands and blood vessels. The aberrant connection results in gustatory sweating and facial flushing with mastication. Aberrant secondary gustatory sweating follows up to 73% of surgical sympathectomies and is particularly common after bilateral procedures.

The consequences of hyperhidrosis are primarily psychosocial in nature. Excessive sweating may be socially embarrassing or may interfere with certain professions. Symptoms such as fever, night sweats, or weight loss require further investigation to rule out secondary causes. Sweat production can be assessed with the minor starch iodine test, which is a simple qualitative measure to identify specific sites of involvement.

A variety of medical therapies have been investigated for treating primary hyperhidrosis, including topical therapy with aluminum chloride or tanning agents, oral anticholinergic medications, iontophoresis, intradermal injections of botulinum toxin, and microwave treatment. Treatment of secondary hyperhidrosis naturally focuses on treatment of the underlying cause.

## **SURGICAL TREATMENT**

This medical policy addresses only surgical treatment of hyperhidrosis. Surgical treatments for axillary hyperhidrosis include transthoracic sympathectomy and surgical excision of axillary sweat glands. Transthoracic sympathectomy may also be used for palmar hyperhidrosis. Surgical removal of axillary sweat glands has been performed in patients with severe isolated axillary hyperhidrosis. Removal may involve removal of the subcutaneous sweat glands without removal of any skin, limited excision of skin and removal of surrounding subcutaneous sweat glands, or a more radical excision of skin and subcutaneous tissue en bloc.

A variety of approaches have been reported for sympathectomy. For transthoracic sympathectomy, transthoracic endoscopic techniques have emerged as minimally invasive alternatives to transaxillary, supraclavicular, or anterior thoracic approaches. Percutaneous radiofrequency (RF) sympathicotomy has also been proposed as a sympathectomy technique in which RF lesions are made in the thoracic sympathetic chain under fluoroscopic guidance without the need for general anesthesia, intubation, or risk of lung collapse. Lumbar sympathectomy may be performed as a surgical treatment of plantar hyperhidrosis and may also be done endoscopically.

While accepted as an effective treatment, sympathectomy is not without complications. In addition to the immediate surgical complications of pneumothorax or temporary Horner's syndrome, compensatory sweating on the trunk can occur in up to 55% of patients, reducing patient satisfaction with the procedure. Gustatory sweating may also occur. Sympathectomy also results in cardiac sympathetic denervation, which in turn can lead to a 10% reduction in the heart rate. In addition to the complications associated with transthoracic sympathectomy, lumbar sympathectomy for plantar hyperhidrosis may have the additional risk of permanent sexual dysfunction in men and women. Medical researchers have investigated whether certain approaches, e.g., T3 versus T4 sympathectomy, result in less compensatory sweating, but there remains a lack of consensus about which approach best minimizes the risk of this side effect.

Tympanic neurectomy is a surgical technique that may be used for treatment of severe gustatory hyperhidrosis. The nerves are transected in the middle ear through a flap created in the ear drum. Possible risks from this surgery include rupture of the tympanic membrane, infection, hearing loss, and loss of taste in certain parts of the tongue.

## EVIDENCE SUMMARY

In order to determine whether surgical treatment of hyperhidrosis results in sustained improvements in clinically meaningful health outcomes, comparisons to conventional therapies in well-designed comparative studies (ideally randomized controlled trials) are needed using standardized functional measurement tools.

For individuals who have primary axillary or palmar hyperhidrosis, a high rate of clinical efficacy after endoscopic transthoracic sympathectomy has been demonstrated,<sup>[2-10]</sup> although the rate of postoperative compensatory sweating was substantial.<sup>[11]</sup> Surgical excision of axillary sweat glands in individuals who have primary axillary hyperhidrosis has been shown to be highly effective. The evidence is sufficient to determine that endoscopic transthoracic sympathectomy and surgical excision of axillary sweat glands results in a meaningful improvement in the net health outcome for individuals who have primary axillary or palmar hyperhidrosis. These procedures are considered standard of care for these indications when a trial of non-surgical treatment has failed.

For individuals who have severe secondary gustatory hyperhidrosis who receive tympanic neurectomy, this treatment has been shown to have high success rates, without the need for repeated interventions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome and this treatment is considered standard of care for this indication when a trial of non-surgical treatment has failed.

The focus of the following evidence summary is on systematic reviews (SRs), technology assessments (TAs), randomized controlled trials (RCT), and comparative nonrandomized studies for the investigational indications listed in the policy criteria.

## **LUMBAR SYMPATHECTOMY**

### **Systematic Review**

Lima (2017) published a SR evaluating the efficacy of lumbar sympathectomy in plantar hyperhidrosis. Among the nine studies included, eight were retrospective studies, and one was a RCT.<sup>[12]</sup> None of the eight retrospective studies were considered to be of high quality, assessed by the Newcastle Ottawa Scale. The protocol was highly variable across trials, with respect to intervention site (ranging from L2/L3 to L5) and surgical technique (seven studies used mechanical clipping or resection sympathectomy, two used chemical sympathectomy). Across all studies, the percent of patients with resolution of symptoms ranged from 5 to 98%. There was a high variation in the incidence of complications across studies, including neuralgia (range, 3% to 42.2%), compensatory sweating, (1.5% to 90%), and sexual dysfunction (not reported by all studies). There is not enough evidence of the safety or long-term clinical outcomes of lumbar sympathectomy in the treatment of plantar hyperhidrosis. Additional RCTs with standardized protocols are needed.

### **Randomized Controlled Trials**

No RCTs beyond those summarized in the SR above were identified.

### **Nonrandomized Studies**

In addition to the nonrandomized studies summarized in the SR above, there have been case series published, however, these observations are not generalizable due to lack of randomization, lack of a control group for comparison, heterogeneous patient characteristics, lack of long-term follow-up, subjective outcomes, and the use of different surgical techniques.<sup>[13-15]</sup> In addition to low success rates, concerns have been reported for side effects in sexual functioning in both males and females.

## **REMOVAL OF AXILLARY SWEAT GLANDS BY LIPOSUCTION OR CURETTAGE**

There is insufficient evidence to determine whether liposuction or curettage of sweat glands is safe or effective as a treatment of axillary hyperhidrosis. In a SR of treatments available in secondary care for the management of primary hyperhidrosis, Wade (2018) evaluated studies on curettage for axillary hyperhidrosis.<sup>[16]</sup> Nine studies were identified including four RCTs and five nonrandomized studies. All were considered to be at high risk for bias. Meta-analysis was not possible due to methodological differences. In four studies, curettage was compared to botulinum treatment and only one small RCT found a statistically significant improvement in symptoms, favoring botulinum.<sup>[17]</sup> No differences were found in sweating, quality-of-life or satisfaction outcomes, although, where reported, the incidence of adverse events was higher with curettage than with botulinum. Although this procedure has been performed for several decades, only scattered reports regarding its effectiveness were identified in a PubMed literature search.<sup>[18-23]</sup>

## **AXILLARY SUBDERMAL LASER TREATMENT**

### **Systematic Reviews and Technology Assessments**

In 2015, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a rapid response review on the clinical effectiveness of laser therapy in axillary hyperhidrosis.<sup>[24]</sup> Five publications were included in the review, three RCTs and two nonrandomized studies. No relevant evidence-based guidelines were identified for inclusion. The authors reported that although the evidence suggests laser therapy may reduce sweating in cases of axillary hyperhidrosis, these results should be interpreted with caution due to the methodological limitations of the studies, which include but are not limited to, small sample sizes, a lack of reporting on efficacy and safety outcomes, potential selection bias, and a lack of long term follow-up data.

### **Randomized Controlled Trials**

No RCTs beyond those summarized in the review above were identified.

### **Nonrandomized Studies**

No studies beyond those summarized in the review above were identified.

## **PERCUTANEOUS RADIOFREQUENCY TREATMENTS**

### **Systematic Reviews**

Hasimoto (2019) published a SR with meta-analysis of nine studies (N=378) evaluating the effectiveness of radiofrequency (RF) treatment of primary hyperhidrosis, including radiofrequency ablation (RFA) sympathectomy (N=238) and fractionated microneedle radiofrequency (FMRF) of the axillary (N=75) compared to video-assisted thoracic sympathectomy (VATS) (N=65). In seven of the nine studies, patients were subjected to RF only, and in two of nine studies RF was compared to VATS. Across the three studies evaluating FMRF, there was a reduction in the severity of hyperhidrosis (mean difference -1.24, 95% CI -1.44 to -1.03) and minor improvement in reported quality of life (QoL) (-9.0, 95% CI -9.15 to -8.85). There was improvement in QoL found after RFA (two studies, mean difference -15.92, 95% CI -17.61 to -14.24), although the one study comparing QoL improvement after RFA or VATS found that VATS showed superior results. In the one study that evaluated symptom recurrence between VATS and RF found higher recurrence rates in RF (5% vs. 25%, respectively,  $p < 0.01$ ). There were no RCTs identified for inclusion, and of the two studies comparing RFA to VATS, one was a non-randomized controlled study and the other was a retrospective observational study. The authors concluded that there is a need for high-quality prospective studies comparing RF to current standard practice, particularly VATS.

### **Randomized Controlled Trials**

No RCTs were identified.

### **Nonrandomized Studies**

No studies beyond those summarized in the SR above were identified.

## **PRACTICE GUIDELINE SUMMARY**

In 2011, an expert consensus statement on the surgical treatment of hyperhidrosis was published by a task force of the Society of Thoracic Surgeons.<sup>[25]</sup> The document stated that endoscopic thoracic sympathectomy is the treatment of choice for patients with primary

hyperhidrosis. They further recommend the following treatment strategies (with R referring to rib and the number to the specific rib):

- R3 interruption for palmar hyperhidrosis; an R4 interruption is also reasonable. The authors note a slightly higher rate of compensatory sweating with an R3, but R3 is also more effective at treating hyperhidrosis.
- R4 or R5 interruption for palmar-axillary, palmar-axillary-plantar or axillary hyperhidrosis alone; R5 interruption is also an option for axillary hyperhidrosis alone.
- R3 interruption for craniofacial hyperhidrosis without blushing; an R2 and R3 procedure is an option but may lead to a higher rate of compensatory sweating, and also increases the risk of Horner's syndrome.

## SUMMARY

There is enough evidence to determine that endoscopic transthoracic sympathectomy and surgical excision of axillary sweat glands results in a meaningful improvement in the net health outcome for individuals who have primary axillary, craniofacial, or palmar hyperhidrosis. These procedures are considered standard of care for these indications when a trial of non-surgical treatment has failed. Clinical guidelines based on research recommend surgical treatment for primary hyperhidrosis. Therefore, endoscopic transthoracic sympathectomy and surgical excision of axillary sweat glands is considered medically necessary when policy criteria are met.

For individuals who have severe secondary gustatory hyperhidrosis who receive tympanic neurectomy, this treatment has been shown to have high success rates without the need for repeated interventions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome and this treatment is considered standard of care for this indication when a trial of non-surgical treatment has failed. Therefore, tympanic neurectomy is considered medically necessary for the treatment of secondary gustatory hyperhidrosis when policy criteria are met.

There is not enough research to show surgical treatment for hyperhidrosis improves health outcomes for all other conditions and/or complications. Therefore, surgical treatment for hyperhidrosis is considered not medically necessary when policy criteria are not met.

There is not enough research to show that surgical treatments of hyperhidrosis including, but not limited to lumbar sympathectomy, axillary liposuction or curettage performed alone or in combination with any other procedure, subdermal laser-assisted axillary hyperhidrosis treatment, percutaneous radiofrequency sympathiclysis or sympathectomy and radiofrequency ablation for palmar hyperhidrosis improves health outcomes for people with hyperhidrosis. There are no evidence-based clinical practice guidelines recommending these procedures for the treatment of hyperhidrosis. Therefore, these techniques are considered investigational.

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## CODES

**NOTE:** Codes 11450 and 11451 should not be reported when there is a diagnosis of hyperhidrosis.

Codes	Number	Description
CPT	32664	Thoracoscopy, surgical; with thoracic sympathectomy
	64818	Sympathectomy, lumbar
	69676	Tympanic neurectomy
HCPCS	None	

**Date of Origin:** November 1999

## ***Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome***

**Effective:** April 1, 2020

**Next Review:** January 2021

**Last Review:** February 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

When conservative therapies for obstructive sleep apnea or upper airway resistance syndrome fail, established surgical interventions may be indicated.

### **MEDICAL POLICY CRITERIA**

**Note:** Contract language takes precedent over medical policy. Some member contracts have specific benefit limitations for orthognathic surgery.

#### **Pediatric Patients**

- I. Surgical treatment may be considered **medically necessary** for obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) in pediatric patients (age 17 years and younger) when the request is not for any of the investigational procedures listed in Criteria III. below.
- II. Surgical treatment of snoring in the absence of documented obstructive sleep apnea in pediatric patients is considered **not medically necessary**.

- III. Surgical treatment of obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) in pediatric patients is considered **investigational** including, but not limited to the following:
- A. Laser-assisted uvulopalatoplasty (LAUP) or volumetric tissue reduction
  - B. Palatal stiffening procedures, including but not limited to the following: Cautery-assisted palatal stiffening operation (CAPSO), injection of sclerosing agent (also known as snoreplasty), and implantation of palatal implants (also known as the pillar procedure)
  - C. Radiofrequency volumetric tissue reduction of the tongue base or palatal tissues
  - D. Tongue base suspension procedures, including but not limited to the AIRvance™ and the Encore™ tongue suspension systems
  - E. Uvulectomy

#### **Adult Patients**

- IV. Surgical procedures for the treatment of obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) in adult patients (age 18 years and older) may be considered **medically necessary** when all of the criteria below (A., B., C., **and** D.) are met:
- A. There is documentation of a sleep study performed within the last 3 years; and
  - B. The patient meets criteria for clinically significant obstructive sleep apnea (OSA) or upper airway resistance syndrome (UARS) as defined by Criteria 1. or 2. below:
    - 1. Clinically significant obstructive sleep apnea (OSA) defined as Criteria a. or b. below:
      - a. An AHI equal to or greater than 15 per hour; or
      - b. An AHI equal to or greater than 5 per hour with at least one of the following associated symptoms:
        - i. Excessive daytime sleepiness that is not better explained by other factors
        - ii. Documented unexplained hypertension
        - iii. Ischemic heart disease or congestive heart failure
        - iv. History of stroke
        - v. Obesity
        - vi. Diabetes and glucose intolerance
        - vii. Two or more of the following that are not better explained by other factors:
          - a.) Choking or gasping during sleep
          - b.) Recurrent awakenings during sleep
          - c.) Unrefreshing sleep with daytime fatigue
          - d.) Impaired concentration or cognition

e.) Insomnia

2. Upper airway resistance syndrome (UARS) that is clinically significant is defined as greater than 10 alpha EEG arousals per hour.

C. All of the following conservative medical therapies have failed to improve apnea/hypopnea including associated conditions such as excess daytime sleepiness:

1. Adjustment in sleep position; and

2. Avoidance of alcohol and sedative drugs; and

3. An adequate continuous positive airway pressure (CPAP) trial must include documentation of either of the following:

a. A minimum of 4 hours per night for 3 weeks of CPAP usage, to include as necessary, reasonable attempts to address any medical, mechanical, or psychological problems associated with CPAP (e.g., adjustment of pressure settings, appropriate medication and humidification, refitting of the mask, trial of alternative pressure delivery systems such as auto-adjusting positive airway pressure or bi-level positive airway pressure); or

b. For patients with severe psychological aversion to CPAP, reasonable attempts have been made to complete a conventional desensitization program. Conventional desensitization programs include progressive steps intended to help the patient adapt first to the mask or nasal pillows, then to the air pressure. There may be more than one group or individual session, and the patient may work through the steps at home. Note: For patients with severe psychological aversion to CPAP, monitoring during desensitization programs (e.g., PAP-NAP) is not necessary.

D. One or more of the following procedures are requested:

a. Hyoid myotomy and suspension

b. Mandible osteotomy with or without genioglossus advancement

c. Mandibular-maxillary advancement (MMA) with documentation of hypopharyngeal obstruction

d. Palatopharyngoplasty (e.g., uvulopalatopharyngoplasty [UPPP], uvulopharyngoplasty)

e. Partial Glossectomy

V. Surgical treatment is considered **not medically necessary** to treat obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) in adult patients when Criteria IV. are not met; or to treat snoring in the absence of documented obstructive sleep apnea in adult patients.

VI. Surgical treatments of obstructive sleep apnea (OSA) and upper airway resistance syndrome (UARS) in adult patients not listed in Criterion IV.D. are considered **investigational** including, but not limited to the following:

A. Laser-assisted uvulopalatoplasty (LAUP) or volumetric tissue reduction

B. Palatal stiffening procedures, including but not limited to cautery-assisted palatal stiffening operation (CAPSO), injection of sclerosing agent (also known as

snoreplasty), or implantation of palatal implants (also known as the pillar procedure)

- C. Radiofrequency volumetric tissue reduction of the tongue base or palatal tissues
- D. Tongue base suspension procedures, including but not limited to the AIRvance™ and the Encore™ tongue suspension systems
- E. Uvulectomy

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

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION

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

- History and Physical/Chart Notes
- Current Symptomology
- Conservative Medical Therapies failed
- CPAP Trial results
- Sleep Study results

## CROSS REFERENCES

1. [Prefabricated Oral Appliances for Obstructive Sleep Apnea](#), Allied Health, Policy No. 36
2. [Orthognathic Surgery](#), Surgery, Policy No. 137
3. [Absorbable Nasal Implant for Treatment of Nasal Valve Collapse](#), Surgery, Policy No. 209
4. [Phrenic Nerve Stimulation for Central Sleep Apnea](#), Surgery, Policy No. 212
5. [Hypoglossal Nerve Stimulation](#), Surgery, Policy No. 215

## BACKGROUND

### OBSTRUCTIVE SLEEP APNEA (OSA)

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction due to the collapse and obstruction of the upper airway during sleep. The hallmark symptom of OSA is excessive daytime sleepiness, and the typical clinical sign of OSA is snoring, which can abruptly cease and be followed by gasping associated with a brief arousal from sleep. The snoring resumes when the patient falls back to sleep, and the cycle of snoring/apnea/arousal may be repeated as frequently as every minute throughout the night.

Sleep fragmentation associated with the repeated arousal during sleep can impair daytime activity. For example, adults with OSA-associated daytime somnolence are thought to be at higher risk for accidents involving motorized vehicles (i.e., cars, trucks, heavy equipment). OSA in children may result in neurocognitive impairment and behavioral problems. In addition, OSA affects the cardiovascular and pulmonary systems. For example, apnea leads to periods of hypoxia, alveolar hypoventilation, hypercapnia, and acidosis. This, in turn, can cause systemic hypertension, cardiac arrhythmias, and cor pulmonale. Systemic hypertension is common in patients with OSA. Severe OSA is associated with decreased survival, presumably

related to severe hypoxemia, hypertension, or an increase in automobile accidents related to overwhelming sleepiness.

A polysomnogram performed in a sleep laboratory and, in adults, home sleep apnea testing with a technically adequate device (see Appendix 1), are considered the gold standard tests used to diagnose OSA in adults.<sup>[1]</sup> Objective measures of OSA are compiled using polysomnography monitors, which document the number of apneic and hypopneic events per hour and combine them into the apnea-hypopnea index (AHI). The respiratory disturbance index (RDI) may be defined as the number of apneas, hypopneas and respiratory effort-related arousals (RERAs) per hour of sleep. The final diagnosis of OSA rests on a combination of objective and subjective criteria (e.g. AHI or RDI and excessive daytime sleepiness) that seek to identify those levels of obstruction which are clinically significant. When sleep onset and offset are unknown (e.g., in home sleep studies) the AHI or RDI may be calculated based on the number of apneas, hypopneas, and/or RERAs per hour of recording time.

An increase in mortality is associated with an AHI greater than 15. More difficult to evaluate is the clinical significance of patients with mild sleep apnea. Mortality has not been shown to be increased in these patients, and frequently the most significant manifestations reported by the patient are snoring, excessive daytime sleepiness, witnessed breathing interruptions, awakenings due to gasping or choking, nocturia, morning headaches, memory loss, irritability, or hypertension.<sup>[2,3]</sup> The hallmark clinical symptom of OSA is excessive snoring, although it is important to note that snoring can occur in the absence of OSA. Isolated snoring in the absence of medical complications, while troubling to the patient's bed partner, is not considered a medical problem requiring surgical intervention.

**Table 1. Definitions of Terms for Obstructive Sleep Apnea**

Terms	Definition
Apnea	The frequency of apneas and hypopneas is measured from channels assessing oxygen desaturation, respiratory airflow, and respiratory effort. In adults, apnea is defined as a drop in airflow by $\geq 90\%$ of pre-event baseline for at least 10 seconds. Due to faster respiratory rates in children, pediatric scoring criteria define an apnea as $\geq 2$ missed breaths, regardless of its duration in seconds.
Hypopnea	Hypopnea in adults is scored when the peak airflow drops by at least 30% of pre-event baseline for at least 10 seconds in association with either at least 4% arterial oxygen desaturation or an arousal. Hypopneas in children are scored by a $\geq 50\%$ drop in nasal pressure and either a $\geq 3\%$ decrease in oxygen saturation or an associated arousal.
Apnea/Hypopnea Index (AHI)	The average number of apneas or hypopneas per hour of sleep
Obstructive sleep apnea (OSA)	Repetitive episodes of upper airway obstruction due to the collapse and obstruction of the upper airway during sleep
Mild OSA	In adults: AHI of 5 to $< 15$  In children: AHI $\geq 1.5$ is abnormal
Moderate OSA	AHI of 15 to $< 30$
Severe OSA	Adults: AHI $\geq 30$  Children: AHI of $\geq 15$
Continuous positive airway pressure (CPAP)	Positive airway pressure may be continuous (CPAP) or auto-adjusting (APAP) or Bi-level (Bi-PAP). CPAP is a more familiar abbreviation and will refer to all types of PAP devices.

Terms	Definition
CPAP Failure	Usually defined as an AHI greater than 20 events per hour while using CPAP
CPAP Intolerance	CPAP use for less than 4 h per night for 5 nights or more per week, or refusal to use CPAP. CPAP intolerance may be observed in patients with mild, moderate, or severe OSA

## UPPER AIRWAY RESISTANCE SYNDROME (UARS)

Upper airway resistance syndrome (UARS) was initially used to describe a variant of OSA which is characterized by a partial collapse of the airway resulting in increased resistance to airflow. This resistance does not result in apnea, but the increased respiratory effort required to move air into the lungs results in fragmented sleep. These sleep fragmentations (RERAs) can be measured using an electroencephalogram (EEG). Diagnosis of UARS rests on documentation of more than 10 EEG arousals per hour of sleep along with documented episodes of abnormally negative intrathoracic pressure (i.e., more negative than -10 cm) associated with the EEG arousals. The drop in intrathoracic pressure can be measured by a variety of tests including use of an esophageal manometer, if available, as part of a polysomnogram. RERAs can also be detected absent manometry during polysomnography. It has been proposed that UARS is a distinct syndrome from OSA that may be considered a disease of arousal.

See Appendix 1 for additional information on diagnostic tests for OSA and UARS.

## SURGICAL TREATMENTS FOR OSA AND UARS

Medical therapy is considered the first-line treatment for OSA and UARS. These therapies include weight loss, various continuous positive airway pressure (CPAP) devices, or orthodontic repositioning devices in appropriate patients. See Appendix 2 for a description of medical devices used in the treatment of OSA and UARS. Most guidelines consider surgical intervention only after all medical treatments for OSA or UARS have failed. Conventional surgeries for OSA include uvulopalatopharyngoplasty (UPPP) and a variety of maxillofacial surgeries such as mandibular-maxillary advancement (MMA).

### Uvulopalatopharyngoplasty (UPPP)

UPPP involves surgical modification of the oropharynx and/or velopharynx by resection of the associated structures (soft palate, uvula, and associated muscles).<sup>[4,5]</sup> The UPPP procedure enlarges the oropharynx but cannot correct obstructions in the hypopharynx. Therefore, if hypopharynx obstruction is identified, then alternate procedures are considered. In addition, patients who fail UPPP may be candidates for additional procedures, depending on the site of obstruction. Additional or alternate procedures include hyoid suspensions, maxillary and mandibular osteotomies, and mandibular and maxillary advancement surgery.

### Mandibular and maxillary advancement (MMA) surgery

Mandibular and maxillary advancement (MMA) surgery (may also be referred to as telegnathic surgery) is more extensive and is proposed for patients who do not have an adequate response to UPPP or other procedures, or who have mandibular or maxillary deficiency. These surgeries may be used to correct obstruction of the hypopharynx, oropharynx, or velopharynx; the areas of the full length of the throat.

## **Laser assisted uvuloplasty (LAUP)**

LAUP is an outpatient procedure that has been proposed as a treatment of snoring with or without associated OSA. In this procedure, the tissues of the soft palate (palatal tissues) are reshaped using a laser. The extent of the surgery is typically different than standard UPPP, since only part of the uvula and associated soft-palate tissues are reshaped. The procedure, as initially described, does not remove or alter tonsils or lateral pharyngeal wall tissues. The patient undergoes from 3 to 7 sessions at 3- to 4-week intervals. LAUP cannot be considered an equivalent procedure to the standard UPPP, with the laser simply representing a surgical tool that the physician may opt to use. LAUP is considered a unique procedure, raising unique issues of safety and effectiveness.

## **Palatal stiffening procedures**

### Radiofrequency ablation of the soft palate/volumetric reduction of the tongue base (RFTBR)

Radiofrequency energy is used to produce thermal lesions within the tissues, rather than using a laser to ablate the tissue surface, which may be painful. These procedures reduce the volume of soft tissue and stiffen the tissue due to the creation of a submucosal scar; and may also be referred to as a somnoplasty.

### Cautery assisted palatal stiffening procedure (CAPSO)

This palatal stiffening procedure uses cautery (electrically heated probes) to induce a midline palatal scar designed to stiffen the soft palate to eliminate excessive snoring.

### Other palatal stiffening procedures

Other palatal stiffening procedures in use include injection sclerotherapy (also known as injection snoreplasty) and the pillar procedure, which involves the permanent implantation of braided polyester filaments into the soft palate through a needle.

## **Suspension of the tongue base and hyoid bone**

Tongue or hyoid bone suspension is performed through a small incision under the chin. A titanium screw is inserted under the chin in the posterior aspect of the lower jaw at the floor of the mouth. For tongue suspension, a loop of suture is passed through the tongue base and attached to the mandibular bone screw. For hyoid suspension a suspension loop is placed around the hyoid bone and anchored to the mandibular bone screw. Once the suspension loop is attached to the screw it is pulled forward to advance the tongue base out of the airway, making it less likely for the base of the tongue to drop backward during sleep.

## **Uvulectomy**

This procedure surgically removes the uvula, the small tissue hanging from the soft palate at the back of the throat above the tongue. The uvula, which helps stiffen and shape the back of the throat and prevents food from going down the airway, is believed to be associated with excessive snoring.

## **Partial Glossectomy**

This procedure, also referred to as midline glossectomy, surgically removes a portion of the tongue in an effort to reduce tongue volume and open the oropharynx and/or hypopharynx.

## REGULATORY STATUS

The Somnoplasty® device has been cleared for marketing by FDA for RFA of palatal tissues for simple snoring and for the base of the tongue for OSA. FDA product code: GEI.

AIRvance® (Medtronic; formerly the Repose™ Bone Screw System from Influence) was cleared for marketing through the FDA 510(k) process in 1999 with intended use for anterior tongue base suspension by fixation of the soft tissue of the tongue base to the mandible bone using a bone screw with prethreaded suture. It is indicated for the treatment of OSA and/or snoring.

The Encore™ Tongue Suspension System (Siesta Medical) received clearance for marketing by FDA in 2011, citing the PRELUDE III Tongue Suspension System (Siesta Medical) as a predicate device.

The Pillar® Palatal Implant System (originally Restore Medical, St. Paul, MN, acquired by Medtronic, Minneapolis, MN) is an implantable device that has been cleared for marketing through the FDA 510(k) process. The labeled indication of the device is as follows: “The Pillar™ Palatal Implant System is intended for the reduction of the incidence of airway obstructions in patients suffering from mild to moderate OSA (obstructive sleep apnea).” FDA product code: LRK.

## EVIDENCE SUMMARY

Continuous positive airway pressure (CPAP) is the most widely accepted medical therapy for treatment of obstructive sleep apnea (OSA) and improvement of primary health outcomes such as cardiovascular disease, type 2 diabetes, and overall mortality associated with OSA.<sup>[5]</sup> Surgical interventions are being proposed as a second line treatment for, patients who have failed CPAP.

Large well-designed, long-term randomized controlled trials (RCTs) are needed to determine the safety and effectiveness of various surgical interventions for treatment of OSA.

The evidence suggests conventional uvulopalatopharyngoplasty (UPPP), hyoid suspension, mandible osteotomy, partial glossectomy, and maxillofacial surgeries such as mandibular-maxillary advancement (MMA), may improve health outcomes for some patients with OSA who have failed medical therapies for OSA.

- The available evidence does not currently support the widespread use of surgical interventions in the management of unselected patients with obstructive sleep apnea. Given the proven efficacy of CPAP in patients with moderate and severe symptoms and significant sleep disordered breathing, surgery cannot be recommended as a first line therapy, ahead of positive airways pressure systems.<sup>[5,6]</sup>
- While studies on UPPP and hyoid suspension procedures were not randomized, data from ten studies which included more than 750 patients consistently reported improved outcomes for patients with OSA as measured by postoperative polysomnographic assessment of sleep disturbance and compared with concurrent groups being treated with CPAP.<sup>[7]</sup>

- UPPP, hyoid suspension, mandible osteotomy, partial glossectomy and MMA procedures are widely practiced among surgeons in the United States. These procedures have been considered a standard of care in the medical community.<sup>[7]</sup>

Evidence is uncertain for use of any other surgical interventions in the treatment of OSA, including but not limited to uvulectomy, tongue base reduction and minimally invasive surgical procedures such as laser-assisted uvuloplasty (LAUP), radiofrequency tongue base reduction (RFTBR), pillar stiffening procedures, and pillar implants. Therefore, the following evidence review will be focused on the investigational indications in this policy.

## **SURGICAL TREATMENTS FOR OSA**

### **Technology Assessments and Systematic Reviews**

A 2011 Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review entitled “Diagnosis and Treatment of Obstructive Sleep Apnea in Adults” included studies conducted only in adults, defined as over 16 years of age. The authors concluded with this statement: “Overall, the strength of evidence is insufficient to evaluate the relative efficacy of surgical interventions for the treatment of OSA.”<sup>[5]</sup> The review cited the lack of head-to-head comparisons between CPAP and proposed surgical modalities, and the lack of study of any long-term health outcomes associated with OSA treatment.

Earlier evidence-based systematic reviews on the use of surgical therapies in OSA cited the lack of well-designed randomized controlled trials (RCTs) assessing different surgical techniques with inactive and active control treatments.<sup>[6,8]</sup> These reviews were not able to make the highest level recommendation supporting the use of any one surgical intervention. Limitations of studies include heterogeneous patient populations with mixed OSA severity, as measured by AHI; and lack of long-term followup. These reviews state that long-term follow-up of patients who undergo surgical correction of upper airway obstruction would help to determine whether surgery is curative, or whether the signs and symptoms of sleep apnea return, prompting patients to seek further treatment.

The 2009 systematic review by Franklin evaluated benefits and adverse effects of surgery for snoring and OSA.<sup>[9]</sup> The authors found only a small number of randomized controlled trials (RCTs) that assessed surgical procedures for snoring or sleep apnea. Key findings are as follows:

- Results from 45 studies reporting adverse events revealed persistent side effects after uvulopalatoplasty (UPP) and uvulopalatopharyngoplasty (UPPP) in about half the patients. Difficulty swallowing, globus sensation, and voice changes were especially common. The authors concluded that additional research with RCTs of surgery other than UPP and UPPP is needed, as these surgical procedures are related to a high risk of adverse effects, especially difficulty swallowing.
- Four RCTs, rated as high quality, were identified for laser-assisted palatoplasty (LAUP) and radiofrequency ablation (RFA).<sup>[10-13]</sup> Study results were mixed and inconclusive for Apnea/Hypopnea Index (AHI), and showed no benefit on daytime sleepiness or quality of life. Interpretation of this result is limited by the inclusion of studies with one-stage procedures and subjects whose main symptom was disruptive snoring.<sup>[12]</sup> The relevant trials are described in greater detail next.

## **RADIOFREQUENCY VOLUMETRIC TISSUE REDUCTION OF THE TONGUE BASE OR PALATAL TISSUES**

### **Systematic Reviews**

Baba (2015) performed a systematic review and meta-analysis that addressed the efficacy of temperature controlled radiofrequency tissue ablation (TCRFTA) to alleviate symptoms of OSA.<sup>[14]</sup> The analyses included three small nonrandomized comparative trials comparing TCRFTA with three different nonsurgical or surgical interventions and seven prospective case series (of which all but one were small). TCRFTA was categorized based on location: base of tongue, soft palate and multilevel. Analysis showed significant reductions in respiratory disturbance index (RDI), Epworth Sleep Scale (ESS), lowest oxygen saturation (LSAT), and snoring for procedures performed at the base of the tongue. TCRFTA at the soft palate showed limited efficacy, although there was a paucity of studies in this area. Multilevel TCRFTA did show a significant reduction in RDI, in the short term. Analysis of AHI was not completed as this outcome was not consistently reported within the studies. The authors reported that the studies were generally of low quality and there was significant heterogeneity which did not allow for strong conclusions. Studies with longer-term outcomes would be useful in evaluating the benefits of this procedure.

In 2008, Farrar published a meta-analysis of RFA for the treatment of OSA in patients with a RDI of 5 or more.<sup>[15]</sup> Sixteen studies met the inclusion criteria; three were randomized and 13 were nonrandomized. Six studies treated both the base of the tongue and the soft palate, two treated the soft palate only, and eight ablated the base of the tongue only. The population was in the overweight, but not obese, category, with a mean BMI of 28.5. In half of the studies, the average baseline RDI was less than 30, and in six of the studies, the average baseline ESS was less than 10. The meta-analysis indicated a 31% reduction in both ESS and RDI. The lowest oxygen saturation level was not improved by RFA. The mean number of treatments required for patient satisfaction was 3.7 for the soft palate, 4.3 for the base of the tongue, and 4.8 for both sites (range, 3-7). Complications were noted in 4% of patients; two tongue abscesses progressed to airway obstruction requiring tracheotomy. Only two of the studies provided 2-year follow-up, with a 32% reduction in ESS and a 45% reduction in RDI. The number of patients who were successfully treated (e.g., 50% reduction in RDI) was not reported. This meta-analysis is limited by the inclusion of poor quality uncontrolled studies.

### **Randomized Controlled Trials**

A single-blinded RCT of single-stage radiofrequency surgery of the soft palate was reported in 2009 by Back.<sup>[16]</sup> Thirty-two patients with mild OSA (AHI between 5 and 15), habitual snoring, and excessive daytime sleepiness according to subjective patient history, were randomized to a single session of RFA or sham ablation. There was no difference between the groups for baseline to posttreatment (4-6 months) changes in the Epworth Sleepiness Scale (ESS) (3-point improvement in ESS for both groups), reports of snoring (1-point improvement in both groups), AHI (no clinically significant change), or any other outcome measure. None of the patients reported any treatment-related symptoms or complications four months after treatment. Results of this small single-blinded RCT indicate that single-stage RFA of the soft palate is not effective for the treatment of mild OSA.

A RCT from 2009 by Fernandez-Julian compared efficacy and adverse effects of two tongue-based procedures (RFA or tongue-base suspension) when combined with UPPP in 57 patients with moderate-to-severe sleep apnea (AHI  $\geq 15$ ).<sup>[17]</sup> Patients with a BMI of 35 kg/m<sup>2</sup> or greater

were excluded. Although interpretation of results is limited by the lack of a control group treated with UPPP alone, the success rate for combined RFA + UPPP (defined as a  $\geq 50\%$  reduction and final AHI  $< 15$ ) was 51%. BMI was the main predictor of success, with success rates of only 12.5% in patients with a BMI between 30 and less than 35 kg/m<sup>2</sup>.

A 2003 two-site RCT study by Woodson compared the use of multilevel RFA with the current criterion standard of CPAP.<sup>[11]</sup> The study included patients with mild obesity levels (BMI  $\geq 34$  kg/m<sup>2</sup>) who had mild to moderate sleep apnea with an AHI between 10 and 30. Statistically significant improvement was noted with RFA and CPAP over placebo in OSA-specific quality of life using the Functional Outcomes of Sleep Questionnaire. However, the small size of the trial resulted in most outcomes not being statistically significant. The same group of authors reported a further subgroup analysis from the same trial, focusing on the 26 patients randomized to the RFA arm of the trial to determine whether additional treatments improved outcomes.<sup>[18]</sup> Specifically, the authors focused on multilevel treatments on various combinations of palatal and tongue tissues. Greater improvements in quality of life were reported for those patients who had a total of five treatments compared with 3. Another subgroup analysis focused on multilevel treatments in 26 patients.<sup>[19]</sup> This subgroup likely contains overlapping patients with the previous report, and the results were similar (i.e., greater improvements were reported in those patients who had a total of five treatments).

### **Nonrandomized Studies**

A 2008 retrospective cohort study assessed the incremental value of RFA of the tongue in combination with UPPP.<sup>[20]</sup> All patients with both palatal and retroglossal obstruction, an RDI between 5 and 50, and no previous OSA surgery were included in the study. Seventy-five patients meeting the inclusion criteria had been treated with UPPP during the three year period, 38 had UPPP alone, 37 had UPPP plus RFA. The groups were comparable for age, sex, BMI, AHI, and mean arterial oxygen saturation (SaO<sub>2</sub>); however, no details were provided regarding the choice of procedure. With surgical success rate defined as more than 50% reduction of the AHI and AHI below 20, the success rate was 42% with UPPP alone and 49% with RFA (not significantly different). Two patients had an additional RFA treatment. No major complications were observed. The study concluded that the addition of RFA to UPPP resulted in only limited improvement, but there was no major downside to it.

Two earlier case series have been published by Steward (2005) and Stuck (2004) on the use of radiofrequency ablation of both tongue base and soft palate tissue, referred to as a combined or multi-level radiofrequency tissue ablation technique.<sup>[21,22]</sup> Both case series reported significant improvements, including reductions in mean respiratory disturbance and apnea-hypopnea indexes, and in one case series these improvements persisted for a median of 23 months. However, both case series are limited by size, including 29 and 20 patients, respectively, and potential selection bias among the included participants. In addition, the ability to detect true long-term efficacy of this treatment is limited by the case series study design with lack of control group.

### **Radiofrequency Volumetric Tissue Reduction of the Tongue Base or Palatal Tissues Section Summary**

The evidence for the use of radiofrequency volumetric tissue reduction of the tongue base or palatal tissues for the treatment of obstructive sleep apnea or upper airway resistance syndrome includes two systematic reviews, three randomized controlled trials, and three non-randomized studies. The considerable heterogeneity of outcomes tested across studies does

not allow for conclusions about the potential benefit of these procedures. Additional appropriately controlled studies are needed to inform the clinical outcomes of these procedures alone or in addition to standard of care, as well as to evaluate the long-term benefits of these procedures.

## **TONGUE BASE SUSPENSION PROCEDURES**

### **Systematic Reviews**

In 2013, Handler reported a systematic review of tongue suspension versus hypopharyngeal surgery for the treatment of OSA.<sup>[23]</sup> The review included 27 studies reporting on four separate procedures; tongue suspension alone, tongue suspension + UPPP, genioglossus advancement (GA) + UPPP, and genioglossus advancement + hyoid suspension (GAHM) + UPPP. A successful treatment was defined as a 50% decrease in the RDI or AHI and a postoperative RDI or AHI less than 20. Tongue suspension alone (six studies, 82 patients) had a success rate of 36.6%, while the success rate of tongue suspension + UPPP (eight studies, 167 patients) was 62.3%. A success rate of 61.1% was found for GA + UPPP (seven studies, 151 patients) and for GAHM + UPPP (12 studies, 467 patients). The adverse effects of tongue suspension appear to be milder than GA or GAHM and are reversible. Most of the studies identified in this review were level IV evidence (case series).

### **Randomized Controlled Trial**

One level II RCT by Fernandez-Julian (2009) included in the systematic review compared two tongue base surgeries (RFA or tongue-base suspension) combined with UPPP for moderate to severe sleep apnea (AHI  $\geq 15$ ).<sup>[17]</sup> In the tongue suspension plus UPPP group (n=28), the mean AHI decreased from 33.1 to 15.1 events per hour. The success rate for the combined procedure (defined as a  $\geq 50\%$  reduction, final AHI  $< 15$ , and ESS  $< 11$ ) was 57.1%, compared with a success rate of 51.7% in the UPPP plus RFA group (p=0.79). BMI was the main predictor of success, with a success rate for tongue base suspension plus UPPP of only 10% in patients with a BMI between 30 and 35 kg/m<sup>2</sup>. Morbidity and complications were higher with the tongue suspension procedure compared with RFA.

### **Nonrandomized Studies**

In 2013, Li conducted a nonrandomized comparative study to evaluate the use of the Repose system in conjunction with UPPP to treat patients with obstructive sleep apnea hypopnea syndrome (OSAHS) caused by suspected glossoptosis.<sup>[24]</sup> Seventy-eight patients with OSAHS caused by suspected glossoptosis were non-randomly divided into two groups. The 45 patients in the first group received UPPP and tongue-base suspension (Repose). The 33 patients in the second group received UPPP alone. Follow-up was conducted over six months, and polysomnography was used to determine the effects of treatment. Follow-up results at six months revealed that the degree of improvement in patients treated with UPPP + Repose was significantly greater than that seen in patients treated with UPPP alone. In the UPPP + Repose group, 17 patients were cured, 23 showed marked improvement, and five did not improve. In the UPPP alone group, one patient was cured, 16 showed marked improvement, and 16 did not improve. The marked improvement rates of the two groups were 88.9 and 51.5 %, respectively, a significant difference.

In a 2010 multicenter, prospective case series, Woodson assessed the safety and effectiveness of an adjustable lingual suspension device (Advance System) for treating

OSA.<sup>[25]</sup> Forty two surgically naive patients with moderate to severe OSA and tongue base obstruction underwent surgical insertion of a midline tissue anchor into the posterior tongue and connected to an adjustable mandibular bone anchor with a flexible tether. Outcomes included changes in AHI, sleepiness, sleep-related quality-of-life, snoring, swallowing, speech and pain. After six months, all patients noted improvement for AHI, sleepiness and sleep-related quality of life. Post implant pain scores were mild to moderate at day one and resolved by day five. Device related adverse events included wound infection (7%) and edema or seroma (5%), which resolved. However, in 31 percent of patients, asymptomatic tissue anchor barb fractures were observed radiographically. The tissue anchor failure rate of the tested device precludes its clinical use. Further investigation is warranted.

In 2002, Miller conducted a retrospective analysis of the Repose System for the treatment of OSA to describe preliminary experience using the system in conjunction with UPPP in the multilevel surgical approach.<sup>[26]</sup> The authors evaluated 19 consecutive patients undergoing UPPP and the Repose System tongue base suspension for the management of OSA during a one-year period. Fifteen patients had complete preoperative and postoperative PSG data. A 46% reduction in RDI was demonstrated at a mean of 3.8 months after surgery. The apnea index demonstrated a 39% reduction. The authors concluded that the Repose System in conjunction with UPPP has been shown to produce significant reductions in the RDI and apnea index, as well as a significant increase in oxygen saturation. Despite the improvement in these objective parameters, the overall surgical cure rate was only 20% (three of 15 patients) in this retrospective series. Further research is warranted to define the role of the Repose System in the management of obstructive sleep apnea patients.

In 2000, DeRowe performed minimally invasive technique for tongue-base suspension with the Repose system in 16 patients with sleep-disordered breathing.<sup>[27]</sup> Fourteen patients reported an improvement in daytime sleepiness, and their bed partners reported an improvement in snoring. The mean respiratory distress index before surgery was 35. Two months after surgery, the mean respiratory distress index was 17, an improvement of 51.4%. These preliminary results show the initial efficacy and safety of this new surgical procedure. Similar improvements were reported in other small case series (n=8-14 patients with OSA) who underwent the same procedure.<sup>[28-30]</sup>

## **Tongue Base Suspension Procedures Section Summary**

Evidence for the tongue base suspension procedures for the treatment of sleep apnea or upper airway resistance syndrome includes one systematic review, one randomized controlled trial, and four non-randomized studies. These studies report low success rates of the procedure, particularly in obese individuals, and adverse events including wound infection, edema, pain, and tissue anchor barb fractures are reported. Long-term outcomes of the procedure are not well characterized. Additional studies with longer end-points including those addressing safety and efficacy are needed.

## **LASER-ASSISTED PALATOPLASTY**

### **Systematic Reviews**

Wischhusen (2019) published a SR evaluating the complications and side effects of laser-assisted uvulopalatoplasty (LAUP) across 42 studies (N=3,093). Mean follow-up was 16.1 months (median six months, range of 0.5 – 134 months).<sup>[31]</sup> Across all 42 studies, the total number of LAUP complications based on a population of 1,000 patients with a 95% CI was

reported as  $255.71 \pm 23.33$ . The authors also calculated relative risk of specific complications compared to published population studies and found significant effects for complications of globus sensation and velopharyngeal (VP) insufficiency with 95% CI of 1.07–2.06 and 1.29–3.94, respectively. In the four studies with the longest follow-up duration with a mean of 100.5 months, these complications were 12.2% and 10.8%, respectively, suggesting that these may be long-term complications of the procedure. The authors conclude “based on the findings of this systematic review, we recommend that LAUP be performed with caution using the tissue-sparing approach or avoided altogether, given the potential for complications identified in the current literature.”

## Randomized Controlled Trials

Ferguson (2003) reported a trial that randomized 45 subjects with mild-to-moderate sleep apnea (defined as an AHI ranging between 10-27 per hour) to either uvulopalatoplasty (LAUP) or no treatment.<sup>[10]</sup> The LAUP procedure was repeated at 1- to 2-month intervals until either the snoring was significantly reduced, no more tissue could safely be removed, or the patient refused further procedures. The primary outcome measurement was the reduction in AHI in the LAUP group versus the control group. An AHI of less than 10 was considered a successful treatment. In the treatment group, 24% were considered treatment successes and 76% were failures. In the control group (who received no therapy), 16.7% were considered treatment successes. The authors concluded that LAUP can be effective in some patients, but the reduction in AHI and the level of symptomatic improvement were minor overall.

## Nonrandomized Studies

In 1995, Walker prospectively evaluated the outcomes of 65 patients who underwent LAUP for the treatment of OSA.<sup>[32]</sup> Of the 65 OSAS patients treated with LAUP, postoperative polysomnograms were obtained in 33 patients (51%). Surgical success was achieved in 16 (48%) of the 33 patients. However, seven patients (21%) had repeat polysomnograms that were worse than their preoperative polysomnograms, and five patients (15%) had no significant change.

## CAUTERY-ASSISTED PALATAL STIFFENING OPERATION

### Systematic Reviews

Llewellyn (2018) published a SR with meta-analysis of outcomes for cauterly-assisted palatal stiffening operation (CAPSO) as a treatment for adult OSA. This SR included eight studies (N=307) conducted in adult patients with sleep disordered breathing.<sup>[33]</sup> Additional inclusion criteria for the SR were: “outcomes for sleep study information, snoring and/or sleepiness; anterior palatoplasty or palatal stiffening operation or CAPSO or modified CAPSO with or without tonsillectomy/expansion pharyngoplasty (plication of palatopharyngeus);” and no other surgical procedures performed at the same time. Among these studies, four were considered to have high risk of bias in patient selection per QUADAS-2. The authors reported the following improvements (mean  $\pm$  standard deviation [M  $\pm$  SD] events per hour, percent change) in AHI: CAPSO alone (N=80 patients), ( $16.8 \pm 11.9$ ) to ( $9.9 \pm 10.9$ ), a 41.1% decrease; mixed CAPSO with/without tonsillectomy (N=92), ( $24.8 \pm 12.6$ ) to ( $10.6 \pm 9.5$ ), a 61.7% decrease; CAPSO with expansion pharyngoplasty (N=78), ( $26.3 \pm 17.7$ ) to ( $12.6 \pm 5.8$ ), a 52.1% decrease. The authors also reported the following improvement in lowest oxygen saturation (LSAT): CAPSO alone (N=90), 5.4 point improvement; mixed CAPSO with/without tonsillectomy (N=77), 10.6 point improvement; and CAPSO with expansion pharyngoplasty (N=78), 5.2 point

improvement. Although the authors reported effect sizes for pre- and post-surgery outcomes across all data, for none of the above analyses evaluating effects of CAPSO alone or in combination with other interventions were assessments of statistical significance (p values) reported. This SR included studies by Mair (2000) and Pang (2007), which focused on patients with simple snoring (AHI <5) or mild sleep apnea (AHI <15).<sup>[34,35]</sup> A study with long-term follow-up reported in this SR found that 38% of patients with mild to moderate OSA had globus sensation and inability to clear phlegm 2 years after the operation.<sup>[36]</sup> Future RCTs evaluating the specific and long-term benefit of CAPSO in OSA are needed.

### **Randomized Controlled Trials**

No additional RCTs beyond those addressed in the SR above on the use of cautery-assisted palatal stiffening operation in the treatment of OSA or UARS have been identified.

## **PALATAL IMPLANTS**

### **Systematic Reviews**

No SRs for the use of palatal implants for the treatment of OSA or UARS have been identified.

### **Randomized Controlled Trials**

In 2012, Maurer reported a randomized double-blind, sham-controlled trial of the Pillar palatal implant in 20 patients with mild to moderate OSA because of palatal obstruction.<sup>[37]</sup> At 90 days, the AHI in the treatment group improved from 19.1 to 8.2 events per hour and lowest oxygen saturation improved from 82.8% to 88.3%. These measures did not improve significantly in the control group, and there was no significant difference in outcomes between the implant and control groups in this small trial. The ESS did not improve significantly in either group.

In a 2008 trial by Steward, 100 patients with mild to moderate OSA and suspected retropalatal obstruction were randomly assigned to palatal implants or sham placebo.<sup>[38]</sup> Patients with BMI greater than 32 kg/m<sup>2</sup> were excluded from the study. About 1000 patients were evaluated to identify the 100 study patients. At three-month follow-up, the average AHI increased in both groups from a baseline of about 17, although the increase was greater in the placebo group (8.9 vs 2.9, respectively). A reduction in AHI by at least 50% or to below 20 was more common in the implant group (26% vs 10%, respectively; p=0.05). Improvement in ESS did not differ from that of sham (p=0.62). Partial implant extrusion occurred in two patients (4%).

In 2008, Friedman reported an industry-sponsored randomized double-blind, sham-controlled trial of palatal implants in 62 patients with symptoms of OSA.<sup>[39]</sup> Other inclusion criteria included: Friedman tongue position I, II, or III; diagnosis of mild to moderate OSA (AHI ≥5 and <40) on baseline polysomnography (PSG); a soft palate of 2 cm or more but less than 3.5 cm; and BMI less than 32 kg/m<sup>2</sup>. AHI at baseline was 23.8 events per hour in the implant group and 20.1 in controls. Seven patients did not return for repeat PSG and were considered treatment failures in the intention-to-treat analysis. At three-month follow-up, the AHI improved to 15.9 events per hour in the implant group but did not change significantly in the controls (21.0). The ESS improved from 12.7 to 10.2 in the implant group and did not change significantly in the controls (11.7 to 11.1). With success defined as an AHI reduction of 50% or more and AHI less than 20, palatal implantation resulted in the successful treatment of 41.9% of implanted patients compared with 0% of controls. Two patients had partial implant extrusion.

### **Nonrandomized Studies**

Neruntarat (2011) reported a case series with a minimum of 24-month follow-up.<sup>[40]</sup> This study included 92 patients with mild to moderate OSA (AHI  $\leq$ 30 with daytime sleepiness or disturbed sleep) who had received palatal implants after failed medical management. At baseline, the mean AHI was 21.7 events per hour, and the lowest oxygen saturation was 87.4%. At mean 28.9-month follow-up, the AHI had decreased to 10.8, and the lowest oxygen saturation improved to 89.2%. Sleep efficiency improved from 80.6% to 87.2%, and the ESS score improved from a mean of 12.3 to 7.9. Implant extrusion occurred in seven patients (7.6%), and palatal abscess occurred in one patient (1.1%). Confounding factors, such as significantly lower BMI in “responders” may have affected the interpretation of the efficacy of this procedure in this patient population.

Walker published 90-day and 15-month follow-up from a multicenter study on palatal implants (Pillar System) in 63 subjects.<sup>[41,42]</sup> The AHI decreased from a baseline of 25 to 22 in the 53 patients (84%) who were evaluated at 90 days. Twenty-two patients (35%) were available for the follow-up study; 13 had shown a decrease in AHI (from a baseline of 20 to 13) at 90 days. Of these, 10 (77% of the 13) maintained the decrease at 15 months. The nine patients whose AHI had not improved at 90 days had no subsequent improvement at the extended follow-up. Mean snoring was rated as eight at baseline (visual analog scale), and 4 at both 90 days and 15 months. Subjective daytime sleepiness measured by the ESS was reduced at 90 days (11 to 7) but returned to a score of 11 at the longer follow-up. In addition to the very large loss to follow-up, questions remain about the clinical significance of a three- to seven-point improvement in AHI.

In a prospective study, Nordgard (2007) assessed the long-term effectiveness of palatal implants for treatment of mild-to-moderate OSA.<sup>[43]</sup> A total of 26 referred patients with a pre-treatment AHI of 10 to 30 and a BMI of less than or equal to 30, representing an extended follow-up of a subset of 41 patients enrolled in previous short-term trials were included. Twenty-one of 26 patients (80.8 %) experienced a decrease in AHI. Fifteen of 26 patients (57.7 %) had a follow-up AHI less than 10 at one year, whereas 13 patients (50 %) had a 50 % or greater reduction to an AHI less than 10 at one year. Mean AHI was reduced from 16.5 +/- 4.5 at baseline to 12.5 +/- 10.5 at three months ( $p < 0.014$ ) and to 12.3 +/- 12.7 at one year ( $p < 0.019$ ). The authors concluded that patients initially responding to palatal implants with improved AHI maintained improvement through long-term follow-up at one year. The main limitation of this study was its small sample size. The authors noted that additional studies with longer follow-up would be appropriate.

Nordgard (2006) conducted a prospective nonrandomized study of 25 patients with untreated OSA with an AHI of 10–30, as determined by preoperative PSG, and BMI  $\leq$  30.<sup>[44]</sup> Three permanent implants were placed in the soft palate of each patient in an office setting under local anesthesia. A repeat PSG showed a mean decrease in AHI from 16.2 to 12.1 for the study group. Twenty of 25 patients demonstrated a reduced AHI, and 12 of 25 patients demonstrated an AHI of 10 or less 90 days post-implant. The mean ESS score decreased from 9.7 to 5.5. The authors concluded that palatal implants can significantly improve AHI and other sleep-related parameters in patients with mild to moderate OSA and BMI  $\leq$  30, with short-term results comparable to those reported for UPPP. The authors acknowledged the lack of long-term outcomes in this study and the limited number of patients. As with other palatal procedures, reduction in effectiveness over time may be expected. The authors further concluded that while short-term durability and effectiveness have been established, longer-term research needs to be conducted.

In a retrospective, nonrandomized, controlled study, Friedman (2006) evaluated the Pillar implant system alone and in combination with other procedures for treatment of mild-to-moderate OSA/hypopnea syndrome (OSAHS).<sup>[45]</sup> A total of 125 patients who had mild-to-moderate OSAHS were assigned to palatal implantation alone (palatal group, n=29), or in combination with other procedures. Most of the procedures other than palatal implantation were not defined clearly. After a mean follow-up of eight months, mean AHI for the palatal group had decreased from 13.8 to 12.13; however, this difference was not statistically significant compared with baseline. Using the criteria of AHI < 20 and > 50% reduction of AHI as "cured," Friedman reported that seven (24%) palatal group patients and 43 (34%) of all patients were "cured." One of the study limitations was that many patients had an AHI < 20 at baseline, particularly in the Palatal Group, which had a baseline AHI of 13.8.

Three other small, uncontrolled studies have been performed to evaluate the Pillar Palatal Implant System for mild-to moderate OSA.<sup>[46,47]</sup> These studies enrolled 16 to 26 patients who had an AHI score of 5 to 30. These studies reported that, compared with baseline, patients obtained small-to-moderate but statistically significant improvements in outcomes such as AHI and Epworth Sleepiness Scale (ESS) scores at up to one year of follow-up; however, these studies do not provide reliable evidence of efficacy since they did not involve any control or comparison groups.

### **Palatal Implants Section Summary**

The literature on palatal implants consists of three moderately-sized RCTs and additional case series with medium-term follow-up. Evidence from sham-controlled trials shows a statistically significant but modest reduction in AHI and improvement in lowest oxygen saturation compared with placebo, with limited effects on daytime sleepiness. Additional studies are needed to determine whether there is a defined subset of patients who might benefit from this procedure. Studies with longer term follow-up are also needed to evaluate the potential for extrusion of the implants at longer time intervals.

## **PRACTICE GUIDELINE SUMMARY**

### **AMERICAN ACADEMY OF OTOLARYNGOLOGY - HEAD AND NECK SURGERY**

The American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) has published a number of consensus-based policy statements on various techniques for surgical management of obstructive sleep apnea.<sup>[4,48-52]</sup> AAO-HNS position statements, by definition are "based on an informal process of expert or committee consensus that draws upon best available evidence and quality products.", thus each of the position statements may be supported to varying degrees by evidence. Procedures the AAO-HNS supports as effective and not considered investigational when part of a comprehensive approach in the medical and surgical management of adults with OSA include palatal advancement, uvulopalatopharyngoplasty, uvulopalatoplasty (including laser assisted and other techniques), genioglossal advancement, hyoid myotomy, midline glossectomy, tongue suspension, and maxillary and mandibular advancement.

No evidence-based practice guidelines from the AAO-HNS were identified.

## SUMMARY

There is enough research to suggest that uvulopalatopharyngoplasty (UPPP) and its variants, hyoid suspension, mandible osteotomy, partial glossectomy, and maxillofacial surgeries such as mandibular-maxillary advancement (MMA) may improve health outcomes for some patients with obstructive sleep apnea (OSA) or airway resistance syndrome (UARS). These procedures have become a standard of care and may therefore be considered medically necessary when the policy criteria are met.

There is not enough research to support surgery as first-line treatment of obstructive sleep apnea (OSA) or upper airway resistance syndrome (UARS). Therefore, surgical treatments may be considered medically necessary only after failed medical therapy, including nasal continuous positive airway pressure (CPAP). In addition, surgical treatments including uvulopalatopharyngoplasty (UPPP) and its variants, hyoid suspension, mandible osteotomy, partial glossectomy, and maxillofacial surgeries such as mandibular-maxillary advancement (MMA) are considered not medically necessary when criteria are not met.

There is not enough research to determine the safety and efficacy of surgical interventions including but not limited to uvulectomy, tongue base reduction, and minimally invasive surgical procedures such as laser-assisted uvuloplasty (LAUP), radiofrequency tongue base or tissue volume reduction, pillar stiffening procedures, and pillar implants. The use of these interventions is considered investigational for the treatment of obstructive sleep apnea (OSA) or airway resistance syndrome (UARS).

Snoring in the absence of clinically significant obstructive sleep apnea (OSA) is not considered a medical condition. Therefore, any surgical intervention, including but not limited to uvulopalatopharyngoplasty (UPPP), laser-assisted uvulopalatoplasty (LAUP), radiofrequency volumetric tissue reduction of the palate, or palatal stiffening procedures for snoring alone is considered not medically necessary.

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## CODES

**NOTE:** There is no specific CPT code for the tongue base reduction procedure. The most appropriate code to use is 41599 (unlisted procedure) or 41530. 41120 (partial glossectomy) describes a surgical resection and is not the appropriate code to use for submitting claims for tongue base reduction.

Codes	Number	Description
CPT	21121	Genioplasty; sliding osteotomy, single piece
	21122	Genioplasty; sliding osteotomies, two or more osteotomies (eg, wedge excision or bone wedge reversal for asymmetrical chin)
	21141	Reconstruction midface, LeFort 1; single piece, segment movement in any direction (eg, for Long Face Syndrome), without bone graft
	21145	Reconstruction midface, LeFort 1; single piece, segment movement in any direction, requiring bone grafts (includes obtaining autografts)
	21196	Reconstruction of mandibular rami and /or body, sagittal split; with internal rigid fixation
	21198	Osteotomy, mandible, segmental
	21199	Osteotomy, mandible, segmental; with genioglossus advancement
	21685	Hyoid myotomy and suspension
	41120	Glossectomy; less than one-half tongue
	41500	<del>Fixation of tongue, mechanical, other than suture (eg, K-wire)</del> (Deleted 1/1/2019)
	41512	Tongue base suspension, permanent suture technique
	41530	Submucosal ablation of the tongue base, radiofrequency, one or more sites, per session
	41599	Unlisted procedure, tongue, floor of mouth
	42140	Uvulectomy, excision of uvula
	42145	Palatopharyngoplasty (eg, Uvulopalatopharyngoplasty, Uvulopharyngoplasty)
	42160	Destruction of lesion, palate or uvula (thermal, cryo, or chemical)
	42299	Unlisted procedure, palate, uvula
HCPCS	S2080	Laser-assisted uvulopalatoplasty (LAUP)

### Appendix 1: Procedures for the Diagnosis of Sleep Disordered Breathing

<b>Polysomnography (PSG)</b>	Full night PSG consists of five to eight hours of monitoring, supervised by a sleep technician, while the patient sleeps. It is performed in a sleep lab and involves the following monitoring modalities: electroencephalogram (EEG) (to stage sleep and detect arousals), electro-oculogram (EOG) (to detect arousal and REM sleep) submental electromyogram, (EMG), electrocardiogram (EKG), two-leg EMG, respiratory airflow and effort (to detect apnea), snoring, oxygen saturation, time and position. In addition, a full night PSG may include additional monitoring modalities as indicated, such as esophageal pressure monitoring, blood pressure monitoring, carbon dioxide trends, and pulse transit time.
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<b>Appendix 1: Procedures for the Diagnosis of Sleep Disordered Breathing</b>	
	<p>The first three elements listed above (EEG, submental electromyogram, and electro-oculogram) are required for sleep staging. By definition, a polysomnogram always includes sleep staging, while a “sleep study” does not include sleep staging. The actual components of the study will be dictated by the clinical situation. Typically, the evaluation of obstructive sleep apnea would include respiratory airflow and effort, electro-oculogram, and oxygen desaturation. An EEG may not be considered necessary to evaluate OSA, although it is required to evaluate UARS, REM sleep behavior disorder (RBD), narcolepsy or other sleep disturbances.</p>
<b>Split Night Polysomnography</b>	<p>A split night study utilizes the first two or three hours for evaluating the presence of sleep apnea and the second half to titrate and adjust CPAP. The same monitoring modalities used in full night PSG are used in split night study. In patients with severe obstructive sleep apnea, a reliable assessment of the respiratory disturbance index is possible with a partial night study. Half night study for CPAP titration is reliable in selected cases of obstructive sleep apnea.</p> <p>Split night studies are appropriate in patients with severe sleep apnea syndrome. The decision to conduct a split night study depends on the technical skill and experience of the staff, the initial sleep latency period, the severity and frequency of respiratory events and patient compliance. Careful patient selection and education is required to conduct a successful split night study.</p>
<b>Home Sleep Apnea Testing Device (HSAT Device)</b>	<p>Per the 2017 American Academy of Sleep Medicine (AACM) Clinical Practice Guideline for diagnostic testing for adult obstructive sleep apnea, home sleep apnea testing with a technically adequate device may be used for the diagnosis of obstructive sleep apnea (OSA) in uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA.<sup>[1]</sup></p> <p>An uncomplicated patient is defined by the absence of:</p> <ol style="list-style-type: none"> <li>1. Conditions that place the patient at increased risk of non-obstructive sleep-disordered breathing (e.g., central sleep apnea, hypoventilation and sleep related hypoxemia). Examples of these conditions include significant cardiopulmonary disease, potential respiratory muscle weakness due to neuromuscular conditions, history of stroke and chronic opiate medication use.</li> <li>2. Concern for significant non-respiratory sleep disorder(s) that require evaluation (e.g., disorders of central hypersomnolence, parasomnias, sleep related movement disorders) or interfere with accuracy of HSAT (e.g., severe insomnia).</li> <li>3. Environmental or personal factors that preclude the adequate acquisition and interpretation of data from HSAT.</li> </ol> <p>An increased risk of moderate to severe OSA is indicated by the presence of excessive daytime sleepiness and at least two of the following three criteria: habitual loud snoring, witnessed apnea or gasping or choking, or diagnosed hypertension.</p>

<b>Appendix 1: Procedures for the Diagnosis of Sleep Disordered Breathing</b>	
	<p>HSAT is to be administered by an accredited sleep center under the supervision of a board-certified sleep medicine physician, or a board-eligible sleep medicine provider.</p> <p>A single HSAT recording is conducted over at least one night.</p> <p>A technically adequate HSAT device incorporates a minimum of the following sensors: nasal pressure, chest and abdominal respiratory inductance plethysmography, and oximetry; or else peripheral arterial tone (PAT) with oximetry and actigraphy.</p> <p>A technically adequate diagnostic test includes a minimum of 4 hours of technically adequate oximetry and flow data, obtained during a recording attempt that encompasses the habitual sleep period.</p> <p>If a single HSAT is negative, inconclusive, or technically inadequate, polysomnography should be performed for the diagnosis of OSA.</p>
<b>SNAP™ Testing</b>	The SNAP testing system is a reflective acoustic device marketed as a screening and analysis system to locate the source of snoring and detect sleep apnea conditions.
<b>Multiple Sleep Latency Tests (MSLT)</b>	The MSLT measures the speed of falling asleep under conditions that favor sleep, in a series of 20-minute trials during the patient's habitual periods of wakefulness. MSLT is the preferred method of establishing the presence of true physiological sleepiness but is accurate only if following strict protocols. MSLT is used in patients with complaints of irresistible daytime sleepiness suggestive of narcolepsy.
<b>Maintenance of Wakefulness Test (MWT)</b>	The patient is monitored during the usual periods of wakefulness but the patient is instructed not to fall asleep as a test of the patient's ability to stay awake. It may be used to evaluate the safety of drivers and their ability to stay alert.
<b>Radiologic Studies</b>	Radiologic images of the head and neck for anatomic abnormalities include MRI, CT scan, and cephalometry. Such studies are intended to assess for hypopharyngeal obstruction or other suspected pathology that might explain the symptoms associated with sleep disordered breathing.
<b>Endoscopic Studies</b>	Nasopharyngeal and laryngeal endoscopic measurements of structure and function of the upper airway are used in selected patients with suspected abnormal anatomy as an aid in the diagnosis of OSA or in the management of complications of treatment.
<b>Epworth Sleepiness Scale</b>	Excessive daytime sleepiness is predominantly a subjective symptom. The Epworth sleepiness scale is a self-administered questionnaire, performed as part of the clinical evaluation, that asks patients their likelihood of falling asleep in eight situations ranked from 0 (would never fall asleep) to 3 (high chance of dozing). The numbers are then added together to give a global score between 0 and 24. A value of 10 or below is considered normal.
<b>Apnea-Hypopnea Index (AHI); Respiratory</b>	Apnea is defined as the cessation of respiration for at least 10 seconds. Hypopnea is a reduction but not cessation of air exchange. Apneic and hypopneic events are combined into the apnea-hypopnea index (AHI). In

<b>Appendix 1: Procedures for the Diagnosis of Sleep Disordered Breathing</b>	
<b>Disturbance Index (RDI)</b>	turn the AHI is often referred to as the respiratory disturbance index (RDI), although more recently the RDI has been redefined by some physicians to include EEG arousals in addition to apneic and hypopneic events. An AHI of greater than or equal to 20 is typically considered moderate OSA, and AHI of greater than 50 is considered severe OSA. An increase in mortality is associated with an AHI of greater than 15.
<b>Polysomnography (PSG)</b>	<p>Full night PSG consists of five to eight hours of monitoring, supervised by a sleep technician, while the patient sleeps. It is performed in a sleep lab and involves the following monitoring modalities: electroencephalogram (EEG) (to stage sleep and detect arousals), electro-oculogram (EOG) (to detect arousal and REM sleep) submental electromyogram, (EMG), electrocardiogram (EKG), two-leg EMG, respiratory airflow and effort (to detect apnea), snoring, oxygen saturation, time and position. In addition, a full night PSG may include additional monitoring modalities as indicated, such as esophageal pressure monitoring, blood pressure monitoring, carbon dioxide trends, and pulse transit time.</p> <p>The first three elements listed above (EEG, submental electromyogram, and electro-oculogram) are required for sleep staging. By definition, a polysomnogram always includes sleep staging, while a “sleep study” does not include sleep staging. The actual components of the study will be dictated by the clinical situation. Typically, the evaluation of obstructive sleep apnea would include respiratory airflow and effort, electro-oculogram, and oxygen desaturation. An EEG may not be considered necessary to evaluate OSA, although it is required to evaluate UARS, REM sleep behavior disorder (RBD), narcolepsy or other sleep disturbances.</p>
<b>Split Night Polysomnography</b>	<p>A split night study utilizes the first two or three hours for evaluating the presence of sleep apnea and the second half to titrate and adjust CPAP. The same monitoring modalities used in full night PSG are used in split night study. In patients with severe obstructive sleep apnea, a reliable assessment of the respiratory disturbance index is possible with a partial night study. Half night study for CPAP titration is reliable in selected cases of obstructive sleep apnea.</p> <p>Split night studies are appropriate in patients with severe sleep apnea syndrome. The decision to conduct a split night study depends on the technical skill and experience of the staff, the initial sleep latency period, the severity and frequency of respiratory events and patient compliance. Careful patient selection and education is required to conduct a successful split night study.</p>

<b>Appendix 2: Nonsurgical Devices for Treatment of OSA or UARS</b>	
<b>CPAP</b>	Nasal or oral continuous positive airway pressure (CPAP) or auto-titrating continuous positive airway pressure (APAP) is continuous positive airway pressure applied through the nose or via oral appliance. It is delivered by a flow generator through a mask to supply a pressure level sufficient to keep the upper airway patent. The pressure used is determined individually with a range of three to 15 centimeters of water.

<b>Appendix 2: Nonsurgical Devices for Treatment of OSA or UARS</b>	
<b>BiPAP®</b>	<p>Bi-level respiratory assist device delivers alternating levels of positive airway pressure instead of the continuous pressure applied by CPAP.</p> <p>A bi-level positive airway pressure device with back-up rate feature is a ventilation support system. These devices are in the FDA category of non-continuous ventilator, and as such, are primarily intended to augment patient ventilation.</p> <p>The term BiPAP® is a registered trademark of <i>Respironics Inc.</i>, but is widely used to describe any bi-level positive airway pressure device as described above.</p>
<b>APAP</b>	<p>Auto-adjusting CPAP (APAP) is a more recent technology which alternates airway pressure between exhalation and inhalation on a breath-by-breath basis. With the C-Flex™ (Respironics, Inc) airway pressure is reduced during early exhalation in proportion to the patient's expiratory flow rate. Pressure is then increased again toward the end of exhalation when airway collapse is most likely. Unlike BiPAP which delivers a static lower expiratory pressure, the C-Flex varies the pressure within the expiratory phase.</p>
<b>Oral Appliances (OA)</b>	<p>OA for the treatment of sleep disordered breathing are devices worn in the mouth during sleep to maintain a patent airway by raising the uvula, depressing the tongue, and/or advancing the mandible (in which case they are also known as mandibular advancement devices [MAD]). Commercially available devices are usually custom-molded or custom-fitted for the individual patient by a qualified dental health professional trained and experienced in the overall care of oral health, the temporomandibular joint, dental occlusion and associated oral structures. According to the American Academy of Sleep Medicine, dental management of patients with oral appliances should be overseen by practitioners who trained in sleep medicine and sleep related breathing disorders.<sup>[53,54]</sup> Oral appliances can range from simple retaining devices, to adjustable, hinged, or two-piece designs. Some designs can be used in conjunction with a CPAP device (e.g., OPAP®).</p>

**Date of Origin:** March 2009

## Occipital Nerve Stimulation

**Effective:** April 1, 2020

**Next Review:** February 2021

**Last Review:** February 2020

### IMPORTANT REMINDER

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

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

### DESCRIPTION

Occipital nerve stimulation (ONS) delivers a small electrical charge to the occipital nerve in an attempt to prevent migraines and other headaches in patients who have not responded to medications. The device consists of a subcutaneously implanted pulse generator (in the chest wall or abdomen) attached to extension leads that are tunneled to join electrodes placed across one or both occipital nerves at the base of the skull. Continuous or intermittent stimulation may be used.

### MEDICAL POLICY CRITERIA

Occipital nerve stimulation is considered **investigational** for all indications, including but not limited to headaches.

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

### CROSS REFERENCES

1. [Interferential Current Stimulation](#), Durable Medical Equipment, Policy No. 83.07
2. [Sphenopalatine Ganglion Block for Headache and Pain](#), Medicine, Policy No. 160
3. [Spinal Cord Stimulation](#), Surgery, Policy No. 45
4. [Peripheral Subcutaneous Field Stimulation](#), Surgery, Policy No. 188
5. [Implantable Peripheral Nerve Stimulation for Chronic Pain of Peripheral Nerve Origin](#), Surgery, Policy No. 205

## BACKGROUND

Implanted peripheral nerve stimulators have been used for treatment of refractory pain for many years but only recently proposed for management of craniofacial pain. Occipital, supraorbital, and infraorbital stimulation have been reported in the literature.

There are four types of headache: vascular, muscle contraction (tension), traction, and inflammatory. Primary (not the result of another condition) chronic headache is defined as headache occurring more than 15 days of the month for at least three months. An estimated 45 million Americans experience chronic headaches. For at least half of these people, the problem is severe and sometimes disabling.

Migraine is the most common type of vascular headache. Migraine headaches are usually characterized by severe pain on one or both sides of the head, an upset stomach, and, at times, disturbed vision. One- year prevalence of migraine ranges from 6% to 15% in adult men and from 14% to 35% in adult women. Migraine headaches may last a day or more and can strike as often as several times a week or as rarely as once every few years. Drug therapy for migraine is often combined with biofeedback and relaxation training. Sumatriptan is commonly used for relief of symptoms. Drugs used to prevent migraine include methysergide maleate, propranolol hydrochloride, ergotamine tartrate; amitriptyline, valproic acid, and verapamil.

Hemicrania continua, also a vascular headache, causes moderate pain with occasional severe pain on only one side of the head. At least one of the following symptoms must also occur; conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, or ptosis and/or miosis. Headache occurs daily and is continuous with no pain-free periods. Hemicrania continua occurs mainly in women, and its true prevalence is not known. Indomethacin usually provides rapid relief of symptoms. Other nonsteroidal anti-inflammatories (NSAIDs), including ibuprofen, celecoxib, and naproxen, can provide some relief from symptoms. Amitriptyline and other tricyclic antidepressants are effective in some patients.

Cluster headache is a vascular headache that occurs in cyclical patterns or clusters of severe or very severe unilateral orbital or supraorbital and/or temporal pain. The headache is accompanied by at least one of the following autonomic symptoms: ptosis (drooping eyelid), conjunctival injection, lacrimation, rhinorrhea, and, less commonly, facial blushing, swelling, or sweating. Bouts of one headache every other day to eight attacks per day may last from weeks to months, usually followed by remission periods when the headache attacks stop completely. The pattern varies from one person to another, but most people have one or two cluster periods a year. During remission, no headaches occur for months, and sometimes even years. The intense pain is caused by the dilation of blood vessels, which creates pressure on the trigeminal nerve. While this process is the immediate cause of the pain, the etiology is not fully understood. It is more common in men than in woman. One-year prevalence is estimated to be 0.5 to 1.0/1,000. Management of cluster headache consists of abortive and preventive treatment. Abortive treatments include subcutaneous injection of sumatriptan, topical anesthetics sprayed into the nasal cavity, and strong coffee. Some patients respond to rapidly inhaled pure oxygen. A variety of other pharmacologic and behavioral methods of aborting and preventing attacks have been reported with wide variation in patient response.

## REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) has not yet cleared any occipital nerve stimulation device for treatment of headache.

The Synergy™ IPG (implantable pulse generator) device from Medtronic received marketing clearance in 1999 for management of chronic, intractable pain of the trunk or limbs, and off-label use for headache is described in the literature.

The Genesis™ neuromodulation system (St. Jude Medical) is approved by the FDA for spinal cord stimulation and has received CE mark approval in Europe for the treatment of chronic migraines.

## EVIDENCE SUMMARY

The principal outcomes associated with treatment of headache are relief of pain, return to work, and improved functional level. Relief of pain can be a subjective outcome associated with a placebo effect. Therefore, data from adequately powered, blinded, randomized controlled trials (RCT) are required to control for the placebo effect and determine whether any treatment effect provides a significant advantage.

The technology must also be evaluated in general groups of patients against existing treatments. In patients with mild to moderate symptoms, occipital nerve stimulation may be compared to other forms of conservative therapy such as topical anesthetics, rest, or non-steroidal anti-inflammatory or migraine medications.

Therefore, the focus of the evidence summary is on RCTs comparing occipital nerve stimulation (ONS)-treated patients with those in a sham treatment or standard of care group.

## SYSTEMATIC REVIEWS

Cadalso (2017) published a systematic review (SR) evaluating the impact occipital nerve stimulation had on healthcare outcomes, for intractable primary headache disorders.<sup>[1]</sup> The SR included four RCTs, one follow-up study, and 19 case series. The authors stated that although the RCTs showed a decrease in headache frequency and improved migraine disability assessment scores, ONS did not improve pain intensity and there was heterogeneity of outcomes. In addition, the RCTs had small sample sizes and risk of bias.

Yang (2016) identified the same five RCTs as the 2015 SR by Chen, summarized below.<sup>[2]</sup> The Yang review only included studies conducted with patients with migraine of at least six months in duration who did not respond to oral medications. In addition to the RCTs, five case series met the inclusion criteria. Yang et al did not pool study findings. The definition of response rate varied across studies and could include frequency and/or severity of headaches. Response rates in three case series with self-reported efficacy were 100% each, and response rates in the other two series were 50% and 89%, respectively. Complication rates in the series ranged from 40% to 100%. The authors noted that the case series were subject to biases (e.g., inability to control for the placebo effect), that RCT evidence was limited, and that complication rates were high.

Two SRs of the literature on occipital nerve stimulation (ONS) were published in 2015. Both included RCTs and observational studies. Chen identified five RCTs and seven case series with at least 10 patients.<sup>[3]</sup> Three of the RCTs were industry-sponsored, multicenter, parallel-group trials and two were single-center crossover trials. All five included a sham control group and one trial also included a medication management group. Risk of bias was judged to be high or unclear for all trials. Meta-analyses were performed on two outcomes. A pooled analysis of 2 studies did not find a significant difference in response rate between active and

sham stimulation (risk ratio [RR], 2.07; 95% confidence interval [CI], 0.50 to 8.55;  $p=0.31$ ) and a pooled analysis of three studies showed a significantly greater reduction in the number of days with prolonged moderate-to-severe headache (mean difference, 2.59; 95% CI, 0.91 to 4.27;  $p=0.003$ ). Sweet (2015) published a SR that identified nine small case series (<15 patients each) assessing the efficacy of ONS for treating medically refractory occipital neuralgia.<sup>[4]</sup> The authors did not pool study findings. No conclusions can be drawn about the impact of ONS on occipital neuralgia due to the lack of RCTs or other controlled studies.

The National Institute for Health and Care Excellence (NICE, 2013) evaluated two RCTs and one case series to determine if ONS was effective in decreasing headache frequency, duration and severity.<sup>[5]</sup> Both RCTs compared ONS with sham stimulation at three months. Although the smaller RCT with 67 patients determined that the ONS group responded better than the sham group, the larger RCT with 157 patients showed no difference in responder rate. NICE concluded that ONS for intractable chronic migraines is efficacious in the short-term, but there is little evidence to indicate long-term outcome effects. NICE stated ONS should only be used for clinical governance, consent, and audit or research.

## **RANDOMIZED CONTROLLED TRIALS**

Serra and Marchioretto (2012) conducted a crossover RCT in which 30 patients with chronic migraine (100% of patients) and medication overuse headache (85% of patients) were implanted with an ONS and randomized to “Stimulation On” or “Stimulation Off” arms.<sup>[6]</sup> After one month, or if headaches worsened during the off period, patients were crossed over to the other arm. The mean number of days when patients randomized to the off condition turned on the generators was 4.65 days (range, 1-12 days). Follow-up examinations were conducted at one, three, six, and 12 months after nerve stimulator implantation, during which time the stimulation parameters were adjusted in order to optimize the perception of paresthesia. In addition, the patients were provided with remote controls to modify the stimulation amplitude. At baseline, the average frequency of migraines was 5.8 days per week and the median headache severity was eight on an 11-point numerical rating scale. Headache intensity and/or frequency were significantly lower in the on arm compared to the off arm and decreased from baseline to each follow-up visit in all patients with Stimulation On. For example, the number of headaches decreased from a median of 6.3 days per week in the off phase to 2.1 days per week in the on phase. The median Migraine Disability Assessment (MIDAS) score decreased from 79 at baseline to 10 at 12-month follow-up. Quality of life measured by the SF-36 significantly improved from baseline throughout the follow-up period. Use of triptans decreased from a median of 20 to three doses/month and use of nonsteroidal anti-inflammatory drug (NSAIDs) use decreased from a median of 25.5 to two doses/month. There were two infections (6.7%) and three lead migrations (10%) during the study. This study is limited by the lack of a control group during follow-up and lack of blinding, although blinding of patients may be difficult due to paresthesia with this treatment.

Silberstein (2012) published a RCT of patients diagnosed with chronic migraine (CM), implanted with a neurostimulation device and randomized 2:1 to active ( $n=105$ ) or sham ( $n=52$ ) stimulation.<sup>[7]</sup> Authors defined the primary endpoint as the difference in the percentage of responders (defined as patients that achieved a  $\geq 50\%$  reduction in mean daily visual analog scale scores) in each group at 12 weeks. A significant difference was reported at a secondary endpoint of 30% reduction; however, no difference was reported between groups at the primary endpoint of 50% reduction. At a 30% reduction, significant difference in reduction of number of headaches, migraine-related disability, and direct reports of pain relief were

reported compared to the sham group, but it is unknown if these results are clinically meaningful considering researchers did not meet their established primary endpoint of at least a 50% reduction in mean daily analog scores. In addition, the overall treatment effect was low, with only 17.1% of the active group and 13.5% of the control group classified as responders.

Results from the 52-week open-label extension of this study were published in 2014.<sup>[8]</sup> Results were reported for the intent-to-treat (ITT) population and for the 125 patients who met criteria for intractable chronic migraine. Twenty-four patients were excluded from analysis due to explantation of the system (n=18) or other loss to follow-up. Mean headache days at baseline were 21.6 for the ITT population and 24.2 for the intractable chronic migraine group. In the ITT population, headache days were reduced by 6.7 days, and a 50% or greater reduction in headache days and/or pain intensity was observed in 47.8% of patients. Sixty-eight percent of patients were satisfied with the headache relief provided by the device. Seventy percent experienced at least one of 183 device-related adverse events, of which 8.6% required hospitalization and 40.7% required surgical intervention. Eighteen percent of patients had persistent pain and/or numbness with the device.

A small industry-sponsored feasibility RCT reported preliminary safety and efficacy data on ONS for treatment of medically intractable chronic migraine (CM).<sup>[9]</sup> However, the findings from this small (n=110) and very short (follow-up=three months) study must be interpreted with caution due to the exploratory nature of the design:

- The sample size was chosen to gain experience with ONS and the study was not prospectively powered for efficacy evaluation.
- No primary end points were specified at the outset; at three months, a range of efficacy measures were evaluated in comparison to baseline.

Although the findings from this study may provide direction for future research, they do not provide reliable evidence on the clinical utility of ONS. Per the authors, “reliable conclusions regarding efficacy cannot be established on the basis of this study alone.”

## **NONRANDOMIZED STUDIES**

Evidence from nonrandomized studies of occipital nerve stimulation (ONS) for treatment of headaches is considered insufficient due to methodological limitation such as nonrandom allocation of treatment, lack of adequate comparison groups, small sample size, and short-term follow-up, all of which limit conclusions regarding the safety and effectiveness of ONS treatment.<sup>[10]</sup> Of note, several of these nonrandomized studies reported high rates of ONS revision (20-60%)<sup>[11-13]</sup> and/or complications (20-40%)<sup>[10,12,14]</sup>.

## **PRACTICE GUIDELINE SUMMARY**

### **CONGRESS OF NEUROLOGICAL SURGEONS**

A 2015 evidence-based guideline from the Congress of Neurological Surgeons states: “the use of occipital nerve stimulation is a treatment option for patients with medically refractory occipital neuralgia.”<sup>[4]</sup> The statement had a level III recommendation based on a SR of the literature that only included case series with methodological limitations.

### **NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

A 2013 National Institute for Health and Care Excellence (NICE) guideline noted that the evidence on ONS for intractable chronic migraine shows some efficacy for short-term outcomes but very little evidence about long-term outcomes.<sup>[5]</sup> With regard to safety, NICE indicated that there are risks of complications that may need further surgery. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. NICE has recommended that clinicians wanting to undertake ONS for intractable chronic migraine should ensure that patients understand the uncertainty about the procedure's safety and efficacy, and provide them with clear written information.

## SUMMARY

There is not enough research to show that occipital nerve stimulation (ONS) improves health outcomes for patients with any condition. Clinical guidelines based on research list ONS as a treatment option, but highlight the uncertainty around safety and health outcomes. Therefore, ONS is considered investigational for all indications, including but not limited to as a treatment of headache.

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15. BlueCross BlueShield Association Medical Policy Reference Manual "Occipital Nerve Stimulation." Policy No. 7.01.125

## CODES

Codes	Number	Description
		Insertion of chest wall respiratory sensor electrode or electrode array, including connection to pulse generator (List separately in addition to code for primary procedure)
	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
	64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
	64555	Percutaneous implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
	64568	Incision for implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
	64569	Revision or replacement of cranial nerve (e.g., vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
	64570	Removal of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
	64575	Incision for implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
	64585	Revision or removal of peripheral neurostimulator electrode array
	64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling
	64999	Unlisted procedure, nervous system
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulsewidth, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional;

Codes	Number	Description
		with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter, programming by physician or other qualified health care professional
	95972	;with complex spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
HCPCS	C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, non- rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator

**Date of Origin:** June 2010

## ***Adipose-derived Stem Cell Enrichment in Autologous Fat Grafting to the Breast***

**Effective:** January 1, 2020

**Next Review:** October 2020

**Last Review:** December 2019

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Autologous fat grafting to the breast has been used as an adjunct to reconstructive breast surgery, for post-mastectomy pain and irradiated skin. Adipose-derived stem cells have been proposed as a supplement to the fat graft in an attempt to improve graft survival.

### **MEDICAL POLICY CRITERIA**

**Notes:**

- This policy does not address the use of autologous fat grafting without adipose stem cell enrichment for breast reconstruction, which may be considered medically necessary.
- This policy does not address free flap autologous fat grafting with micro vascularization.
- This policy does not address the use of autologous fat tissue in aesthetic breast augmentation (i.e., cosmesis).

The use of autologous fat grafting to the breast with supplemented adipose-derived stem cells is considered **investigational**.

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

## CROSS REFERENCES

1. [Gender Affirming Interventions for Gender Dysphoria](#), Medicine, Policy No. 153
2. [Endometrial Ablation](#), Surgery, Policy No. 01
3. [Cosmetic and Reconstructive Surgery](#), Surgery, Policy No. 12
4. [Reconstructive Breast Surgery/Mastopexy, and Management of Breast Implants](#), Surgery, Policy No. 40
5. [Reduction Mammoplasty](#), Surgery, Policy No. 60

## BACKGROUND

### AUTOLOGOUS FAT GRAFTING TO THE BREAST

Autologous fat grafting to the breast has been proposed for indications which include breast augmentation and following oncologic surgery. Proposed indications following oncologic surgery include as an adjunct to reconstruction post mastectomy or lumpectomy for contour deformities and improved shape and volume of the breast, for post mastectomy pain syndrome (neuropathic pain), and for irradiated skin to soften the skin and restore it to non-irradiated appearance and consistency.

### ADIPOSE-DERIVED STEM CELLS (ADSCS)

Stem cell biology, and the related field of regenerative medicine, involves multipotent stem cells that exist within a variety of tissues, including bone marrow and adipose tissue. Studies have shown that 1 gram of adipose tissue yields approximately  $5 \times 10^3$  stem cells, which is up to 500 times greater than the number of mesenchymal stem cells in 1 gram of bone marrow.<sup>[1]</sup> Stem cells, because of their pluripotentiality and unlimited capacity for self-renewal, offer promise for tissue engineering and advances in reconstructive procedures. Adipose tissue in particular represents an abundant and easily accessible source of adipose-derived stem cells (ADSCs), which can differentiate along multiple mesodermal lineages.<sup>[1]</sup> ADSCs may allow for improved graft survival and generation of new fat tissue after transfer from another site.

This identification of several potentially beneficial therapeutic properties of ADSC has led to proposed novel techniques of fat grafting in conjunction with ADSC therapy for breast fat grafting, including the differentiation of ADSC into adipocytes as a reservoir for adipose tissue turnover, the differentiation of ADSC into endothelial cells and the subsequent increase in blood supply to the grafted fat tissue, thereby decreasing the rate of graft resorption, the release of angiogenic growth factors by ADSC and the induction of angiogenesis, protection of the graft from ischemic reperfusion injury by ADSC, and acceleration of wound healing at the recipient site.<sup>[1]</sup>

Current methods for isolating ADSCs can involve various processes, which may include centrifugation and enzymatic techniques that rely on collagenase digestion followed by centrifugal separation to isolate the stem cells from primary adipocytes. Isolated ADSCs can be expanded in monolayer on standard tissue culture plastic with a basal medium containing 10% fetal bovine serum,<sup>[2]</sup> and newly developed culture conditions provide an environment

within which the study of ADSCs can be done without the interference of animal serum. They also allow rapid expansion of autologous ADSCs in culture for use in human clinical trials. A standard expansion method has not yet been established.

Yoshimura (2008), in an effort to address the problems of unpredictability and low rates of fat graft survival, developed a technique known as cell-assisted lipotransfer (CAL), which produces autogenous fat rich in ADSCs.<sup>[3]</sup> In CAL, half of the lipoaspirate is centrifuged to obtain a fraction of concentrated ADSCs, while the other half is washed, enzymatically digested, filtered, and spun down to an ADSC-rich pellet. The latter is then mixed with the former, converting a relatively ADSC-poor aspirated fat to ADSC-enriched fat.

## REGULATORY STATUS

A point-of care system is available for concentrating ADSCs from mature fat. The Celution™ system (Cytosol Therapeutics, Inc.) is designed to transfer a patient's own adipose tissue from one part of the body to another in the same surgical procedure. The system received 510(k) marketing clearance from the U.S. Food and Drug Administration as a cell saver device. The system is cleared for the collection, concentration, washing and re-infusion of a patient's own cells for applications that may include, but are not limited to, cardiovascular, plastic and reconstructive, orthopedic, vascular, and urological surgeries and procedures.

## EVIDENCE SUMMARY

The literature on the use of fat grafting to the breast with the use of adipose-derived stem cell (ADSC) enrichment consists of retrospective cohort studies, case series, and case reports. The following is a summary of the key literature to date, including all identified case series using fat grafting to the breast with the supportive use of ADSCs.

### Systematic Reviews

In 2017, Lazole conducted a SR to evaluate the safety and efficacy of CAL. Twenty-five studies addressing fat grafting to the breast and face were included in the systematic review and 16 in the meta-analysis.<sup>[4]</sup> The fat survival rate was significantly higher with CAL than non-CAL fat graft, only for injection volumes < 100 mL. There was no significant difference between groups in frequency of multiple procedures after fat grafting. The incidence of complications was significantly higher in the CAL group.

In 2016, Zhou conducted a SR with the same purpose as the above systematic review, and included seventeen articles (n=387) for all indications, including breast.<sup>[5]</sup> For all indications combined, the pooled fat survival rate was significantly higher in the CAL group than in the nonlipotransfer group (60% vs. 45%, p=0.0096). Complication incidence was similar in the two groups. In breast fat grafting fat survival was improved by only 9% in the CAL group, which was not statistically significant. In addition, lipotransfer in breast cases was associated with a higher complication incidence compared with other indications (p<0.001).

### Nonrandomized Studies

Mazur (2018) evaluated the risk of cancer recurrence in 56 patients having the breast reconstructed with autologous ASC (transplanted as the subpopulation present in the stromal vascular fraction [SVF]).<sup>[6]</sup> Tumor recurrence in these patients was compared with tumor recurrence in 252 matched patients that did not receive breast reconstruction. Cancer

recurrence in the ASC and control groups was 3.7% and 4.13%, respectively, which was not significantly different ( $p=1.0$ ).

In 2016, Jung conducted a small single-arm, prospective study to evaluate the impact of ADSCs, using CAL, on graft survival, including five patients.<sup>[7]</sup> One year after CAL, breast volume had decreased to 47% of the initial postoperative volume. The ratio of ADSC cell count to grafted fat volume showed no correlation with graft survival. The addition of SVF cells did not appear to improve the retention of grafted fat in these patients. Skin tension may be an important factor influencing the absorption pattern of grafted fat.

In 2013, Peltoniemi conducted a prospective comparative study to evaluate if stem cell enrichment is important for success in lipofilling for cosmetic breast augmentation.<sup>[8]</sup> A total of 18 women underwent breast augmentation, with 10 of the cases including transferred lipoaspirate enriched with ADSCs using the Cytori Celution(®) system MRI-based volumetric analysis was done preoperatively and six months post-procedure. MRI analysis revealed mean graft survival was not significantly different between groups (54% in nonADSC group vs. 50% in the ADSC-enrichment patients). After centrifugation survival was not significantly different between groups (79% in nonADSC group vs. 74% in the ADSC-enrichment patients). The investigators concluded that they did not see any advantage in stem cell enrichment by the Celution(®) system in cosmetic fat transplantation to the breast.

In 2012, Pérez-Cano conducted a single-arm, prospective, multicenter clinical trial of 71 women who underwent breast conserving surgery for breast cancer and autologous adipose-derived regenerative cell (ADRC)-enriched fat grafting for reconstruction of defects  $\leq 150$  mL (the RESTORE-2 trial).<sup>[9]</sup> Trial endpoints included patient and investigator satisfaction with functional and cosmetic results and improvement in overall breast deformity at 12 months post-procedure. Female patients (18-75 years of age) presenting with partial mastectomy defects and without breast prosthesis were eligible. The RESTORE-2 protocol allowed for up to two treatment sessions and 24 patients elected to undergo a second procedure following the six-month follow-up visit. Of the 67 patients treated, 50 reported satisfaction with treatment results through 12 months. Sixty-one patients underwent radiation therapy as part of their treatment; two patients did not receive radiation and the status of radiation treatment was not known for the other four patients. Using the same metric, investigators reported satisfaction with 57 out of 67 patients. There were no serious adverse events associated with the ADRC-enriched fat graft injection procedure. There were no reported local cancer recurrences. The LENT-SOMA scale included investigator and patient assessment of post-radiation signs and symptoms. The investigators of the trial found that LENT-SOMA was insufficiently sensitive to adequately reflect the clinical improvements seen in the trial population. Patients with LENT-SOMA III and IV scores (most severe symptoms) were excluded during screening, which may have contributed to the subtle LENT-SOMA score changes observed in the trial. The investigators reported improvement from baseline through 12 months in the degree of retraction or atrophy in 29 out of 67 patients, while 34 patients had no change and four patients reported worse symptoms. Post-radiation fibrosis at 12 months was reported as improved in 29 patients, while 35 patients had no change and three patients had worse symptoms. Management of atrophy was reported as improved in 17 patients, with 48 patients having no change and two patients reporting worse symptoms. Improvement in these measures reached statistical significance. The authors concluded that future comparative studies are needed to determine the incremental benefit of ADRC-enriched fat grafting as compared to traditional fat grafting in various clinical circumstances.

In 2011, Kamakura and Ito reported on the use of ADSC enriched fat grafting for breast augmentation in a prospective, nonrandomized open-label study of 20 Japanese women.<sup>[10]</sup> After the adipose tissue was harvested by liposuction, it was processed in the Celution 800 System® to wash and isolate the adipose-derived regenerative cells and produce a fat graft enriched with the regenerative cells. Clinical outcomes measured included improvement in circumferential breast measurement from baseline state. There was improvement in circumferential breast measurement in all patients, and breast measurements were stable by three months after grafting. At nine months, the mean breast measurement had increased 3.3 cm from preoperative measurements. The procedure was well-tolerated without any serious adverse events. Postoperative cyst formation was seen in two patients.

In 2008, Yoshimura and colleagues reported on the development of CAL, in which autologous ADSCs are used in combination with lipoinjection.<sup>[3]</sup> From 2003-2007, the group performed CAL in 70 patients: in the breast in 60 patients (including eight who had breast reconstruction after mastectomy). They reported outcomes for 40 patients with healthy thoraxes and breasts who underwent CAL for purely cosmetic breast augmentation; patients undergoing breast reconstruction for an inborn anomaly or after mastectomy were not included. Nineteen of the 40 patients had been followed for more than six months, with a maximum follow-up of 42 months. The authors observed that the transplanted adipose tissue was gradually absorbed during the first two postoperative months, and the breast volume showed a minimal change thereafter. Final breast volume showed augmentation by 100 to 200 mL after a mean fat amount of 270 mL was injected. The difference in breast circumference (defined as the chest circumference at the nipple minus the chest circumference at the inframammary fold) had increased in all cases by 4 to 8 cm at six months. Cyst formation or microcalcification was detected in four patients. The authors concluded that their preliminary results suggest that CAL is effective and safe for soft tissue augmentation and superior to conventional lipoinjection but that additional study is necessary to further evaluate the efficacy of this technique.

In 2007, Rigotti reported the results of a pilot study on the presence and effectiveness of ADSCs in 20 consecutive patients undergoing therapy for adverse effects of radiation treatment to the breast, chest wall or supraclavicular region, with severe symptoms or irreversible function damage (LENT-SOMA scale grade 3 and 4). LENT-SOMA is one of the most common systems to assess the late effects of radiotherapy.<sup>[11]</sup> The mean patient age was 51 years (range, 37-71 years). The rationale behind the study was that the ADSCs, which have been shown to secrete angiogenic and antiapoptotic factors and to differentiate into endothelial cells, could promote neovascularization in ischemic tissue such as irradiated tissue. Targeted areas included the supraclavicular region, the anterior chest wall after mastectomy with or without breast prosthesis, and breast after quadrantectomy. A lipoaspirate purification procedure was performed by centrifugation to remove a large part of the triglyceride portion of the tissue and disrupt the cytoplasm of the mature adipocytes to favor their rapid clearance after injection. A stromal-vascular fraction was isolated by enzymatic digestion of extracellular matrix, centrifugation and filtration, and the fractions were cultured for two to three weeks to obtain a homogenous cell population. To assess the presence of mesenchymal stem cells, the stromal-vascular fraction derived from the adipose tissue was cultured and characterized by flow cytometry. The number of procedures was one in five patients, two in eight patients, three in six patients, and six in one patient. Clinical follow-up varied between 18 and 33 months (mean, 30 months). Clinical results after treatment with lipoaspirates were assessed by LENT-SOMA scoring. The 11 patients initially classified as LENT-SOMA grade 4 (irreversible functional damage) progressed to grade 0 (no symptoms), grade 1 and grade 2 in four, five, and one cases, respectively. In one case, no improvements were observed. In the four patients

who had undergone mastectomy and had breast prostheses and areas of skin necrosis, the necrosis showed complete remission. In the group of nine patients classified as LENT-SOMA grade 3, fibrosis, atrophy, and retraction progressed to grade 0 and 1 in five and four cases, respectively.

## PRACTICE GUIDELINE SUMMARY

### NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE (NICE)

In 2012 NICE published an evidence-based clinical practice guideline addressing breast reconstruction using lipomodelling after breast cancer treatment. Regarding the use of stem cell enrichment, it states, “ Further information about the outcomes of this and other adaptations of the technique of lipomodelling is desirable for guiding their future use in clinical management.”<sup>[12]</sup>

### AMERICAN SOCIETY OF AESTHETIC PLASTIC SURGERY AND AMERICAN SOCIETY OF PLASTIC SURGEONS<sup>[13]</sup>

A joint task force of the American Society for Aesthetic Plastic Surgery (ASAPS) and the American Society of Plastic Surgeons released a position statement on the use of stem cells in aesthetic surgery during the 2011 annual meeting of ASAPS.<sup>[13]</sup> Based on a systematic review of the peer-reviewed literature, the task force concluded that while there is potential for the future use of stem cells in aesthetic surgical procedures, the scientific evidence and other data are very limited in terms of assessing the safety or efficacy of stem cell therapies in aesthetic medicine.

## SUMMARY

The current research on the use of supplemented adipose-derived stem cells in combination with fat grafting to the breast has many limitations and is starting to show that the use of these cells does not increase graft survival or decrease resorption rates. More research is needed for the long-term effectiveness and safety of enrichment of adipose-derived stem cells in fat grafting to the breast. In addition, no evidence-based clinical practice guidelines recommend the use of adipose-derived stem cell enrichment in fat grafting to the breast. Therefore, the use of adipose-derived stem cell enrichment in conjunction with fat grafting to the breast is considered investigational.

## REFERENCES

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3. Yoshimura, K, Sato, K, Aoi, N, Kurita, M, Hirohi, T, Harii, K. Cell-assisted lipotransfer for cosmetic breast augmentation: supportive use of adipose-derived stem/stromal cells. *Aesthetic Plast Surg*. 2008 Jan;32(1):48-55; discussion 6-7. PMID: 17763894

4. Laloze, J, Varin, A, Gilhodes, J, et al. Cell-assisted lipotransfer: friend or foe in fat grafting? Systematic review and meta-analysis. *Journal of tissue engineering and regenerative medicine*. 2017 Jul 18. PMID: 28719946
5. Zhou, Y, Wang, J, Li, H, et al. Efficacy and Safety of Cell-Assisted Lipotransfer: A Systematic Review and Meta-Analysis. *Plastic and reconstructive surgery*. 2016;137:44e-57e. PMID: 26710060
6. Mazur, S, Zolocinska, A, Siennicka, K, Janik-Kosacka, K, Chrapusta, A, Pojda, Z. Safety of adipose-derived cell (stromal vascular fraction - SVF) augmentation for surgical breast reconstruction in cancer patients. *Advances in clinical and experimental medicine : official organ Wroclaw Medical University*. 2018 Aug;27(8):1085-90. PMID: 29989681
7. Jung, HK, Kim, CH, Song, SY. Prospective 1-Year Follow-Up Study of Breast Augmentation by Cell-Assisted Lipotransfer. *Aesthet Surg J*. 2016;36:179-90. PMID: 26342099
8. Peltoniemi, HH, Salmi, A, Miettinen, S, et al. Stem cell enrichment does not warrant a higher graft survival in lipofilling of the breast: a prospective comparative study. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS*. 2013 Nov;66(11):1494-503. PMID: 23845909
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11. Rigotti, G, Marchi, A, Galie, M, et al. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells. *Plastic and reconstructive surgery*. 2007 Apr 15;119(5):1409-22; discussion 23-4. PMID: 17415234
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13. American Society for Aesthetic Plastic Surgery and American Society of Plastic Surgeons. ASAPS and ASPS Issue Joint Position Statement on Stem Cells and Fat Grafting. [cited 12/6/2019]; Available from: <http://www.apspavilion.com/downloads/ASAPSandASPSIssueJointPositionStatementOnStemCellsAndFatGrafting.pdf>
14. BlueCross BlueShield Association Medical Policy Reference Manual "Adipose-Derived Stem Cells in Autologous Fat Grafting to the Breast." Policy No. 7.01.153

## CODES

**NOTE:** There is no specific code to report the use of the additional adipose-derived stem cell enrichment in autologous fat grafting. CPT indicates code 20926 is the code to report for all autologous fat grafting including reconstructive breast surgery, with or without additional adipose-derived stem cells (aka, stem cell enrichment). This code includes harvest and placement of the graft and encompasses harvesting the fat graft material by any method, closing the donor site (if indicated) and applying the appropriate dressing, processing the fat graft material, injecting the fat graft into the

recipient site, and dressing the recipient site. The procedure involves a donor site, preparation of the graft, and a recipient site. This code may be reported for any site when performed and is the only code needed to report the autogenous fat grafting procedure. (CPT Assistant Coding. October, 2016)

Codes	Number	Description
CPT	11950	Subcutaneous injection of filling material (eg, collagen); 1 cc or less
	11951	Subcutaneous injection of filling material (eg, collagen); 1.1 to 5.0 cc
	11952	Subcutaneous injection of filling material (eg, collagen); 5.1 to 10.0 cc
	11954	Subcutaneous injection of filling material (eg, collagen); over 10.0 cc
	15769	Grafting of autologous soft tissue, other, harvested by direct excision (eg, fat, dermis, fascia)
	15771	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; 50 cc or less injectate
	15772	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; each additional 50 cc injectate, or part thereof (List separately in addition to code for primary procedure)
	19366	Breast reconstruction with other technique
	19380	Revision of reconstructed breast
	19499	Unlisted procedure, breast
	<del>20926</del>	<del>Tissue grafts, other (e.g., paratenon, fat, dermis) (Deleted 1/1/2020)</del>
HCPCS	None	

**Date of Origin:** November 2011

## ***Gastroesophageal Reflux Surgery***

**Effective:** April 1, 2020

**Next Review:** December 2020

**Last Review:** February 2020

### **IMPORTANT REMINDER**

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

### **DESCRIPTION**

Surgical fundoplication involves wrapping the fundus of the stomach around the lower esophagus in order to create a high-pressure zone that reduces gastroesophageal reflux.

### **MEDICAL POLICY CRITERIA**

- I. Esophagogastric fundoplication may be considered **medically necessary** for one or more of the following:
  - A. In children and adolescents age 17 years and younger; or
  - B. In patients with pulmonary fibrosis with symptomatic or asymptomatic gastroesophageal reflux disease; or
  - C. When the procedure is performed with a paraesophageal hiatal hernia, and the paraesophageal hiatal hernia is confirmed by imaging; or
  - D. When the procedure is performed with esophageal myotomy in patients with achalasia; or
  - E. Initial esophagogastric fundoplication to treat symptomatic gastroesophageal reflux disease (e.g., heartburn, regurgitation) when all of the following criteria (1.-3.) are met:

1. Symptoms are unresponsive to lifestyle modifications as appropriate to the individual patient (e.g., weight loss for overweight or obese patients, avoidance of late meals, elevation of the head of the bed); and
  2. Medication therapy that meets one or more of the following:
    - i. A 4-month total trial of proton pump inhibitors (PPIs) is ineffective, contraindicated, or not tolerated; or
    - ii. PPIs are used for 12 or more consecutive months within the past 18 months, and surgery is considered an alternative to long-term medication use.
  3. There is objective diagnostic confirmation by either of the following:
    - i. Reflux and/or esophagitis is confirmed via endoscopy; or
    - ii. If endoscopy is normal, objective evidence of reflux should include one or more of the following:
      - a.) 24-hour ambulatory esophageal pH monitoring; or
      - b.) Barium swallow.
- F. Repeat esophagogastric fundoplication for a failed previous antireflux procedure when one or more of the following criteria are met:
1. Criteria I.E.1.-3. for initial esophagogastric fundoplication above are met; or
  2. Repeat surgery is for a documented mechanical failure of previous antireflux procedure (e.g., obstruction).
- II. Esophagogastric fundoplication is considered **not medically necessary** for the treatment of symptomatic gastroesophageal reflux disease (e.g., heartburn, regurgitation) when Criterion I. is not met.
- III. The following surgical procedures are considered **investigational** for the treatment of gastroesophageal reflux:
- A. Distal or partial gastrectomy performed with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction.
  - B. Hiatal hernia repair without current or prior fundoplication, including repair of sliding or paraesophageal hernia.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION:

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

- The specific surgical procedure and treatment plan;
- Medical records must document the following:

- symptomatic gastroesophageal reflux disease (GERD; e.g., heartburn, regurgitation, etc);
  - any lifestyle modifications attempted and the outcomes (e.g., weight loss if appropriate, avoidance of late meals or foods that cause heartburn, avoidance of activities that cause heartburn, elevation of the head, etc.);
  - medication therapies that have been attempted, and their outcomes;
  - diagnostic confirmation of reflux and/or esophagitis via endoscopy, 24-hour ambulatory esophageal pH monitoring, or barium swallow.
  - A paraesophageal hernia must be clearly documented by imaging for coverage of paraesophageal hernia repair. For example, esophagram, upper GI study, and CT scan are acceptable forms of documentation.
- Indicate if request is for an initial treatment or a repeat esophagogastric fundoplication and reason for the need to repeat the procedure (e.g., continued symptoms, mechanical failure, etc.)
  - Presence of other conditions, such as pulmonary fibrosis, hiatal hernia, achalasia, etc.

## CROSS REFERENCES

1. [Bariatric Surgery](#), Surgery, Policy No. 58
2. [Transesophageal Endoscopic Therapies for Gastroesophageal Reflux Disease \(GERD\)](#), Surgery, Policy No. 110
3. [Magnetic Esophageal Ring to Treat Gastroesophageal Reflux Disease \(GERD\)](#), Surgery, Policy No. 190
4. [Peroral Endoscopic Myotomy for Treatment of Esophageal Achalasia](#), Surgery, Policy No. 196
5. [Hiatal Hernia Repair Gastropexy](#), Reimbursement Policy, Surgery, Policy No. 104

## BACKGROUND

Gastroesophageal reflux disease (GERD) is a chronic medical condition, defined as “troublesome symptoms and/or complications” caused by reflux or regurgitation of stomach acid.<sup>[1]</sup> GERD is a common disorder; the proportion of North American adults with GERD (those who report experiencing symptoms such as heartburn or acid reflux at least once a week, or those with a physician diagnosis of GERD) is estimated to be around 19.8-20%.<sup>[2]</sup> GERD has also been associated with extraesophageal symptoms or conditions, such as cough, laryngitis, asthma and pulmonary fibrosis, although a direct causal relationship with GERD has not been established.

Standard treatment of GERD may address lifestyle modifications as appropriate to individual patients such as weight loss, smoking cessation, avoidance of specific foods that may precipitate reflux or heartburn, elevating the head of the bed, and avoiding recumbent positions until 2-3 hours after a meal.<sup>[1]</sup> When these actions are not successful, treatment generally consists of a daily regimen of proton pump inhibitors (PPIs). However, some patients with chronic GERD are unable or unwilling to continue ongoing medical treatment. For these patients, surgical treatment may be considered.

Surgical fundoplication involves wrapping the fundus of the stomach around the lower esophagus in order to create a high pressure zone that reduces gastroesophageal reflux. The fundal wrap can be either total (360 degrees) or partial (<360 degrees). Fundoplication may be performed as an open procedure but is more commonly performed laparoscopically.

## **ESOPHAGOGASTRIC FUNDOPLICATION WITH PARAESOPHAGEAL HIATAL HERNIA REPAIR**

Paraesophageal hiatal hernias, also known as Type II or III hiatal hernias, occur when the stomach, and in some cases the gastroesophageal junction (GEJ), herniates through the diaphragmatic esophageal hiatus into the mediastinum. These cases are rare compared to the more common Type I or “sliding” type hiatal hernia. Diagnosis of a “true” paraesophageal hiatal hernia is confirmed through endoscopy or imaging studies. Prophylactic surgical treatment of paraesophageal hiatal hernias is usually required as they account for most of the complications associated with hiatal hernias, including but not limited to obstruction, perforation and strangulation.<sup>[3]</sup> In some cases, patients may exhibit a paraesophageal hiatal hernia with additional symptoms of GERD, requiring not only a hiatal hernia repair, but additionally a fundoplication.<sup>[4]</sup>

### **Hiatal hernia classification**

The hiatus is an opening in the diaphragm where the distal esophagus passes through to enter the abdomen. A hiatal hernia occurs when intrabdominal contents, such as the stomach, bulge up into the chest through the hiatus. There are four types of hiatal hernias:<sup>[5]</sup>

- Type I – A hiatal hernia (type I), occurs when there is protrusion of the upper part of the stomach and esophagus (gastroesophageal junction) into the chest. This is the most common type (about 95%) of all hiatal hernias. This is also called a sliding hiatal hernia. A hiatal hernia of this type may also contain the upper segment of a sleeve gastrectomy or the pouch of a gastric band or gastric bypass. Additionally, if less than 50% of the stomach is located above the diaphragm, this is still considered a type I hiatal hernia and is not considered a paraesophageal hiatal hernia.
- Type II - A paraesophageal hernia (type II) occurs when the esophagus and the gastroesophageal junction remain in their normal location but a part of the stomach, typically the fundus, protrudes through the hiatus next to the esophagus into the chest. These ‘pure’ type II paraesophageal hiatal hernias seldom occur.
- Type III – A paraesophageal hiatal hernia (type III) occurs when there is a combination of both type I and II hiatal hernias, when the stomach and esophagus protrude into the chest AND the fundus of the stomach lies above the gastroesophageal junction and rotates along its long axis in a rolling or twisting fashion, referred to as an organo-axial torsion. A “giant” hiatal hernia is a subset of type III hiatal hernias and defined when greater than 50% of the stomach has protruded into the chest. The majority of paraesophageal hernias are type III. However, all types of paraesophageal hiatal hernias make up about 5% of hiatal hernias but account for most of the hiatal hernia complications. The complications are primarily due to interference with the blood flow from the left gastric artery to the twisted fundus.
- Type IV – A paraesophageal hiatal hernia (type IV) occurs when a structure other than the stomach, such as the large intestine, small intestine, or omentum protrude through the hiatus into the chest.

## **ESOPHAGOGASTRIC FUNDOPLICATION IN PATIENTS WITH PULMONARY FIBROSIS**

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease which is often associated with

additional comorbidities (e.g., pulmonary hypertension and gastroesophageal reflux) and symptoms (e.g., dyspnea, exercise limitation, fatigue, anxiety, mood disturbance, sleep disorders) that negatively affect patients' lives. GERD is highly prevalent in patients with IPF with up to 50% of patients with asymptomatic disease. Although the pathological significance of GERD in IPF remains uncertain, studies indicate that medical or surgical treatment of GERD may stabilize lung function and increase oxygenation.<sup>[6-9]</sup> It is hypothesized that fundoplication surgery may offer increased benefit over medication treatment by reducing acid as well as microaspirations of the gastric contents in to the lungs.<sup>[6]</sup>

Due to the complexities of IPF, treatment protocols are not rigid or standardized and often require a management approach which is tailored to the patients' specific conditions and symptoms. Nissen fundoplication surgery is one option which may be considered for treating patients with pulmonary fibrosis with symptomatic or asymptomatic GERD.

Note: This policy does not address transesophageal endoscopic therapies for GERD, which are addressed separately in Surgery Policy No. 110 (see Cross References).

## EVIDENCE SUMMARY

In order to determine whether the benefits of surgical fundoplication in patients with chronic GERD outweigh the risks, well-designed randomized controlled trials (RCTs) are necessary, comparing medical therapy (proton pump inhibitors) with surgical fundoplication and reporting on relevant clinical outcomes.

The focus of the following literature review is on systematic reviews, randomized trials published after the systematic reviews, and clinical practice guidelines.

### FUNDOPLICATION

#### Systematic Reviews

In 2018, Richter reported results from a systematic review with network meta-analysis or randomized controlled trials comparing efficacy of laparoscopic Nissen fundoplication (LNF) to proton pump inhibitors in patients with GERD.<sup>[10]</sup> The authors also compared the Nissen procedure to transoral incisionless fundoplication, which is not within the scope of this policy, but is summarized elsewhere (see Cross References). Overall, 7 trials were included, totalling 1128 patients. Network meta-analysis using Bayesian methods under random-effects multiple treatment comparisons were implemented for analysis, as well as ranking probability by surface under the cumulative ranking curve. Patients who underwent LNF had a higher probability of persistent esophagitis (0.38) than those on PPI therapy (0.19). Out of all the interventions studied, LNF had the highest probability of increasing percent time at pH <4 (0.99), followed by PPIs (0.64), and LNF also had a higher probability of increasing patients' health-related quality of life (0.66) than those on PPI therapy (0.05).

In 2010, The Cochrane Collaboration published a systematic review on medical versus surgical management for GERD in adults.<sup>[11]</sup> Included in the review were all randomized or quasi-randomized controlled trials comparing laparoscopic fundoplication with medical management; nonrandomized studies were excluded. Four trials with a total of 1232 patients were included.<sup>[12-15]</sup> All reported outcomes at one year, with only one reporting outcomes up to three years. There were no studies that followed patients longer than three years. Overall, the

authors concluded that in the short- to medium-term there is evidence that laparoscopic fundoplication is more effective than medical management.

A 2015 update concluded that there is considerable uncertainty in the balance of benefits versus harms of laparoscopic fundoplication compared to long-term medical treatment with proton pump inhibitors.<sup>[16]</sup> Four randomized controlled trials were included for meta-analysis, consisting of three studies previously reported in the 2010 review, and longer term follow-up for the Anvari study.<sup>[17]</sup> The available evidence was rated low or very low, and further high-quality studies are needed.

## Randomized Controlled Trials

In 2017, Emken reported results of a secondary analysis of an industry sponsored multicenter randomized controlled trial comparing anti-reflux surgery (open fundoplication) to proton pump inhibitor (omeprazole) therapy.<sup>[18]</sup> From the same study, 3-year trial results were described by Lundell in 2000,<sup>[19]</sup> followed by 12-year outcomes in 2009<sup>[20]</sup>. Several of the authors were former employees of the industry sponsor.

**Study design:** Three hundred and ten patients across 16 centers in 4 Nordic countries were originally enrolled in the trial, randomized in a 1:1 design (N=155 in each arm). Overall study duration was 14 years, from 1991-2005. In a pre-entry study period, all patients were treated with omeprazole 20mg twice daily with the option of increasing to 40mg if needed to achieve healing of esophageal lesions and control of symptoms. Of the 155 patients randomized to open fundoplication, 144 went on to have surgery; 129 had data available at 3-years follow-up. Of the 154 patients in the omeprazole therapy group (one dropped out prior to starting therapy), 139 had 3-year data available. The secondary analysis report (2017) included 1- and 10-year outcomes from patients who underwent surgery (N=137) and long-term treatment with omeprazole 20–60mg daily (N=108).

Outcomes from 1-, 3-, 10-, and 12-years are summarized here:

- At 3-years follow-up, the authors concluded efficacy from both approaches when omeprazole dose was adjusted over time.
- In 2009, 12-year results were available for 71 who were given omeprazole (46%) and 53 treated with surgery (37%).
  - There was no difference in percent of patients in continuous remission between treatment groups (including those who had a dose adjustment and those who did not).
  - Of the patients who underwent surgery, 38% required a change in therapeutic strategy (e.g., to medical therapy or additional surgeries), compared to 15% of those on omeprazole.
  - Adverse events: Therapies were generally well-tolerated in both groups, though heartburn and regurgitation were significantly more common in patients given omeprazole; whereas dysphagia, rectal flatulence, and the inability to belch or vomit were significantly more common in surgical patients. Over the entire follow-up period, fatal outcomes and those of heart-related cause were more common in the omeprazole group than the surgery group. Mean hemoglobin values did not change over time in either group, though mean ferritin levels increased after ten years in the medication treated group. Procedural complications were listed as more common serious adverse

events in the surgery group as compared to the omeprazole group, as expected. Authors reported no surgery-related deaths in the original study; two of the surgery patients died of heart-related causes, and two experienced non-fatal heart attacks. In the omeprazole treated group, 8 patients died of heart-related causes, and 9 experienced non-fatal heart attacks. The authors reported that an Food and Drug Administration analysis of these events concluded that baseline differences between groups may have biased the safety outcomes. For example, the median age was four years greater in the medication group, and more patients had experienced a previous heart attack in the medication group as compared to the surgery group (six and zero, respectively).

- At 1- and 10-years follow-up, data were available for 108 patients in the omeprazole group, and 137 patients in the surgery group. One hundred fourteen patients had complete data for both timepoints, and 79 had only 1-year data. There were no statistically significant differences in demographics, manometry measurements, or 24-hour pH-monitoring measurements between those with complete data versus those with only 1-year of data.
  - In those who underwent surgery, measurement of lower esophageal sphincter (LOS) function (via manometry) showed statistically significant increase in median resting pressure at 1-year, which was sustained at 10-years. There were no significant changes in resting pressure in the omeprazole group.
  - Those in the surgery group had statistically significant increases in median total and intra-abdominal length of LOS at 1- and 10-years. In the omeprazole group, the median total and intra-abdominal length of LOS did not change from baseline to the 1-year manometry, however, at 10-years the results were comparable to the surgery group.

Included in the publication of the 2015 Cochrane review, Anvari reported 3-year outcomes from a prospective RCT (one-year results were included in the 2010 Cochrane review).<sup>[17]</sup> Of note, *a priori*, a sample size of 216 was calculated for this study at a statistical significance level of  $\alpha = 0.05$ ; however only 104 participants were ultimately randomized which may have impacted the ability of the study to detect significant changes.

Of the original 104 subjects, 93 were available for the 3-year follow-up assessment. The authors reported the following outcomes:

- Improvement from baseline in GERD symptoms was significant in both the medical treatment and surgical groups. Differences between the two groups were not significant. (Primary outcome)
- Surgical patients experienced a mean of 1.35 more heartburn-free days per week compared with the medical group, a significant difference. (Primary outcome)
- Both groups demonstrated improvements in acid reflux and did not differ significantly in change from baseline. (Secondary outcome)
- The surgical group had significantly better lower esophageal sphincter pressure than the medical group. (Secondary outcome)
- With respect to global symptom control compared with baseline measurements, medically treated patients maintained their control, but the surgical patients demonstrated a statistically significant improvement from baseline. (Secondary outcome)

- Significant improvements in quality of life scores were also seen in the surgical group compared with the medical group. (Secondary outcome)
- 6 (11.8%) patients in the surgical group and 8 (16%) patients in the medical group failed their primary treatment.
- No adverse events were reported in the medical treatment group. In the surgical group:
  - There were no intraoperative complications, major morbidities, or mortality
  - 7 patients experienced minor postoperative complications
  - 4 patients reported dysphagia; 7 reported postprandial bloating at 3 months
  - 2 patients required dilation of the wrap

## **SURGICAL TREATMENT OF GERD PATIENTS WITH PULMONARY FIBROSIS**

Current evidence regarding fundoplication in patients with pulmonary fibrosis (PF) mainly consist of case series<sup>[21-23]</sup> and review articles, which indicated that silent reflux, or asymptomatic GERD, occurs in about one third of PF patients.<sup>[7,9]</sup> Only a single case series was identified regarding the efficacy of reflux surgery in patients with idiopathic PF (IPF) and GERD symptoms who were awaiting lung transplant:

In 2006, Linden and colleagues evaluated Laparoscopic fundoplication in patients with GERD symptoms and end-stage lung disease awaiting transplantation.<sup>[8]</sup> Of 149 patients on the transplant wait list, 19 were identified as having a history of reflux and of those, 14 were diagnosed with IPF. All 14 IPF patients underwent a Nissen fundoplication and were compared to 31 patients with IPF on the transplant list who did not have fundoplication surgery. No perioperative complications or decreases in lung function were reported over a mean 15-month follow-up period. Authors reported that, "patients with idiopathic pulmonary fibrosis treated with fundoplication had stable oxygen requirements, whereas control patients with idiopathic pulmonary fibrosis on the waiting list had a statistically significant deterioration in oxygen requirement."

Overall, the evidence regarding Nissen fundoplication as a treatment of gastrointestinal reflux disease (GERD) in patients with pulmonary fibrosis (PF) is limited; however, treatment of PF is often tailored to treat a patients' specific condition and symptoms. Potential benefits of fundoplication surgery in PF patients include improved oxygenation and reduction of acid and microaspiration into the lungs. Considering no standardized treatment protocol for patients with PF if available, Nissen fundoplication surgery may be considered in patients with symptomatic or asymptomatic GERD to reduce acid reflux and microaspirations to the lungs.

## **GASTRECTOMY**

Gastrectomy involves a partial or full surgical removal of the stomach and is most often performed to treat cancer, non-cancerous tumors, perforation, polyps, ulcers, or obesity. In order to determine whether the benefits of surgical gastrectomy in patients with chronic GERD outweigh the risks, well-designed RCTs are necessary, comparing gastrectomy to medical therapy and accepted surgical interventions (fundoplication).

## **Systematic Reviews and Randomized Controlled Trials**

In 2016, Oor published results of a systematic review and meta-analysis of 33 studies examining the impact of laparoscopic sleeve gastrectomy on prevalence of GERD.<sup>[24]</sup> Pooled data from seven studies using validated symptom questionnaires for new-onset of GERD

symptoms resulted in a 20% incidence following LSG (follow-up time ranging from one- to 60-months). There was heterogeneity amongst these studies ( $I^2=68\%$ ). For difference in prevalence of GERD before and after LSG, as reported by questionnaire, the pooled risk difference was found to be 4.3%; with heterogeneity present ( $I^2=89\%$ ). Of the 24 studies reviewed, the authors found new-onset GERD symptom incidence to range from zero to 34.9%. Data for new-onset esophagitis, changes in the use of antireflux medication, 24-hour pH monitoring, manometry, and combined pH-impedance results could not be pooled. The authors therefore concluded that LSG could induce serious GERD symptoms in patients with no preoperative GERD complaints. The heterogeneity found in analyses may be due to a lack of a standardized approach to LSG, as well as the variability in follow-up length. The authors also noted that range in prevalence of GERD symptoms may be in part due to the variability in reported preoperative BMI, as the LSG will be a more technically challenging procedure in those with a BMI of 60 kg/m<sup>2</sup> versus those with a BMI of 40 kg/m<sup>2</sup>.

### **Nonrandomized Studies**

Current evidence regarding the use of distal, partial or complete gastrectomy with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction as a treatment of gastric reflux disease consists of small case series.<sup>[25-27]</sup> These studies do not permit conclusions due to the small sample size, lack of a control group, differences in patient characteristics and surgical techniques, and other methodological limitations. In addition, several studies<sup>[27-31]</sup> were identified which reported on GERD reduction after sleeve gastrectomy in obese patients; however, the primary focus of these studies was on weight reduction and the reduction of GERD symptoms was a secondary outcome. In order to isolate the direct effects of gastrectomy upon chronic GERD symptoms, well-designed RCTs are required which compare health outcomes of patients treated with gastrectomy versus medication or fundoplication.

### **HIATAL HERNIA REPAIR WITHOUT FUNDOPLICATION**

Several studies were identified which reported an improvement in GERD symptoms associated with sliding type hernia repair; however, no studies were identified which evaluated the use of hiatal hernia repair as an independent treatment of gastric reflux disease.

## **PRACTICE GUIDELINE SUMMARY**

Three evidence-based clinical practice guidelines address surgical treatment of GERD. These guidelines offer differing recommendations concerning indications for surgery. No evidence-based clinical practice guidelines were identified which recommend fundoplication surgery as a treatment of GERD in patients with pulmonary fibrosis. In addition, no evidence-based clinical practice guidelines were identified which address the use of gastrectomy or hiatal hernia repair as a treatment of GERD.

### **SOCIETY OF AMERICAN GASTROINTESTINAL AND ENDOSCOPIC SURGEONS**

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines recommend surgical therapy when the diagnosis of reflux is objectively confirmed, in individuals who:<sup>[32]</sup>

- 1) have failed medical management (inadequate symptom control, severe regurgitation not controlled with acid suppression, or medication side effects)

OR

- 2) opt for surgery despite successful medical management (due to quality of life considerations, lifelong need for medication intake, expense of medications, etc.)

OR

- 3) have complications of GERD (e.g., Barrett's esophagus, peptic stricture)

OR

- 4) have extra-esophageal manifestations (asthma, hoarseness, cough, chest pain, aspiration)

“Surgical therapy for GERD is an equally effective alternative to medical therapy and should be offered to appropriately selected patients by appropriately skilled surgeons (Grade A\*). Surgical therapy effectively addresses the mechanical issues associated with the disease and results in long-term patient satisfaction (Grade A). For surgery to compete with medical treatment, it has to be associated with minimal morbidity and cost.”

#### *\*Definitions*

- Grade A: “Based on high level (Level I or II), well-performed studies with uniform interpretation and conclusions by the expert panels”
- Level I Evidence: “Evidence from properly conducted randomized, controlled trials
- Level II Evidence: “Evidence from controlled trials without randomization; cohort or case-control studies; multiple time series; dramatic uncontrolled experiments

## **AMERICAN GASTROENTEROLOGICAL ASSOCIATION**

In 2008, the American Gastroenterological Association (AGA) published a guideline regarding the management of gastroesophageal reflux disease which made the following recommendations:<sup>[1]</sup>

- “When antireflux surgery and PPI therapy are judged to offer similar efficacy in a patient with an esophageal GERD syndrome, PPI therapy should be recommended as initial therapy because of superior safety.” (Grade A\*\*)
- “When a patient with an esophageal GERD syndrome is responsive to, but intolerant of, acid suppressive therapy, antireflux surgery should be recommended as an alternative.” (Grade A)
- Antireflux surgery is recommended “for patients with an esophageal GERD syndrome with persistent troublesome symptoms, especially troublesome regurgitation, despite PPI therapy. The potential benefits of antireflux surgery should be weighed against the deleterious effect of new symptoms consequent from surgery, particularly dysphagia, flatulence, an inability to belch, and postsurgery bowel symptoms.” (Grade B\*\*)
- “Patients with an extraesophageal GERD syndrome with persistent troublesome symptoms despite PPI therapy should be considered for antireflux surgery. The potential benefits of antireflux surgery should be weighed against the deleterious effect of new symptoms consequent from surgery, particularly dysphagia, flatulence, an inability to belch, and postsurgery bowel symptoms.” (Grade C\*\*)
- The AGA recommends against antireflux surgery (Grade D\*\*):
  - “for patients with an esophageal syndrome with or without tissue damage who are symptomatically well controlled on medical therapy.”
  - “as an antineoplastic measure in patients with Barrett's metaplasia.”

#### *\*\*Definitions*

- Grade A: “strongly recommended based on good evidence that it improves important health outcomes.”
- Grade B: “recommended with fair evidence that it improves important outcomes”
- Grade C: “balance of benefits and harms is too close to justify a general recommendation”
- Grade D: “recommend against, fair evidence that it is ineffective or harms outweigh benefits”

## AMERICAN COLLEGE OF GASTROENTEROLOGY

In 2013, the American College of Gastroenterology (ACG) issued a guideline for the diagnosis and management of gastroesophageal reflux disease and made numerous recommendations regarding the management and surgical options for GERD.<sup>[33]</sup> The following are some of the major recommendations regarding PPI use and fundoplication:

- In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief. (Conditional recommendation, low level evidence)
- Surgical therapy is a treatment option for long-term therapy in GERD patients. (Strong recommendation, high level of evidence)
- Surgical therapy is generally not recommended in patients who do not respond to PPI therapy. (Strong recommendation, high level of evidence)
- Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon. (Strong recommendation, high level of evidence)

### \*\*Definitions

- The strength of a recommendation was graded as "strong" when the desirable effects of an intervention clearly outweigh the undesirable effects and as "conditional" when there is uncertainty about the trade-offs.
- The level of evidence could range from "high" (implying that further research was unlikely to change the authors' confidence in the estimate of the effect) to "moderate" (further research would be likely to have an impact on the confidence in the estimate of effect) or "low" (further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the estimate).

## SUMMARY

### ESOPHAGOGASTRIC FUNDOPLICATION

There is enough research to show that initial or repeat esophagogastric fundoplication improves symptomatic gastroesophageal reflux disease (GERD) for most patients with chronic GERD who have tried lifestyle changes and long-term use of proton pump inhibitors (PPIs), or in those with a documented mechanical failure from a previous antireflux procedure. It appears that initial or repeat esophagogastric fundoplication may also improve symptoms in patients with pulmonary fibrosis. When esophagogastric fundoplication is performed with a paraesophageal hiatal hernia repair, patients with a paraesophageal type of hiatal hernia may also benefit. Patients with achalasia may also have improved health

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outcomes when esophagogastric fundoplication is performed with an esophageal myotomy. Clinical guidelines based on research recommend fundoplication for select patients. Therefore, initial or repeat esophagogastric fundoplication may be considered medically necessary when policy criteria are met.

There is not enough research to show that initial or repeat esophagogastric fundoplication for GERD improves health outcomes when policy criteria are not met. Therefore, initial or repeat esophagogastric fundoplication for GERD when policy criteria are not met is considered not medically necessary.

## **GASTRECTOMY**

There is not enough research to show that distal, partial or complete gastrectomy with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction improves health outcomes for people with gastrointestinal reflux disease (GERD). No clinical practice guidelines based on research recommend gastrectomy for people with GERD. Therefore, distal, partial or complete gastrectomy with or without gastroduodenostomy, gastrojejunostomy, or Roux-en-Y reconstruction is considered investigational as a treatment of GERD.

## **HIATAL HERNIA REPAIR WITHOUT FUNDOPLICATION**

There is not enough research to show that hiatal hernia repair without fundoplication, including repair of sliding or paraesophageal hernia, improves health outcomes for people with gastrointestinal reflux disease (GERD). No clinical practice guidelines based on research recommend independent hiatal hernia repair as a treatment for GERD. Therefore hiatal hernia repair without fundoplication is considered investigational as an independent treatment of GERD.

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## CODES

### NOTES:

- Repair of the typical Type I hiatal hernia cannot be coded by a paraesophageal hernia repair code per CPT code definitions.
- The paraesophageal hiatal hernia repair codes cannot be reported unless a paraesophageal hiatal hernia is clearly documented.
- CPT 43280 cannot be reported unless a fundoplication is performed.
- There are related procedures without specific CPT codes, including sliding hiatal hernia repair and the Hill procedure, and these are reported by unlisted codes.

Codes	Number	Description
CPT	43279	Laparoscopy, surgical, esophagomyotomy (Heller type), with fundoplasty, when performed
	43280	Laparoscopy, surgical, esophagogastric fundoplasty (eg, Nissen, Toupet procedures)
	43281	Laparoscopy, surgical, repair of paraesophageal hernia, includes fundoplasty, when performed; without implantation of mesh
	43282	; with implantation of mesh
	43325	Esophagogastric fundoplasty; with fundic patch (Thal-Nissen procedure)
	43327	Esophagogastric fundoplasty partial or complete; laparotomy
	43328	;thoracotomy
	43332	Repair, paraesophageal hiatal hernia (including fundoplication), via laparotomy, except neonatal; without implantation of mesh or other prosthesis
	43333	; with implantation of mesh or other prosthesis
	43334	Repair, paraesophageal hiatal hernia (including fundoplication), via thoracotomy, except neonatal; without implantation of mesh or other prosthesis
	43335	; with implantation of mesh or other prosthesis
	43336	Repair, paraesophageal hiatal hernia (including fundoplication), via thoracoabdominal incision, except neonatal; without implantation of mesh or other prosthesis
	43337	; with implantation of mesh or other prosthesis
	43338	Esophageal lengthening procedure (eg, Collis gastroplasty or wedge gastroplasty) (List separately in addition to code for primary procedure)
	43631	Gastrectomy, partial, distal; with gastroduodenostomy
	43632	;with gastrojejunostomy
	43633	;with roux-en-Y reconstruction
	43634	;with formation of intestinal pouch
HCPCS	None	

**Date of Origin:** November 2012

## ***Microwave Tumor Ablation***

**Effective:** March 1, 2020

**Next Review:** November 2020

**Last Review:** January 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Microwave ablation (MWA) uses microwave thermal energy to create thermal coagulation and localized tissue necrosis. MWA is proposed as a treatment of tumors, palliate symptoms.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy does not address liver tumors (primary or metastatic). See Cross References.

- I. Microwave ablation may be considered **medically necessary** to treat tumors when one or more of the following criteria are met:
  - A. Isolated peripheral non-small cell lung cancer (NSCLC) lesion that is no more than 3 cm in size when both of the following criteria are met:
    1. Surgical resection or radiation treatment with curative intent is considered appropriate based on stage of disease, however, medical co-morbidity renders the individual unfit for those interventions; and
    2. Tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.

- B. Malignant non-pulmonary tumor(s) metastatic to the lung that are no more than 3 cm in size when all of the following criteria (1 – 3) are met:
1. In order to preserve lung function when surgical resection or radiation treatment is likely to substantially worsen pulmonary status, or the patient is not considered a surgical candidate; and
  2. There is no evidence of extrapulmonary metastases; and
  3. The tumor is located at least 1 cm from the trachea, main bronchi, esophagus, aorta, aortic arch branches, pulmonary artery and the heart.
- II. Microwave ablation is considered **investigational** as a technique for ablating all other benign or malignant tumors other than liver tumors that do not meet the policy criteria above.

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

## CROSS REFERENCES

1. [Radioembolization, Transarterial Embolization \(TAE\), and Transarterial Chemoembolization \(TACE\)](#), Medicine, Policy No. 140
2. [Radiofrequency Ablation \(RFA\) of Tumors Other than Liver](#), Surgery, Policy No. 92
3. [Cryosurgical Ablation of Miscellaneous Solid Organ and Breast Tumors](#), Surgery, Policy No. 132
4. [Magnetic Resonance \(MR\) Guided Focused Ultrasound \(MRgFUS\) and High Intensity Focused Ultrasound \(HIFU\) Ablation](#), Surgery, Policy No. 139
5. [Ablation of Primary and Metastatic Liver Tumors](#), Surgery, Policy No. 204

## BACKGROUND

### MICROWAVE ABLATION

MWA is a technique in which the use of microwave energy induces an ultra-high speed, 915 MHz or 2.450 MHz (2.45 GHz), alternating electric field which causes water molecule rotation and the creation of heat. This results in thermal coagulation and localized tissue necrosis. In MWA, a single microwave antenna or multiple antennas connected to a generator are inserted directly into the tumor or tissue to be ablated; energy from the antennas generates friction and heat. The local heat coagulates the tissue adjacent to the probe, resulting in a small, approximately 2-3 cm elliptical area (5 x 3 cm) of tissue ablation. In tumors greater than 2 cm in diameter, 2-3 antennas may be used simultaneously to increase the targeted area of MWA and shorten operative time. Multiple antennas may also be used simultaneously to ablate multiple tumors. Tissue ablation occurs quickly, within one minute after a pulse of energy, and multiple pulses may be delivered within a treatment session depending on the size of the tumor. The cells killed by MWA are typically not removed but are gradually replaced by fibrosis and scar tissue. If there is local recurrence, it occurs at the edges. Treatment may be repeated as needed. MWA may be used to: 1) control local tumor growth and prevent recurrence; 2) palliate symptoms; and 3) extend survival duration.

Complications from MWA are usually considered mild and may include pain and fever. Other potential complications associated with MWA include those caused by heat damage to normal tissue adjacent to the tumor (e.g., intestinal damage during MWA of the kidney or liver), structural damage along the probe track (e.g., pneumothorax as a consequence of

procedures on the lung), liver enzyme elevation, liver abscess, ascites, pleural effusion, diaphragm injury or secondary tumors if cells seed during probe removal. MWA should be avoided in pregnant patients since potential risks to the patient and/or fetus have not been established and in patients with implanted electronic devices such as implantable pacemakers that may be adversely affected by microwave power output.

MWA is an ablative technique similar to radiofrequency or cryosurgical ablation; however, MWA may have some advantages. In MWA, the heating process is active, which produces higher temperatures than the passive heating of radiofrequency ablation and should allow for more complete thermal ablation in a shorter period of time. The higher temperatures reached with MWA (over 100° C) can overcome the “heat sink” effect in which tissue cooling occurs from nearby blood flow in large vessels potentially resulting in incomplete tumor ablation. MWA does not rely on the conduction of electricity for heating, and therefore, does not have electrical current flow through patients and does not require grounding pads be used during the procedure to prevent skin burns. Unlike radiofrequency ablation, MWA does not produce electric noise, which allows ultrasound guidance to occur during the procedure without interference. Finally, MWA can be completed in less time than radiofrequency ablation since multiple antennas can be used simultaneously.

## **APPLICATIONS**

MWA was first used percutaneously in 1986 as an adjunct to liver biopsy. Since then, MWA has been used to ablate tumors and tissue to treat many conditions including hepatocellular carcinoma, breast cancer, colorectal cancer metastatic to the liver, renal cell carcinoma, renal hamartoma, adrenal malignant carcinoma, non-small-cell lung cancer, intrahepatic primary cholangiocarcinoma, secondary splenomegaly and hypersplenism, abdominal tumors, and other tumors not amenable to resection. Well-established local or systemic treatment alternatives are available for each of these malignancies. The potential advantages of MWA for these cancers include improved local control and other advantages common to any minimally invasive procedure (eg, preserving normal organ tissue, decreasing morbidity, shortening length of hospitalization). MWA also has been investigated as a treatment for unresectable hepatic tumors, as both primary and palliative treatment, and as a bridge to liver transplant. In the latter setting, MWA is being assessed to determine whether it can reduce the incidence of tumor progression while awaiting transplantation and thus maintain a patient’s candidacy while awaiting a liver transplant.

## **REGULATORY STATUS**

There are several devices cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for MWA. Covidien’s (a subsidiary of Tyco Healthcare) Evident Microwave Ablation System has 510(k) clearance for soft tissue ablation, including partial or complete ablation of non-resectable liver tumors. The following devices have 510(k) clearance for MWA of (unspecified) soft tissue:

- BSD Medical Corporation’s MicroThermX® Microwave Ablation System (MTX-180);
- Valleylab’s (a subsidiary of Covidien) VivaWave™ Microwave Ablation System;
- Vivant’s (acquired by Valleylab in 2005) Tri-Loop™ Microwave Ablation Probe;
- MicroSurgeon Microwave Soft Tissue Ablation Device;
- Microsulis Medical’s Acculis Accu2i;
- Microsulis Americas, Inc’s Microsulis Tissue Ablation System;
- MedWaves Microwave Coagulation/Ablation System;

- Covidien's Emprint™ Ablation System and Emprint™ SX Ablation Platform with Thermosphere™ Technology;
- Angiodynamics' Solero Microwave Tissue Ablation System;
- Surgnova Healthcare Technologies' Microwave Ablation System; and
- NeuWave Medical's Certus 140™ Ablation System and NEUWAVE Flex Microwave Ablation System

FDA determined that these devices were substantially equivalent to existing radiofrequency and MWA devices. FDA product code: NEY.

## EVIDENCE SUMMARY

The principal health outcomes associated with treatment of malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment.

In order to understand the impact of microwave ablation (MWA) on these outcomes, well-designed randomized controlled trials (RCTs) are needed that compare this therapy with standard medical and/or surgical treatment of primary and metastatic tumors.

### BREAST

#### SYSTEMATIC REVIEWS

A 2017 systematic review of imaging-guided breast cancer treatments by Mauri compared technical success, efficacy, and complications.<sup>[1]</sup> 1,156 patients and 1,168 lesions were included in the analysis. The results showed that the microwave technique had the lowest technical success (93%) amongst the techniques that were analyzed including laser (98%), HIFU (96%), radiofrequency (96%), and cryoablation (75%). Additionally, there were significant differences and heterogeneity in the technical efficacy of the methods used.

A 2010 review of ablation techniques by Zhao for breast cancer found only 0-8% of breast tumors were completely ablated with microwave ablation (MWA).<sup>[2]</sup> The authors noted that studies identified for the review were mostly feasibility and pilot studies conducted in research settings.

#### NONRANDOMIZED STUDIES

In 2012, Zhou reported on 41 patients treated with MWA directly followed by mastectomy for single breast tumors with a mean volume of 5.26 cm + 3.8 (range, 0.09 to 14.14 cm).<sup>[3]</sup> Complete tumor ablation was found by microscopic evaluation in 37 of the 41 tumors ablated (90%; 95% confidence interval [CI]: 76.9-97.3%). Reversible thermal injuries to the skin and pectoralis major muscle occurred in three patients. Results from this study should be met with caution due to its small sample size and lack of comparison group.

### LUNG

#### SYSTEMATIC REVIEWS

Three recent systematic reviews have compared MWA to RFA for lung cancer.

Nelson (2019) included 12 retrospective observational studies of MWA in patients with primary or metastatic lung tumors.<sup>[4]</sup> The reviewers did not pool results due to clinical and methodological heterogeneity across the studies. The studies varied with regard to patient characteristics (tumor size, histology, number of treated nodules), outcome measures, and technical experience of surgeons performing the procedures. The primary outcome was local recurrence, and survival outcomes were not assessed. Overall, local recurrence rates ranged from 9% to 37% across the studies. Newer reports and those that targeted smaller tumors showed more favorable efficacy rates. Results in patients with multiple tumors were not reported separately. Four studies reported results by tumor size; the local recurrence rate for large tumors (> 3 or 4cm depending on the study) were 50%, 75%, 36%, and 26%. In the same four studies, for small tumors (<3 or 3.5 cm depending on the study), local recurrence rates were 19%, 18%, 18%, and 5%, respectively. The most frequent adverse event with MWA was a pneumothorax requiring a chest tube. The reviewers concluded that MWA may be a useful tool in selected patients who are not ideal surgical candidates.

In a meta-analysis of observational studies, Yuan (2019) found higher overall survival for patients who received RFA compared to those who received MWA.<sup>[5]</sup> However, these estimates were not directly comparable because they came from different sets of studies, and the reviewers concluded that percutaneous RFA and MWA were both effective with a high safety profile. The studies used different patient eligibility criteria (e.g., tumor size, lesion number, age, follow-up). Subgroup analyses by tumor size or tumor number were not possible from the data reported.

Jiang (2018) conducted a network meta-analysis to determine the effectiveness of different ablation techniques in patients with lung tumors.<sup>[6]</sup> Tumor size, stage of disease, and primary versus metastatic disease were not accounted for in the analysis. For MWA, weighted average overall survival rates were 82.5%, 54.6%, 35.7%, 29.6%, and 16.6% at one, two, three, four, and five years, respectively. According to the meta-analysis, RFA and MWA were more effective in decreasing the progression rate of lung malignancies than cryoablation (OR 0.04, 95% CI 0.002 to 0.38, p=0.005 and OR 0.02, 95% CI 0.002 to 0.24, p=0.001, respectively). Major complications were not significantly different between RFA, MWA, and cryoablation (p>0.05).

## **RANDOMIZED CONTROLLED TRIAL**

In a 2017 RCT published by Macchi, 52 patients were randomized into a radiofrequency ablation group or a microwave ablation group.<sup>[7]</sup> Within each group, the technical and clinical success were measured along with survival and complication rates. The radiofrequency ablation group saw significant reduction in tumor size between 6 and 12 months and the microwave ablation group saw a significant reduction in tumor size from pre-therapy to 12 months including from 6-12 months. There was no significant difference in survival between the groups. The authors reported that the microwave ablation group experienced less pain than the radiofrequency ablation group (p=0.0043).

## **NONRANDOMIZED STUDIES**

Das (2020) performed a retrospective analysis to compare the safety and efficacy of cryoablation and MWA for the treatment of NSCLC.<sup>[8]</sup> Patients who were treated with microwave ablation (n=56) or cryoablation (n=45) for stage IIIB or IV NSCLC were included. The primary endpoint was PFS, which was not significantly different between groups (10 months for cryoablation versus 11 months for MWA; p=0.36). The secondary endpoints were

OS (27.5 months for cryoablation versus 18 months for MWA;  $p=0.07$ ) and adverse events ( $p>0.05$ ). Dividing the group by tumor size showed that for large tumors ( $>3$  cm;  $p=0.04$ ), but not for small tumors ( $\leq 3$  cm;  $p=0.79$ ), the microwave ablation group had significantly longer median PFS.

Aufranc (2019) reported the efficacy and complication rate of cryoablation and MWA for the treatment of primary and secondary lung tumors.<sup>[9]</sup> The authors performed a retrospective analysis of 115 patients with primary ( $n=41$ ) or secondary ( $n=119$ ) lung tumors. Mean overall follow-up was 488 days. Ablation volumes, local recurrence, and mean length of hospital stay were not significantly different between groups at one month ( $24.1\pm 21.7$  cm<sup>3</sup> for RFA and  $30.2\pm 35.9$  cm<sup>3</sup> for MWA;  $p=0.195$ ; 6/79 in the radiofrequency group and 3/81 in the MWA group;  $p=0.049$ ;  $4.5\pm 3.7$  days for RFA and  $4.7\pm 4.6$  days for MWA;  $p=0.76$ ). However, the difference in pneumothoraces between groups was statistically significant (32/79 for radiofrequency and 20/81 for MWA;  $p=0.049$ ).

In 2016, Vogl evaluated local tumor control, time to tumor progression, and survival rates among patients with lung metastatic colorectal cancer who underwent ablation therapy ( $N=109$ ) performed using laser-induced thermotherapy (LITT), radiofrequency ablation (RFA), or microwave ablation (MWA).<sup>[10]</sup> Twenty-one patients underwent LITT (31 ablations), 41 patients underwent RFA (75 ablations), and 47 patients underwent MWA (125 ablations). Local tumor control was achieved in 17 of 25 lesions (68.0%) treated with LITT, 45 of 65 lesions (69.2%) treated with RFA, and 91 of 103 lesions (88.3%) treated with MWA. The progression-free survival rate at one, two, three, and four years was 96.8%, 52.7%, 24.0%, and 19.1%, respectively, for patients who underwent LITT; 77.3%, 50.2%, 30.8%, and 16.4%, respectively, for patients who underwent RFA; and 54.6%, 29.1%, 10.0%, and 1.0%, respectively, for patients who underwent MWA, with no statistically significant difference noted among the three ablation methods.

Other evidence regarding MWA for lung tumors is limited to nonrandomized retrospective studies.<sup>[11-24]</sup> These studies all have limitations, including lack of comparison group, small sample size, short-term follow-up. Larger studies with a randomized design are needed to isolate the effect of MWA upon PFS and OS in patients with lung cancer.

## PRIMARY RENAL TUMORS

### SYSTEMATIC REVIEWS

In a 2014 systematic review and meta-analysis, Katsanos compared thermal ablation (MWA and RFA) with surgical nephrectomy for small renal tumors (mean size 2.5 cm).<sup>[25]</sup> Included in the analysis were one randomized study<sup>[26]</sup> on MWA and five cohort studies on RFA with a total of 587 patients. In the ablation group, the complication rates and renal function decline were significantly lower than in the nephrectomy group ( $p=0.04$  and  $p=0.03$ , respectively). The local recurrence rate was 3.6% in both groups (risk ratio=0.92, 95% CI, 0.4 to 2.14,  $p=0.79$ ) and disease-free survival up to five years was not significantly different between groups (hazard ratio=1.04, 95% CI, 0.48 to 2.24,  $p=0.92$ ). The authors indicated additional RCTs were needed to compare MWA to nephrectomy and other ablative techniques.

Martin (2013) reported on a meta-analysis of MWA versus cryoablation for small renal tumors in 2013.<sup>[27]</sup> Included in the analysis were seven MWA studies ( $n=164$ ) and 44 cryoablation studies ( $n=2989$ ). The studies were prospective or retrospective, nonrandomized, noncomparative studies. The mean follow-up duration was shorter for MWA than cryoablation

(17.86 months vs 30.22 months,  $p=0.07$ ). While the mean tumor size was significantly larger in the MWA studies than the cryoablation studies (2.58 cm vs 3.13 cm, respectively,  $p=0.04$ ), local tumor progression (4.07% vs 2.53%, respectively;  $p=0.46$ ), and progression to metastatic disease (0.8% vs 0%, respectively;  $p=0.12$ ) were not significantly different.

## **RANDOMIZED CONTROLLED TRIALS**

In 2012, Guan reported on a prospective randomized study to compare the use of MWA to partial nephrectomy (the gold standard of nephron-sparing surgical resection) for solitary renal tumors less than 4 cm.<sup>[26]</sup> Forty-eight patients received MWA and 54 had partial nephrectomy. Patients in the MWA group had significantly fewer postoperative complications than the partial nephrectomy group (6 [23.5%] vs. 18 [33.3%];  $p=0.0187$ ). MWA patients also had significantly less postoperative renal function declines ( $p=0.0092$ ) and estimated perioperative blood loss ( $p=0.0002$ ) than partial nephrectomy patients. At last follow-up, estimated glomerular filtration rate declines in both groups were similar ( $p=1.0000$ ). Disease-specific deaths did not occur and overall local recurrence-free survival by Kaplan-Meier estimates at three years were 91.3% for MWA and 96.0% for partial nephrectomy ( $p=0.5414$ ). Studies with longer follow-up are needed in order to assess the benefits of MWA compared to nephrectomy.

## **NONRANDOMIZED STUDIES**

Shapiro (2020) compared outcomes in patients with clinical T1b renal cell carcinoma treated with MWA, partial nephrectomy, or radical nephrectomy.<sup>[28]</sup> A retrospective analysis was completed of 40 MWA, 74 partial nephrectomy, and 211 radical nephrectomy patients. Median follow-up was 34, 35, and 49 months for MWA, partial nephrectomy, and radical nephrectomy, respectively. The decrease in post-treatment estimated glomerular filtration rate was significantly greater in radical nephrectomy patients (29%,  $p<0.001$ ) than partial nephrectomy (3.2%) or microwave ablation (4.5%). The local recurrence rates were 5%, 1.4%, and 0.5% in the MWA, partial nephrectomy, and radical nephrectomy treatment groups, respectively. The estimated five-year local recurrence-free survival rates were 94.5%, 97.9%, and 99.2% for the MWA, partial nephrectomy, and radical nephrectomy treatment groups, respectively. Although the estimated five-year local recurrence-free survival rate was significantly lower for the MWA group, after a univariable Cox regression, local recurrence was not associated with microwave ablation treatment.

De Cobelli (2019) performed a retrospective evaluation of the comparative safety and effectiveness of cryoablation and MWA for the treatment of T1a renal tumors.<sup>[29]</sup> T1a renal cancer patients with either a contraindication to surgery or a refusal of surgery were treated at a single center for with either cryoablation ( $n=44$ ) or MWA ( $n=28$ ). Median follow-up was 20 and 22 months, for cryoablation and MWA, respectively. Technical success, defined as the absence of arterial enhancement in the ablation zone at the one-month cross-sectional imaging, was not significantly different between groups (92% vs. 94% for cryoablation and MWA, respectively;  $p=0.8$ ), nor was the occurrence of complications (cryoablation 5/51, MWA 2/32;  $p=0.57$ ), or disease recurrence (cryoablation 3/47, MWA 1/30;  $p=0.06$ ). The median procedure time was significantly lower in the MWA group (110 min. and 40 min. for cryoablation and MWA, respectively;  $p=0.003$ ).

Zhou (2019) compared the outcomes following three ablation techniques for the treatment of T1a biopsy-proven renal cell carcinoma.<sup>[30]</sup> A total of 297 patients were treated with radiofrequency ablation ( $n=244$ ), cryoablation ( $n=26$ ), and MWA ( $n=27$ ). They were retrospectively assessed for adverse events, treatment efficacy, and therapeutic outcomes.

Technical success rates were not significantly different between groups ( $p=0.33$ ). The authors reported that primary efficacy one month following ablation was more likely following RF ablation and MW ablation than cryoablation. At the two-year follow-up, there were no reports of local recurrence, metastatic progression, or renal cell carcinoma-related deaths in any treatment group. Also at two years, there was also no significant change in estimated glomerular filtration rate compared with baseline ( $p=0.71$ ).

Additional evidence regarding MWA treatment in patients with primary renal tumors primarily consists of several nonrandomized case studies, all of which are limited by lack of comparison and small sample size.<sup>[31-36]</sup> In addition, one study was also limited by short-term follow-up.<sup>[32]</sup>

## OTHER TUMORS OR CONDITIONS

Nonrandomized studies of MWA for other indications are limited by lack of comparison group. Examples of other indications include adrenal carcinoma,<sup>[37]</sup> oligometastases,<sup>[38]</sup> bone tumors,<sup>[39]</sup> benign thyroid tumors,<sup>[40,41]</sup> pancreatic cancer<sup>[42]</sup>, and other non-oncologic conditions (e.g., bleeding peptic ulcers, esophageal varices, secondary hypersplenism).

## PRACTICE GUIDELINE SUMMARY

### NATIONAL COMPREHENSIVE CANCER NETWORK

National Comprehensive Cancer Network (NCCN) guidelines for non-small cell lung cancer (v2.2020) recommend “image-guided thermal ablation [as] an option for selected patients.”

### AMERICAN COLLEGE OF CHEST PHYSICIANS

The American College of Chest Physicians (ACCP) evidence-based guidelines on the treatment of non-small cell lung cancer note the role of ablative therapies in the treatment of high-risk patients with stage I non-small cell lung cancer (NSCLC) is evolving. However, the ACCP does not recommend MWA for patients with NSCLC.<sup>[44]</sup>

## SUMMARY

Surgical resection is the treatment of choice for primary non-small cell lung cancer (NSCLC) or metastatic tumors in the lung. For those patients who are unable to tolerate surgery, microwave ablation (MWA) may be a treatment option in certain cases. While available studies are limited by study design, accumulating evidence suggests that MWA may be similar to surgery in survival rates, and rates of procedure-related complications and mortality. Therefore, in patients with NSCLC or metastatic tumors in the lung who are ineligible for surgical treatment, MWA may be considered medically necessary when the policy criteria are met.

For patients with tumors that do not meet policy criteria, it appears that microwave ablation (MWA) may improve health outcomes, though more research is needed to know for sure. Therefore, MWA is considered investigational as a treatment of tumors.

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45. BlueCross BlueShield Association Medical Policy Reference Manual "Microwave Tumor Ablation." Policy No. 7.01.133

## CODES

Codes	Number	Description
CPT	19499	Unlisted procedure, breast
	32998	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral, radiofrequency
	32999	Unlisted procedure, lungs and pleura
	38589	Unlisted laparoscopy procedure, lymphatic system
	49999	Unlisted procedure, abdomen, peritoneum and omentum
	50592	Ablation, renal tumor(s), unilateral, percutaneous, radiofrequency
	53899	Unlisted procedure, urinary system
	60699	Unlisted procedure, endocrine system
HCPCS	C9751	Bronchoscopy, rigid or flexible, transbronchial ablation of lesion(s) by microwave energy, including fluoroscopic guidance, when performed, with computed tomography acquisition(s) and 3-d rendering, computer-assisted, image-guided navigation, and endobronchial ultrasound (ebus) guided transtracheal and/or transbronchial sampling (eg, aspiration[s]/biopsy[ies]) and all mediastinal and/or hilar lymph node stations or structures and therapeutic intervention(s)

**Date of Origin:** October 2013

## ***Sacroiliac Joint Fusion***

**Effective:** October 1, 2020

**Next Review:** June 2021

**Last Review:** August 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

The sacroiliac (SI) joint is a strong weight bearing joint with a self-locking mechanism that provides stability with movement on the left and right side of the sacrum. Similar to other structures in the spine, it is assumed that the SI joint may be a source of low back pain but there are currently no reference standards for diagnosis. If conservative therapies fail to adequately treat symptoms, SI joint fusion may be used to stabilize the SI joint including open, percutaneous, and minimally invasive techniques.

### **MEDICAL POLICY CRITERIA**

- I. Sacroiliac joint fusion performed by an open procedure may be considered **medically necessary** when one of the following criteria is met:
  - A. As an adjunct to sacrectomy or partial sacrectomy related to tumors involving the sacrum; or
  - B. As an adjunct to the medical treatment of sacroiliac joint infection (e.g., osteomyelitis, pyogenic sacroiliitis)/sepsis; or
  - C. As a treatment for severe traumatic injuries associated with pelvic ring fracture.
- II. Sacroiliac joint fusion performed by an open procedure, for any other indication not listed above in Criterion I. is considered **not medically necessary**.

- III. Minimally invasive fusion/stabilization of the sacroiliac joint using an FDA-approved titanium triangular implant may be considered **medically necessary** when ALL of the following criteria have been met:
- A. Clinical documentation that pain limits activities of daily living (ADL). ADLs are defined as feeding, bathing, dressing, grooming, meal preparation, household chores, and occupational risks that are required for daily functioning; and
  - B. Patients have undergone and failed a minimum 6 months of intensive physician-directed non-operative treatment that must include medication optimization, activity modification, and active therapeutic exercise targeted at the lumbar spine, pelvis, sacroiliac joint, and hip; and
  - C. There is at least 75% reduction of pain following an image-guided, contrast-enhanced intra-articular sacroiliac joint injection on 2 separate occasions; and
  - D. A trial of a therapeutic sacroiliac joint injection (i.e., corticosteroid injection) has been performed on at least one occasion (see Policy Guidelines); and
  - E. A thorough physical examination demonstrates findings consistent with sacroiliac joint disease including a positive response to a cluster of three provocative tests (e.g., thigh thrust test, compression test, Gaenslen's test, distraction test, Patrick's sign, posterior provocation test); and
  - F. Diagnostic imaging studies include ALL of the following:
    - 1. Imaging of the sacroiliac joint indicates evidence of injury and/or degeneration; and
    - 2. Imaging of the sacroiliac joint excludes the presence of destructive lesions (e.g., tumor, infection) or inflammatory arthropathy of the sacroiliac joint and rules out concomitant hip pathology; and
    - 3. Advanced imaging of the lumbar spine (CT or MRI) is performed to rule out neural compression or other degenerative conditions that can be causing low back or buttock pain and excludes the presence of destructive lesions or inflammatory arthropathy of the sacroiliac joint.
- IV. Minimally invasive fusion/stabilization of the sacroiliac joint for the treatment of back pain presumed to originate from the sacroiliac joint is considered **investigational** under all other conditions including but not limited to when Criterion III is not met.

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

## POLICY GUIDELINES

A successful trial of controlled diagnostic SI joint or lateral branch blocks consists of two separate positive blocks on different days with local anesthetic only (no steroids or other drugs), or a placebo-controlled series of blocks, under fluoroscopic guidance, that has resulted in a reduction in pain for the duration of the local anesthetic used (e.g., three hours longer with bupivacaine than lidocaine). There is no consensus on whether a minimum of 50% or 75% reduction in pain would be required to be considered a successful diagnostic block, although evidence supports a criterion standard of 75% to 100% reduction in pain with dual blocks. No therapeutic intra-articular injections (i.e., steroids, saline, other substances) should be

administered for a period of at least four weeks before the diagnostic block. The diagnostic blocks should not be conducted under intravenous sedation unless specifically indicated (e.g., the patient is unable to cooperate with the procedure).

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and Physical/Chart Notes
- Current Symptomology including indication for procedure (diagnostic or treatment of specific condition) and whether procedure will be open or minimally invasive
- Documentation of specific conservative pain management including length of time utilized including rheumatologic evaluation when indicated
- Documentation of diagnostic blocks including agents used, duration of action and if completed under imaging guidance
- If request is for minimally invasive fusion/stabilization with a titanium triangular implant provide the following; documentation of specifically how pain limits ADLs, failure of minimum of six months of specific nonoperative therapy attempted, percentage of pain reduction achieved using the specific image guided injections listed above on two separate occasions, trial of injection has been performed at least once, absence of generalized pain behavior/disorders, documentation of location of pain on spine/joint, documentation per physical exam of location of pain including tenderness, positive response to at least three provocative tests and diagnostic imaging studies/reports completed.
- Documentation of specific device being utilized if applicable

## CROSS REFERENCES

1. [Percutaneous Vertebroplasty, Kyphoplasty, Sacroplasty, and Coccygeoplasty](#), Surgery, Policy No. 107
2. [Lumbar Spinal Fusion](#), Surgery Policy No. 187

## BACKGROUND

The sacroiliac (SI) joint is a joint between the sacrum and ilium of the pelvis. The SI joint is a strong weight bearing joint with a self-locking mechanism that provides stability with movement on the left and right side of the sacrum. Similar to other structures in the spine, it is assumed that the SI joint may be a source of low back pain.

Currently, there are no reference standards for the diagnosis of SI joint pain. SI joint pain is typically without any consistent, demonstrable radiographic or laboratory features and most commonly exists in the setting of morphologically normal joints. Clinical tests for SI joint pain may include various movement tests, palpation to detect tenderness, and pain descriptions by the patient. Research into sacroiliac joint pain has been inhibited by the lack of any criterion standard to measure its prevalence and against which various clinical examinations can be validated. Further confounding study of the SI joint is that multiple structures, such as posterior facet joints and lumbar discs, may refer pain to the area surrounding the SI joint.

There are many methods for the treatment of chronic SI joint pain including nonsurgical and surgical approaches. Conservative management may include nonsteroidal anti-inflammatory

medications, prescription analgesics, spinal manipulation, physical therapy, a home exercise program, and evaluation and management of cognitive, psychological, or behavioral issues.

If conservative therapies fail to adequately treat symptoms, SI joint fusion may be used to stabilize the SI joint. Surgical approaches include open, percutaneous, and minimally invasive techniques. The open surgery technique involves the iliac crest bone and the sacrum being held together with plates and/or screws until fusion occurs between the two bones. The use of minimally invasive techniques to fuse the SI joint has increased over the last several years. Minimally invasive procedures use specially designed implants for the stabilization of the SI joint.

Some procedures have been referred to as SIJ fusion but may be more appropriately called fixation (this is because there is little to no bridging bone on radiographs). Devices for SIJ fixation/fusion that promote bone ingrowth to fixate the implants include a triangular implant (iFuse Implant System) and cylindrical threaded devices (Rialto, SImmetry, Silex, SambaScrew, SI-LOK). Some devices also have a slot in the middle where autologous or allogeneic bone can be inserted. This added bone is intended to promote fusion of the SIJ.

## REGULATORY STATUS

Several percutaneous or minimally invasive fixation/fusion devices have received marketing clearance by the Food and Drug Administration. These include the Rialto™ SI Joint Fusion System (Medtronic), SIJ-Fuse (Spine Frontier), IFUSE® Implant System (SI Bone), SImmetry® Sacroiliac Joint Fusion System (Zyga Technologies), Silex™ Sacroiliac Joint Fusion System (XTANT Medical), SambaScrew® (Orthofix), and the SI-LOK® Sacroiliac Joint Fixation System (Globus Medical). FDA Product Code: OUR.

Note: This policy does not address percutaneous sacroplasty which is addressed in the *Percutaneous Vertebroplasty and Kyphoplasty* policy (SUR107).

## EVIDENCE SUMMARY

SI joint fusion performed by open procedure is considered standard of care to stabilize the sacroiliac joint due to trauma, infection, and tumors involving the sacrum. Therefore, the focus of the literature review is on the use of diagnostic blocks for the diagnosis of SI joint pain and the use of percutaneous or minimally invasive fusion techniques.

Due to the volume of published literature regarding minimally invasive sacroiliac joint fusion with varying study design and quality, the following is a summary of key references published to date. It is important to note that many of the systematic reviews include similar studies in addition to those studies being summarized below.

## DIAGNOSTIC BLOCKS

The use of diagnostic blocks to evaluate SI joint pain builds on the experience of diagnostic block use in other joints to evaluate pain. Blinded studies with placebo controls (although difficult to conduct when dealing with invasive procedures) are ideally required for scientific validation of sacroiliac joint blocks, particularly when dealing with pain relief well-known to respond to placebo controls. In the typical evaluation of a diagnostic test, the results of SI diagnostic block would then be compared with a criterion standard. However, there is no current criterion standard for SI joint injection. A search for systematic reviews, randomized

controlled trials, and comparative studies on diagnostic blocks was conducted and is summarized below.

## **Systematic Reviews**

In 2013, the American Society of Interventional Pain Physicians published an updated evidence review with guidelines on diagnosis of SIJ pain.<sup>[1]</sup> Various studies evaluating diagnostic blocks were reviewed in which the criteria for a positive test varied from 50% to 100% relief from either single or dual blocks. The most stringent criterion, 75% to 100% relief with dual blocks, was evaluated in seven studies. The prevalence of a positive test in the seven studies ranged from 10% to 44.4% in patients with suspected sacroiliac disease. The evidence for diagnostic sacroiliac intra-articular injections was considered to be good using 75% to 100% pain relief with single or dual blocks as the criterion standard.

A 2012 systematic review<sup>[2]</sup> evaluated the accuracy of diagnostic sacroiliac joint interventions. The methodological quality of the studies was evaluated and only the studies meeting at least 50% of the applicable appraisal inclusion criteria were included. A total of 17 studies met inclusion criteria with a range of diagnostic interventions and relief cutoff thresholds. Only one placebo-controlled study was identified with methodological limitations. The review concluded that there is good evidence for the use of controlled diagnostic local anesthetic blocks. Uncontrolled blocks had a false positive rate of approximately 20%. Overall, the systematic review concluded, based on what the authors determined to be good evidence, “there was no significant difference when 70% or greater relief is utilized as the criterion standard with dual blocks.” In addition, the systematic review concluded that “there is no evidence to support the use of ultrasound or landmark-guided injections for sacroiliac joint pain. These injections must be performed under fluoroscopic or radiologic guidance.” Limitations of this systematic review include the lack of high quality evidence, significant variation in interventions, and discrepancies in a gold standard to measure against.

A systematic review was commissioned by the American Pain Society and conducted by the Oregon Evidence-based Practice Center in 2009.<sup>[3]</sup> The systematic review concluded that no studies were identified that evaluated validity or utility of diagnostic sacroiliac joint block as a diagnostic procedure for low back pain with or without radiculopathy.

## **Randomized Controlled Trials**

No RCTs identified after the above SRs were published.

## **Section Summary**

Although there is no independent reference standard for the diagnosis of SIJ pain, SIJ blocks are considered the reference standard for the condition. The utility of this test ultimately depends on its ability to identify patients who benefit from treatment. Sacroiliac Joint Fusion

## **SACROILIAC JOINT FUSION**

### **Systematic Reviews**

Lingutla (2016) published a systematic review with meta-analysis evaluating SI joint fusion for low back pain where it has been determined that the cause of the pain is originating from the sacroiliac joint and not the lumbar spine.<sup>[4]</sup> Six nonrandomized studies were included with a mean follow-up of 17.6 months. The authors concluded that all outcome measures showed a

statistical improvement for alleviating pelvic girdle pain. However, the review consisted of nonrandomized studies with some methodological limitations. More research is needed for this patient population.

Zaidi (2015) conducted a systematic review of the evidence evaluating SI joint fusion interventions for treating SI joint pain or dysfunction.<sup>[5]</sup> A comprehensive literature search was conducted and the authors included five case series, eight retrospective studies, and three prospective studies with at least two patients (N=430). The mean duration of follow-up was 60 months with the most common pathology being SI joint degeneration/arthrosis followed by SI joint dysfunction, postpartum instability among other less common pathologies. Study participants reported satisfaction after the procedures which varied widely. The rates of reoperation for open surgery were 5% to 65% (mean 15%) and for minimally invasive 0% to 17% (mean 6%). Major complications ranged from 5% to 20% with one study reporting a 56% adverse event rate. The authors concluded that surgical intervention is beneficial for a subset of patients and that serious consideration of alternatives should be considered prior to surgery.

A 2012 systematic review found that the quality of evidence for surgical treatment (débridement, fusion) compared to injection treatment (corticosteroid, botulinum toxin, prolotherapy) for chronic sacroiliac pain was very low.<sup>[6]</sup> No studies were identified that directly compared surgery to injection therapy. Seven case series using a range of surgical techniques that evaluated a range of surgical treatments were included and summarized. The literature was considered heterogeneous and insufficient to evaluate the comparative effectiveness of surgical treatments compared to other treatments. Several surgical studies reported complications including but not limited to infections, nonunion, further surgery, and intraoperative fracture. Studies had small sample sizes and provided little information on determining successful fusion.

In 2010, Ashman<sup>[7]</sup> conducted a systematic review comparing fusion to denervation for chronic SI joint pain. Six case series on fusion were identified that evaluated a single treatment. As a result, no conclusions could be drawn for the comparative efficacy of the treatments.

## **Randomized Controlled Trials**

No RCTs identified after the above SRs were published.

## **SIJ FUSION/FIXATION WITH A TRIANGULAR IMPLANT SYSTEM**

### **Systematic Reviews**

Tran (2019) published a systematic review comparing the effectiveness of minimally invasive joint fusion (e.g. utilizing the iFuse device) compared to screw-type surgeries. A total of twenty studies was pooled to calculate a standardized mean difference across pain, disability, and global/quality-of-life outcomes, including 14 studies evaluation the iFuse system and 7 studies evaluated cylindrical, threaded implants. Studies evaluating cylindrical threaded implants consisted of case series and cohort studies. Patients receiving these implants experienced significantly worse pain outcomes ( $p=0.03$ ) compared to patients receiving iFuse, with a standardized mean difference of 1.28 and 2.04, respectively. A statistically significant difference in disability scores was reported between screw-type and iFuse implant groups (0.26 vs 1.68), with improved outcomes in the iFuse population. For global/quality-of-life outcomes, a statistically significant difference in scores was reported between screw-type and iFuse implants groups (0.60 vs 0.99 with improved outcomes in the iFuse population).

Heiney (2015) evaluated clinical outcomes and operative measures of minimally invasive sacroiliac joint fusion utilizing a lateral transarticular technique.<sup>[8]</sup> A total of 12 studies, including those for triangular implants were included. The authors concluded, for this particular technique, patients reported improvements in pain, disability, and quality of life scores.

## Randomized Controlled Trials

Whang (2015) reported an industry-sponsored nonblinded RCT of the iFuse Implant System in 148 patients.<sup>[9]</sup> Twelve-month follow-up to this RCT was reported by Polly et al in 2015.<sup>[10]</sup> However, by 12 months, almost all patients in the control group had crossed over to SI JOINT fusion. Two-year follow-up of this trial was reported by Polly et al in 2016.<sup>[11]</sup> This last publication will be discussed in the case series section of this report. Trial inclusion was based on a determination of the SI JOINT as a pain generator from a combination of a history of SI JOINT-localized pain, positive provocative testing on at least three of five established physical tests, and at least a 50% decrease in SI JOINT pain after image-guided local anesthetic injection into the SI JOINT. The duration of pain before enrollment averaged 6.4 years (range, 0.47-40.7 years). A large proportion of subjects (37%) had previously undergone lumbar fusion, steroid SI JOINT infections (86%), and RFA (16%).

Patients were assigned 2:1 to minimally invasive SI joint fusion (n=102) or to nonsurgical management (n=46). Nonsurgical management included a stepwise progression of nonsurgical treatments, depending on individual patient choice. During follow-up, control patients received physical therapy (97.8%), intra-articular steroid injections (73.9%), and RFA of sacral nerve roots (45.7%). The primary outcome measure was six month success rate, defined as the proportion of treated subjects with a 20-mm improvement in SI JOINT pain in the absence of severe device-related or neurologic adverse events or surgical revision. Patients in the control arm could crossover to surgery after six months. Baseline scores indicated that the patients were severely disabled, with VAS pain scores averaging 82.3 out of 100 and ODI scores averaging 61.9 out of 100 (0=no disability, 100=maximum disability).

At six months, success rates were 23.9% in the control group versus 81.4% in the surgical group (posterior probability of superiority >0.999). A clinically important ( $\geq 15$ -point) improvement in ODI score was found in 27.3% of controls compared with 75.0% of fusion patients. Measures of QOL (36-Item Short-Form Health Survey, EuroQol-5D) also improved to a greater extent in the surgery group. Of the 44 nonsurgical management patients still participating at six months, 35 (79.5%) crossed over to fusion. Compared to baseline, opioid use at six months decreased from 67.6% to 58% in the surgery group, and increased from 63% to 70.5% in the control group ( $p=0.082$ ). At 12 months, opioid use was similar between groups (55% vs 52%,  $p=0.61$ ). Although these results generally favored fusion, the trial is limited due to the high number of patients that crossed over from the control group to the fusion group. This limits the comparative long-term conclusions that can be drawn.

Stuesson (2016) reported another industry-sponsored nonblinded RCT of the iFuse Implant System in 103 patients.<sup>[12]</sup> Selection criteria were similar to those of the Whang trial, including at least 50% pain reduction on SI JOINT block. Mean pain duration was 4.5 years. Thirty-three percent of patients had undergone prior lumbar fusion. Nonsurgical management included physical therapy and exercises at least twice per week; interventional procedures (eg, steroid injections, RFA) were not allowed. The primary outcome was change in VAS pain score at six months.

Of 109 randomized subjects, six withdrew before treatment. All patient assigned to iFuse underwent the procedure, and follow-up at six months was in 49 of 51 patients in the control group and in all 52 patients in the iFuse group. At six months, VAS pain scores improved by 43.3 points in the iFuse group and by 5.7 points in the control group ( $p<0.001$ ). ODI scores improved by 25.5 points in the iFuse group and by 5.8 points in the control group ( $p<0.001$ , between groups). QOL outcomes showed a greater improvement in the iFuse group than in the control group. Changes in pain medication use are not reported. Although these results favored fusion, with magnitudes of effect in a range similar to the Whang RCT, this trial was also not blinded and lacked a sham control. Outcomes were only assessed to six months. Six-month results for the Whang and Stureson trials are shown in Table 1.

**Table 1. Summary of 6-Month iFuse Results From Whang et al<sup>[9]</sup> and Stureson et al<sup>[12]</sup>**

Whang et al (2015)										
Baseline	82.2	82.3			61.1	62.2	30.8	30.2	0.47	0.44
Follow-up	70.4	29.8	23.9%	81.4% <sup>a</sup>	56.4	31.9	32.0	42.8	0.52	0.72
Change	-12.1	-52.6 <sup>a</sup>			-4.9	-30.3 <sup>a</sup>	1.2	12.7	0.05	0.29
Stureson et al (2016)										
Baseline	73.0	77.7								
Follow-up	67.8	34.4								
Change	-5.7	-43.3			-5.8	-25.5			0.11	0.37

The success end point was defined as a reduction in pain VAS score of  $\geq 20$ , absence of device-related events, absence of neurologic worsening, and absence of surgical intervention.

Ctl: control; EQ-5D TTO: EuroQoL Time Tradeoff Index; ODI: Oswestry Disability Index; SF-36 PCS: 36-Item Short-Form Health Survey Physical Component Summary; VAS: visual analog scale.

<sup>a</sup>  $p<0.001$ .

## Nonrandomized Studies

Two retrospective nonrandomized comparative studies were published in 2017. Vanaclocha (2017) found greater pain relief with SIJ fusion than with conservative management or SIJ denervation.<sup>[13]</sup> Spain and Holt (2017) reported a retrospective review of surgical revision rates following SIJ fixation with either surgical screws or the iFuse triangular implant.<sup>[14]</sup> Revision rates were lower with the iFuse device than observed with surgical screws.

Twelve-month results from the iMIA trial were reported by Dengler (2017).<sup>[15]</sup> Twenty-one patients in the conservative management group had little or no improvement in symptoms and crossed over to SIJ fusion after the 6-month visit. Fourteen (56%) of the 25 patients who remained in the conservative management group had at least a 20-point improvement in VAS back pain score (22.4% of patients assigned to conservative management). At 12 months, low back pain had improved by 42 points (SD=27.0) on a 100-point VAS in the SIJ fusion group compared with 14 (SD=33.4) points in the conservative management group ( $p<0.001$ ). The authors noted that there were methodological limitations including lack of blinding and subjective assessments of outcomes.

**Table 2. Extended Follow-Up From the INSITE and iMIA Trials**

Outcome Measures	Baseline	6 Months (SD)	12 Months (SD)	24 Months (SD)
Sacroiliac joint fusion pain score	82.3	29.8		26.7
Percent $\geq 20$ -point improvement pain				83.1%
Sacroiliac joint fusion ODI score	57.2	31.9		28.7
% $\geq 15$ -point improvement ODI				68.2%

Outcome Measures	Baseline	6 Months (SD)	12 Months (SD)	24 Months (SD)
iMIA <sup>[15]</sup>				
Low back pain				
Conservative management	73.0 (13.8)	67.8 (20.3)	58.9 (28.2)	
Leg pain				
Sacroiliac joint fusion	52.7 (31.5)	22.6 (25.1)	24.0 (27.8)	
Conservative management	55.6 (13.7)	50.2 (17.2)	46.9 (20.8)	
	57.5 (14.4)		32.1 (19.9)	

Adapted from Dengler et al (2017).<sup>[15]</sup>  
ODI: Oswestry Disability Index.

### Case Series With Good Reported Follow-Up Rates

Case series with good follow-up rates are more likely to provide valid estimates of outcomes. Principal results of the studies at 2- to 3-year follow-up are shown in Table 3.

Polly (2016) reported two-year outcomes from the RCT of SI JOINT fusion.<sup>[11]</sup> When reported, without an untreated control group, the study was a case series. Of 102 subjects originally assigned to SI JOINT fusion and treated, 89 (87%) were evaluated at two years. Although the clinical trial used a different composite end point, in this report, clinical outcomes were based on the amount of improvement in SI JOINT pain and in ODI scores. Improvement was defined as a change of 20 points in SI JOINT pain score and 15 points in ODI score. Substantial improvement was defined as a change in 25 points in SI JOINT pain score or a score of 35 or less and an improvement of 18.8 points in ODI score. At 24 months, 83.1% and 82% had improvement and substantial improvement in SI JOINT pain score, and 68.2% and 65.9% had improvement and substantial improvement in ODI. By 24 months, the proportion taking opioids was reduced from 68.6% at baseline to 48.3%.

Results from a case series of 172 patients undergoing SI JOINT fusion reported to two years were published by Duhon (2016).<sup>[17,18]</sup> Patients were formally enrolled in a single-arm trial (NCT01640353) with planned follow-up for 24 months. Success was defined as a reduction of VAS pain score of 20 mm (out of 100 mm), absence of device-related adverse events, absence of neurologic worsening, and absence of surgical reintervention. Enrolled patients had a mean VAS pain score of 79.8, a mean ODI score of 55.2, and had a mean pain duration of 5.1 years. At six months, 136 (80.5%) of 169 patients met the success end point, which met the prespecified Bayesian probability of success rate. Mean VAS pain scores were 30.0 at six months and 30.4 at 12 months. Mean ODI scores were 32.5 at six months and 31.4 at 12 months. At two years, 149 (87%) of 172 patients were available for follow-up. VAS pain score at two years was 26.0 and ODI score was 30.9. Thus, 1-year outcomes were maintained at two years. Other outcomes (eg, QOL scores) showed similar maintenance or slight improvement compared to 1-year outcomes. Use of opioid analgesics decreased from 76.2% at baseline to 55% at two years. Over the 2-year follow-up, 8 (4.7%) patients required revision surgery.

Rudolph and Capobianco (2014) described 5-year follow-up for 17 of 21 consecutive patients treated at their institution between 2007 and 2009.<sup>[19]</sup> Of the four patients lost to follow-up, two had died and one had become quadriplegic due to severe neck trauma. For the remaining patients, mean VAS score (range, 0-10) improved from 8.3 before surgery to 2.4 at five years; 88.2% of patients had substantial clinical benefit, which was defined as a 2.5-point decrease in

VAS score or a raw score less than 3.5. Mean ODI score at five years was 21.5. Imaging by radiograph and computed tomography showed intra-articular bridging in 87% of patients with no evidence of implant loosening or migration.

Rudolf (2012) retrospectively analyzed his first 50 consecutive patients treated with the iFuse Implant System.<sup>[20]</sup> There were 10 perioperative complications, including implant penetration into the sacral neural foramen (two patients) and compression of the L5 nerve (1 patient); these three patients required surgical retraction of the implant. At three years postsurgery, 1 patient required additional implants due to worsening symptoms. At a minimum of 24 months of follow-up (mean, 40 months), the treating surgeon was able to contact 45 patients. The mean pain score was two (1 to 10 scale), and 82% of patients had attained the minimal clinically important difference in pain score (defined as  $\geq 2$  of 10).

### Case Series With Unknown Follow-Up Rates

The following case series did not report follow-up rates or study methodologies did not permit calculation of the complete number of patients treated.

Smith (2013) retrospectively compared open with minimally invasive SI JOINT fusion. Because all patients received fusion, this study should be interpreted as a case series, with attention paid to the minimally invasive fusion group.<sup>[21]</sup> Only patients with medical records documenting 12- or 24-month pain scales were included, resulting in 114 patients selected for the minimally invasive group. Losses to follow-up could not be determined. At 12 months, VAS pain scores decreased to a mean of 2.3 from a baseline of 8.1. At 24 months, mean VAS pain score was 1.7, but data for only 38 patients were analyzed. These improvements in VAS pain score were greater than those for open fusion, but conclusions of comparative efficacy should not be made given this type of study. Implant repositioning was performed in 3.5% of patients in the minimally invasive group.

A large (N=144) industry-sponsored, multicenter retrospective series was reported by Sachs et al in 2014.<sup>[22]</sup> Consecutive patients from 6 sites were included if preoperative and 12-month follow-up data were available. No information was provided on the total number of patients treated during the same time interval. Mean baseline pain score was 8.6. At a mean 16-month follow-up, VAS score was 2.7 (/10), an improvement of 6.1. Ten percent of patients reported an improvement of 1 point or less. Substantial clinical benefit, defined as a decrease in pain score by more than 2.5 points or a score of 3.5 or less, was reported in 91.9% of patients.

Sachs (2016) reported outcomes of 107 patients with a minimum follow-up of 3 years.<sup>[23]</sup> The number of potentially eligible patients was not reported, so the follow-up rate is unknown. Pain scores improved from a mean of 7.5 at baseline to 2.5 at a mean follow-up time of 3.7 years. ODI score at follow-up was 28.2, indicating moderate residual disability. Overall satisfaction rate was 87.9% (67.3% very satisfied, 20.6% somewhat satisfied). Revision surgery was reported in five (4.7%) patients. Without knowing the number of eligible patients, the validity of this study cannot be determined.

**Table 3. Two- to 3-Year Outcomes of the iFuse Implant in Cohorts and Case Series**

Studies and Outcomes	Mean Baseline Value	Mean 2- to 3-Year Value	Difference or % Achieving Outcome	Follow-Up Rate
Pain score (range, 0-10)	7.59	2.0	5.59	90% (45/50)
			82%	
Duhon et al (2016) <sup>[17]</sup>				

Studies and Outcomes	Mean Baseline Value	Mean 2- to 3-Year Value	Difference or % Achieving Outcome	Follow-Up Rate
Pain score (range, 0-100)	79.8	26.0	53.3	86.6% (149/172)
Oswestry Disability Index score	55.2	30.9	24.5	
SF-36 score	31.7	40.7	8.9	
EQ-5D TTO score	0.43	0.71	0.27	
Pain score (range 0-10)	7.5	2.5		

All differences between baseline and 2- to 3-year values were statistically significant.  
EQ-5D TTO Index: EuroQoL Time Tradeoff Index; SF-36: 36-Item Short-Form Health Survey.

## Database Analysis

Schoell (2016) analyzed postoperative complications tracked in an administrative database of minimally invasive SIJ fusions to determine complications coded in postoperative claims. Using the Humana insurance database, patients with complications were identified using ICD-9 codes corresponding to a surgical complication within 90 days or 6 months if the codes were used for the first time. Of 469 patients, the overall incidence of complications was 13.2% at 90 days and 16.4% at 6 months. For specific complications, the infection rate was 3.6% at 90 days and the rate of complications classified as nervous system complications was 4.3%. Authors noted that the infection rate observed was consistent with the infection rates reported by Polly et al (2015), 20 but much higher than those reported for other types of minimally invasive spine procedures. The incidence of complications in this study may differ from those reported by registries. However, determining the true incidence of adverse events after procedures from either registries or insurance claims data can be difficult due to uncertainty about the completeness of reporting in registries and the accuracy of coded claims in claims databases.

Cher (2015) reported rates of implant revision using the Humana insurance database of procedures.<sup>[24]</sup> Between April 2009 and July 2014, 11,416 cases with the iFuse system took place. After minor adjustments of numbers to account for non-recommended uses and inability to match revision cases, the cumulative revision rate at 4 years was 3.54%. Overall, 24% of revision surgeries occurred in the first month and 63% occurred within the first 12 months. One-year revision rates fell over time (9.7% to 1.4% from 2009 to 2014).

## Adverse Events

From 9/1/2016 to 12/8/2017 a total of 47 MAUDE database injury reports were identified (product code OUR). Many reports were for revisions needed and/or user error/wrong placement e.g. too deep, wrong size device, with a few noting infection or hematoma.

From January 2010 through August 2016, a total of 438 MAUDE database injury reports were identified (product code OUR): 355 mentioned revision, 188 malposition, 32 radicular pain, 24 impingement or impingement, and 14 infection.

## Summary

For individuals who SIJ pain who receive SIJ fusion/fixation with a triangular implant, the evidence includes two non-blinded RCTs of minimally invasive fusion and 2 case series with more than 85% follow-up at 2 to 3 years. Relevant outcomes are symptoms, functional outcomes, quality of life, medication use, and treatment-related morbidity. Both RCTs reported

superior short-term results for fusion, however, a preferable design for assessing pain outcomes would be independent, blinded assessment of outcomes or, when feasible, a sham-controlled trial. Longer term follow-up from these RCTs indicated that the results obtained at six months persist to two years. Two additional cohort studies or case series, with sample sizes ranging from 45 to 149 patients and low dropout rates (<15%), have also shown reductions in pain and disability at two years. One small case series showed outcomes that persisted to five years. The cohort studies and case series are consistent with the durability of treatment benefit. Analysis of an insurance database reported an overall incidence of complications to be 16.4% at six months and cumulative revision rate at four years of 3.54%. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

## SIJ FUSION/FIXATION WITH A CYLINDRICAL THREADED IMPLANT

### Systematic Reviews

No systematic reviews identified for SIJ Fusion/Fixation with a Cylindrical Threaded Implant that are not already addressed.

### Randomized Controlled Trials

Rappoport (2017) reported on an industry-sponsored prospective study of SIJ fusion with a cylindrical threaded implant (SI-LOK).<sup>[25]</sup> The study included 32 patients with a diagnosis of SIJ dysfunction who had failed nonoperative treatment, including medication, physical therapy, and therapeutic injections. A diagnostic injection was performed to confirm the source of pain to the SIJ. The procedure included drilling to prepare for screw insertion and implantation of three screws, at least one of which was slotted. The slotted screws were packed with autogenous bone graft from the drill reamings. Pain and disability scores were reduced following device implantation, and revisions within the first 12 months of the study were low (n=2). Follow-up will continue through two years

**Table 4. Pain and Disability Scores After Implantation With a Cylindrical Threaded Implant**

Outcome Measures	Baseline	3 Months (SD)	6 Months (SD)	12 Months (SD)	p
Low back pain	55.8 (26.7)	28.5 (21.6)	31.6 (26.9)	32.7 (27.4)	<0.01
Left leg pain	40.6 (29.5)	19.5 (22.9)	16.4 (25.6)	12.5 (23.3)	<0.01
Right leg pain	40.0 (34.1)	18.1 (26.3)	20.6 (25.4)	14.4 (21.1)	<0.05
Oswestry Disability Index	55.6 (16.1)	33.3 (16.8)	33.0 (16.8)	34.6 (19.4)	<0.01

Adapted from Rappoport et al (2017).<sup>[25]</sup>

### Summary

There is limited evidence on fusion of the SIJ with devices other than the triangular implant. One-year results from a prospective cohort of 32 patients who received a cylindrical slotted implant showed reductions in pain and disability similar to results obtained for the triangular implant. However, there is uncertainty in the health benefit of SIJ fusion/fixation with this implant design. Therefore, controlled studies with a larger number of patients and longer follow-up are needed to evaluate this device.

## PRACTICE GUIDELINE SUMMARY

## **NORTH AMERICAN SPINE SOCIETY**

The North American Spine Society (NASS) published coverage recommendations for percutaneous sacroiliac joint fusion in 2015.<sup>[26]</sup> NASS indicated that there was relatively moderate evidence. In the absence of high-level data, policies reflect the multidisciplinary experience and expertise of the committee members in order to present reasonable standard practice indications in the United States. NASS recommended coverage when all of the following criteria are met:

1. “[Patients] have undergone and failed a minimum 6 months of intensive nonoperative treatment that must include medication optimization, activity modification, bracing and active therapeutic exercise targeted at the lumbar spine, pelvis, SI JOINT and hip including a home exercise program.
2. Patient’s report of typically unilateral pain that is caudal to the lumbar spine (L5 vertebra), localized over the posterior SI JOINT, and consistent with SI JOINT pain.
3. A thorough physical examination demonstrating localized tenderness with palpation over the sacral sulcus (Fortin’s point, ie, at the insertion of the long dorsal ligament inferior to the posterior superior iliac spine or PSIS) in the absence of tenderness of similar severity elsewhere (eg, greater trochanter, lumbar spine, coccyx) and that other obvious sources for their pain do not exist.
4. Positive response to a cluster of 3 provocative tests (eg, thigh thrust test, compression test, Gaenslen’s test, distraction test, Patrick’s sign, posterior provocation test). Note that the thrust test is not recommended in pregnant patients or those with connective tissue disorders.
5. Absence of generalized pain behavior (eg, somatoform disorder) or generalized pain disorders (eg, fibromyalgia).
6. Diagnostic imaging studies that include ALL of the following:
  - a. Imaging (plain radiographs and a CT [computed tomography] or MRI [magnetic resonance imaging]) of the SI joint that excludes the presence of destructive lesions (eg, tumor, infection) or inflammatory arthropathy that would not be properly addressed by percutaneous SI JOINT fusion.
  - b. Imaging of the pelvis (AP [anteroposterior] plain radiograph) to rule out concomitant hip pathology.
  - c. Imaging of the lumbar spine (CT or MRI) to rule out neural compression or other degenerative condition that can be causing low back or buttock pain.
  - d. Imaging of the SI joint that indicates evidence of injury and/or degeneration.
7. At least 75% reduction of pain for the expected duration of the anesthetic used following an image-guided, contrast-enhanced intra-articular SI JOINT injection on 2 separate occasions.
8. A trial of at least one therapeutic intra-articular SI JOINT injection (ie, corticosteroid injection).”

## **INTERNATIONAL SOCIETY FOR THE ADVANCEMENT OF SPINE SURGERY**

The International Society for the Advancement of Spine Surgery (ISASS) published a policy statement on minimally invasive sacroiliac joint fusion. These recommendations were updated in 2016.<sup>[27]</sup> ISASS lists criteria for determining a patient’s eligibility regarding minimally invasive SI joint fusion. However, the statement has several limitations including but not limited to the literature review methods are not transparent, there is no formal assessment of the quality of the evidence, and there is not a clear link between the recommendations and supporting

evidence. ISASS recommendations state that patients who have all of the following criteria may be eligible for minimally invasive SI JOINT fusion:

- “Significant SI joint pain ... or significantly limitations in activities of daily living because of pain from the SI joint(s).
- “SI joint pain confirmed with ... at least three positive physical provocation examination maneuvers that stress the SI joint.
- “Confirmation of the SI joint as a pain generator with  $\geq 75\%$  acute decrease in pain immediately following fluoroscopically guided diagnostic intra-articular SI joint block using local anesthetic.
- “Failure to respond to at least six months of non-surgical treatment consisting of non-steroidal anti-inflammatory drugs and/or ... one or more of the following: ... physical therapy.... Failure to respond means continued pain that interferes with activities of daily living and/or results in functional disability;
- “Additional or alternative diagnoses that could be responsible for the patient’s ongoing pain or disability have been considered, investigated and ruled out.”

### **AMERICAN SOCIETY OF INTERVENTIONAL PAIN PHYSICIANS (ASIPP)**

The ASIPP guidelines published in 2013 have a recommendation for diagnostic sacroiliac joint injections which were based on a systematic review of the evidence.<sup>[1]</sup> The guideline indicates that sacroiliac joint blocks appear to be the evaluation of choice to provide appropriate diagnosis, due to the inability to make the diagnosis of sacroiliac joint-mediated pain with noninvasive tests. The ASIPP guidelines conclude and recommend the following for diagnostic sacroiliac joint blocks:

- The evidence for diagnostic intraarticular sacroiliac joint injections is good with 75% to 100% pain relief as the criterion standard with controlled local anesthetic or placebo blocks, and fair due to the limitation of the number of studies with 50% to 74% relief with a dual block.
- Controlled sacroiliac joint blocks with placebo or controlled comparative local anesthetic blocks are recommended when indications are satisfied with suspicion of sacroiliac joint pain.

### **AMERICAN SOCIETY OF ANESTHESIOLOGISTS TASK FORCE ON CHRONIC PAIN MANAGEMENT AND THE AMERICAN SOCIETY OF REGIONAL ANESTHESIA AND PAIN MEDICINE PRACTICE**

In 2010, the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine Practice updated their guidelines for chronic pain management.<sup>[28]</sup> The guidelines recommend that diagnostic sacroiliac joint injections or lateral branch blocks may be considered for the evaluation of patients with suspected sacroiliac joint pain.

### **AMERICAN PAIN SOCIETY (APS)**

The 2009 practice guidelines from the APS were based on a systematic review that was commissioned by the APS and conducted at the Oregon Evidence-based Practice Center.<sup>[3,29]</sup> The APS guideline states that there is insufficient evidence to evaluate the validity or utility of

diagnostic sacroiliac joint block as a diagnostic procedure for low back pain with or without radiculopathy.

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)

NICE guidance was published in April 2017 on minimally invasive SIJ fusion surgery for chronic sacroiliac pain.<sup>[30]</sup> The recommendations included:

1.1 “Current evidence on the safety and efficacy of minimally invasive sacroiliac (SI) joint fusion surgery for chronic SI pain is adequate to support the use of this procedure.....

1.2 Patients having this procedure should have a confirmed diagnosis of unilateral or bilateral SI joint dysfunction due to degenerative sacroiliitis or SI joint disruption.

1.3 This technically challenging procedure should only be done by surgeons who regularly use image-guided surgery for implant placement. The surgeons should also have had specific training and expertise in minimally invasive SI joint fusion surgery for chronic SI pain.

## SUMMARY

Sacroiliac joint fusion or fixation performed by open procedure is considered standard of care for traumatic injuries, tumors involving the sacrum, and SI joint infection/sepsis as outlined in the Medical Policy Criteria and therefore may be considered medically necessary. Sacroiliac joint fusion performed by an open procedure for any other indication is considered not medically necessary.

There is enough research to show that minimally invasive fusion/stabilization of the sacroiliac joint using a titanium triangular implant improves health outcomes. Additionally, clinical guidelines based on research recommend the use of minimally invasive fusion/stabilization of the sacroiliac joint using a titanium triangular implant. Therefore, minimally invasive fusion/stabilization of the sacroiliac joint using a titanium triangular implant may be considered medically necessary when policy criteria are met.

There is not enough research to show that minimally invasive fusion/stabilization of the sacroiliac joint using any other device improves health outcomes. Therefore, minimally invasive fusion/stabilization of the sacroiliac joint using any other device or when policy criteria are not met is considered investigational.

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## CODES

Codes	Number	Description
CPT	22899	Unlisted procedure, spine
	27096	Injection procedure for sacroiliac joint, anesthetic/steroid, with image guidance (fluoroscopy or CT) including arthrography when performed
	27279	Arthrodesis, sacroiliac joint, percutaneous or minimally invasive (indirect visualization), with image guidance, includes obtaining bone graft when performed, and placement of transfixing device
	27280	Arthrodesis, open, sacroiliac joint, including obtaining bone graft, including instrumentation, when performed
	27299	Unlisted procedure, pelvis or hip joint
HCPCS	None	

**Date of Origin:** December 2014

## ***Left-Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation***

**Effective:** January 1, 2020

**Next Review:** November 2020

**Last Review:** November 2019

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Left atrial appendage (LAA) closure devices have been developed as a nonpharmacologic alternative to anticoagulation for stroke prevention in atrial fibrillation.

### **MEDICAL POLICY CRITERIA**

- I. The use of the WATCHMAN device for percutaneous left atrial appendage closure may be considered **medically necessary** for the prevention of stroke in patients with atrial fibrillation when the following criteria are met:
  - A. There is an increased risk of stroke and systemic embolism based on CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score and systemic anticoagulation therapy is recommended; and
  - B. Clinical documentation that the patient is suitable for short-term anticoagulation but unable to take long-term oral anticoagulation.
- II. The use of any other device for percutaneous left atrial appendage closure or when Criteria I. are not met is considered **investigational**.

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

## POLICY GUIDELINES

The balance of risks and benefits associated with implantation of the Watchman device for stroke prevention, as an alternative to systemic anticoagulation with warfarin, must be made on an individual basis.

Bleeding is the primary risk associated with systemic anticoagulation. A number of risk scores have been developed to estimate the risk of significant bleeding in patients treated with systemic anticoagulation. An example is the HAS-BLED score, which is validated to assess the annual risk of significant bleeding in patients with atrial fibrillation treated with warfarin (Pisters et al, 2010). Scores range from 0 to 9, based on a number of clinical characteristics (see Table PG1).

Risk of major bleeding in patients with scores of 3, 4, and 5 has been reported at 3.74 per 100 patient-years, 8.70 per 100 patient-years, and 12.5 per 100 patient-years, respectively. Scores of 3 or greater are considered to be associated with high risk of bleeding, potentially signaling the need for closer monitoring of patients for adverse risks, closer monitoring of international normalized ratio, or differential dose selections of oral anticoagulants or aspirin (January et al, 2014).

**Table PG1. Clinical Components of the HAS-BLED Bleeding Risk Score**

Letter	Clinical Characteristics	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile international normalized ratios	1
E	Elderly (>65 y)	1

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION:

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

- History and Physical/Chart Notes
- Documentation of FDA approved device to be utilized
- Documentation that supports an increased risk of stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc score and systemic anticoagulation therapy is recommended
- Documentation long-term risks of systemic anticoagulation outweigh the risks of the device implantation

## CROSS REFERENCES

None

## BACKGROUND

Stroke is the most serious complication of atrial fibrillation (AF). The estimated incidence of stroke in untreated patients with AF is 5% per year. Stroke associated with AF is primarily embolic in nature, tends to be more severe than the typical ischemic stroke, and causes higher rates of mortality and disability. As a result, stroke prevention is one of the main goals of AF treatment.

Stroke in AF occurs primarily as a result of thromboembolism from the left atrium. The lack of atrial contractions in AF leads to blood stasis in the left atrium, and this low flow state increases the risk for thrombosis. The area of the left atrium with the lowest blood flow in AF, and therefore the highest risk of thrombosis, is the left atrial appendage (LAA). The LAA is the region responsible for an estimated 90% of left atrial thrombi.

The main treatment for stroke prevention in AF is anticoagulation, which has proven efficacy. The risk for stroke among patients with AF is stratified on the basis of several factors. A commonly used score, the CHADS2 score, assigns 1 point each for the presence of heart failure, hypertension, age 75 years or older, diabetes, or prior stroke or transient ischemic attack. The CHADS2-VASc score includes sex, more age categories, and the presence of vascular disease, in addition to the risk factors used in the CHADS2 score. Warfarin is the predominant agent in clinical use. A number of newer anticoagulant medications, including dabigatran, rivaroxaban, and apixaban, have recently received U.S. Food and Drug Administration (FDA) approval for stroke prevention in nonvalvular AF and have demonstrated noninferiority to warfarin in clinical trials. While anticoagulation is effective for stroke prevention, there is an increased risk of bleeding. Also, warfarin requires frequent monitoring and adjustments, as well as lifestyle changes. Other anticoagulants e.g. apixaban and dabigatran do not require monitoring. However, unlike warfarin, the antithrombotic effects of these anticoagulants are not always reversible with hemostatic drugs. Guidelines from the American College of Chest Physicians recommend the use of oral anticoagulation for patients with AF who are at high risk of stroke (ie, CHADS2 score  $\geq 2$ ), with more individualized choice of antithrombotic therapy in patients with lower stroke risk.<sup>[1]</sup>

Bleeding is the primary risk associated with systemic anticoagulation. A number of risk scores have been developed to estimate the risk of significant bleeding in patients treated with systemic anticoagulation. An example is the HAS-BLED score, which is validated to assess the annual risk of significant bleeding in patients with AF treated with warfarin.<sup>[2]</sup> The score ranges from 0 to 9, based on a number of clinical characteristics, including the presence of hypertension, renal and liver function, history of stroke, bleeding, labile international normalized ratios (INRs), age, and drug/alcohol use. Scores of 3 or greater are considered to be associated with high risk of bleeding, potentially signaling the need for closer monitoring of the patient for adverse risks, closer monitoring of INRs, or differential dose selections of oral anticoagulants or aspirin.<sup>[3]</sup>

Surgical removal, or exclusion, of the LAA is often performed in patients with AF who are undergoing open heart surgery for other reasons. Percutaneous LAA closure devices have been developed as a nonpharmacologic alternative to anticoagulation for stroke prevention in AF. The devices may prevent stroke by occluding the LAA, thus preventing thrombus formation.

Several versions of LAA occlusion devices have been developed. The WATCHMAN™ left atrial appendage system (Boston Scientific, Maple Grove, MN) is a self-expanding nickel

titanium device. It has a polyester covering and fixation barbs for attachment to the endocardium. Implantation is performed percutaneously through a catheter delivery system, using venous access and transseptal puncture to enter the left atrium. Following implantation, patients are anticoagulated with warfarin or alternative agents for approximately 1 to 2 months. After this period, patients are maintained on antiplatelet agents (ie, aspirin and/or clopidogrel) indefinitely. The Lariat® Loop Applicator is a suture delivery device that is intended to close a variety of surgical wounds in addition to left atrial appendage closure. The Cardioblate® closure device developed by Medtronic is currently being tested in clinical studies. The Amplatzer® cardiac plug (St. Jude Medical, Minneapolis, MN), is FDA-approved for closure of atrial septal defects but not LAA closure device. A second-generation device, the Amplatzer Amulet, has been developed. The Percutaneous LAA Transcatheter Occlusion device (eV3, Plymouth, MN) has also been evaluated in research studies but has not received FDA approval.

## REGULATORY STATUS

In 2009, the WATCHMAN™ Left Atrial Appendage Closure Technology (Boston Scientific, Marlborough, MA) was originally considered by the FDA for approval based on the results the results of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT-AF) randomized controlled trial (RCT). The device underwent three panel reviews before it was approved by FDA through the premarket approval process in March 2015. This device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with nonvalvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a nonpharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

The Atriclip™ LAA Exclusion System was cleared for marketing by the FDA through the 510(k) process. The FDA indicates the device is indicated for the occlusion of the heart's left atrial appendage, under direct visualization, in conjunction with other open cardiac surgical procedures. Direct visualization, in this context requires that the surgeon is able to see the heart directly, without assistance from a camera, endoscope, etc., or any other viewing technology. This includes procedures performed by sternotomy (full or partial as well as thoracotomy (single or multiple)).<sup>[4]</sup>

At least two other devices have been studied for LAA occlusion, but are not approved in the US for percutaneous closure of the LAA. In 2006, the Lariat® Loop Applicator device (SentreHEART, Redwood City, CA), a suture delivery system, was cleared for marketing by the FDA through the 510(k) process. The intended use is to facilitate suture placement and knot tying in surgical applications where soft tissues are being approximated or ligated with a pretied polyester suture. The Amplatzer Amulet® device (St. Jude Medical, Plymouth, MN) has a CE approval in Europe for LAA closure, but is not currently approved in the US for any indication.

## EVIDENCE SUMMARY

The standard treatment for stroke prevention in atrial fibrillation is anticoagulation, which has

proven effectiveness. In order to determine the safety and effectiveness of left atrial appendage (LAA) closure devices for the prevention of stroke in atrial fibrillation, large, well-designed randomized controlled trials (RCTs) that compare LAA to no therapy (patients with a prohibitive risk for oral anticoagulation), oral anticoagulation, or open surgical repair are needed. For chronic conditions such as atrial fibrillation, RCTs with long-term follow-up are necessary in order to determine the durability of any beneficial treatment effects.

The evidence on the efficacy of LAA closure devices consists of numerous nonrandomized studies of various occlusion devices, and two published RCTs of the WATCHMAN™ device that compared LAA closure with warfarin anticoagulation. The evidence for each device is summarized separately since the devices are not similar in design and may have unique considerations.

## **WATCHMAN™ DEVICE**

The review of the evidence related to the efficacy of the WATCHMAN™ device is based, in part, on a Blue Cross Blue Shield Association (BCBSA) TEC Assessment developed in June 2014, which evaluated use of the WATCHMAN™ device for patients who were eligible and ineligible for anticoagulation therapy and determined that it does not meet Technology Evaluation Criteria.<sup>[5]</sup> In addition, the PROTECT-AF and the PREVAIL RCTs evaluated the WATCHMAN™ device. The PROTECT-AF study by Holmes reported outcomes for 18 months of follow-up.<sup>[6]</sup> Noninferiority criteria were met and then the results of the final analysis were published by Reddy at a mean follow-up of 2.3 years.<sup>[7]</sup> The FDA reviewed the trial data in 2009 but the data was at a slightly earlier time point than the Holmes analyses. The FDA revealed several concerns during their review that were not reported by the peer reviewed published evidence.<sup>[8]</sup> As a result, the FDA in coordination with the trial sponsors, developed the PREVAIL trial which had different entry criteria. Study participants from the PROTECT-AF trial were included in the analysis of the PREVAIL trial if they met inclusion criteria. The quality of the two RCTs were assessed as fair by the BCBSA TEC report indicating important methodological limitations in both studies. BCBSA TEC assessment reports the following regarding the quality of the PROTECT-AF and PREVAIL trials:

“Subject characteristics were balanced between groups. Losses to follow-up in the PROTECT-AF trial were not reported in peer-reviewed publications, and, according to FDA documents, appear to be unbalanced between treatment groups. Losses to follow-up are not clearly reported in FDA documents on the PREVAIL trial, but also appear to be unbalanced between treatment groups. Patients receiving the WATCHMAN™ device underwent more intensive surveillance for thrombosis after device implantation, and continued anticoagulation if concerns about thrombosis arose. Although this was part of the treatment protocol, it makes determinations of efficacy less certain, because there could be a benefit to imaging surveillance alone.”

## **SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS**

Blue Cross Blue Shield Association (BCBSA) TEC Assessment developed in June 2014 evaluated the use of the WATCHMAN™ device for patients who were eligible and ineligible for anticoagulation therapy and determined that the WATCHMAN™ device did not meet Technology Evaluation Criteria. Although the WATCHMAN™ device and other LAA closure devices would ideally represent an alternative to oral anticoagulation for the prevention of stroke in patients with AF, during the postimplantation period, the device may be associated with increased thrombogenicity and, therefore, anticoagulation is used during the

periprocedural period. Most studies evaluating the WATCHMAN™ device have included patients who are eligible for anticoagulation. There are two main RCTs for the WATCHMAN™ device and the quality of the two RCTs were assessed as fair by the BCBSA TEC report indicating important methodological limitations in both studies. The TEC assessment made the following conclusions about the use of LAA closure in patients without contraindications to anticoagulation:

“We identified two randomized controlled trials (RCTs) and one case series evaluating the WATCHMAN™ device. The RCTs were noninferiority trials and compared LAAC with anticoagulation. The first trial showed a lower rate of a composite outcome (stroke, death, and embolism) in patients receiving LAAC and met noninferiority criteria compared with anticoagulation, but FDA review noted problems with patient selection, potential confounding with other treatments, and losses to follow-up. The second trial, which incorporated the first trial’s results as a discounted informative prior in a Bayesian analysis, showed similar rates of the same composite outcome but did not meet noninferiority criteria. The second trial met its second principal outcome noninferiority criteria in one of two analyses and a performance goal for short-term complication rate. When assessing the results of both trials, the relative performance of LAAC and anticoagulation is uncertain.”<sup>[5]</sup>

In addition, the BCBSA TEC concluded that the evidence is insufficient to make conclusions about improvement in net health outcomes compared to established alternatives.

There are several meta-analyses but the most rigorous is a patient level meta-analysis by Holmes. Holmes (2015) reported results of a patient-level meta-analysis that included data from the industry-sponsored PROTECT AF and PREVAIL trials.<sup>[9]</sup> The PROTECT AF and PREVAIL registries were designed to include patients with similar baseline characteristics as their respective RCTs. The meta-analysis included a total of 2,406 patients, 1,877 treated with the WATCHMAN™ device and 382 treated with warfarin alone. Mean patient follow-up durations were 0.58 years and 3.7 years, respectively, for the PREVAIL continued access registry and the PROTECT AF continued access registry. In a meta-analysis of 1,114 patients treated in the RCTs, compared with warfarin, LAA closure met the study’s noninferiority criteria for the primary composite efficacy end point of all-cause stroke, systemic embolization, and cardiovascular death (hazard ratio [HR], 0.79, 95% confidence interval [CI], 0.52 to 1.2;  $p=0.22$ ). All-cause stroke rates did not differ significantly between groups (1.75 per 100 patient-years for LAA closure vs 1.87 per 100 patient-years for warfarin; HR=1.02; 95% CI, 0.62 to 1.7;  $p=0.94$ ). However, LAA closure–treated patients had higher rates of ischemic stroke (1.6 events/100 patient-years vs 0.9 events/100 patient-years; HR=1.95,  $p=0.05$ ) when procedure-related strokes were included, but had lower rates of hemorrhagic stroke (0.15 events/100 patient-years vs 0.96 events/100 patient-years; HR=0.22; 95% CI, 0.08 to 0.61;  $p=0.004$ ).

A second patient-level meta-analysis of the two RCTs evaluated bleeding outcomes.<sup>[10]</sup> There were a total of 54 episodes of major bleeding, with the most common types being gastrointestinal (GI) bleed (31/54 [57%]) and hemorrhagic stroke (9/54 [17%]). On combined analysis, the rate of major bleeding episodes over the entire study period did not differ between groups. There were 3.5 events per 100 patient-years in the WATCHMAN™ group compared with 3.6 events per 100 patient-years in the anticoagulation group, for a rate ratio (RR) of 0.96 (95% CI, 0.66 to 1.40;  $p=0.84$ ). However, there was a reduction in bleeding risk for the WATCHMAN™ group past the initial periprocedural period. For bleeding events

occurring more than seven days postprocedure, the event rates were 1.8 per 100 patient-years in the WATCHMAN™ group compared with 3.6 per 100 patient-years in the anticoagulation group (RR=0.49; 95% CI, 0.32 to 0.75; p=0.01). For bleeding events occurring more than six months post procedure (the time at which antiplatelet therapy is discontinued for patients receiving the WATCHMAN™ device), the event rates were 1.0 per 100 patient-years in the WATCHMAN™ group compared with 3.5 per 100 patient-years in the anticoagulation group (RR=0.28; 95% CI, 0.16 to 0.49; p<0.001).

## Randomized Controlled Trials

The first RCT published was the PROTECT AF study,<sup>[6]</sup> which was a randomized, unblinded trial that evaluated the noninferiority of an LAA closure device compared with warfarin for stroke prevention in AF. The trial randomized 707 patients from 59 centers in the United States and Europe to the WATCHMAN™ device or warfarin treatment in a 2:1 ratio. Mean follow-up was 18±10 months. The primary efficacy outcome was a composite end point of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism. There was also a primary safety outcome, a composite end point of excessive bleeding (intracranial or gastrointestinal [GI] bleeding) and procedure-related complications (pericardial effusion, device embolization, and procedure-related stroke). There were noted limitations to this study including inclusion of patients with low stroke risk (CHADS2 scores of 1), high rates of adjunctive antiplatelet therapy use in both groups, and generally poor compliance with warfarin therapy in the control group.

The primary efficacy outcome occurred at a rate of 3.0 per 100 patient years in the LAA closure group compared with 4.9 per 100 patient years in the warfarin group (rate ratio [RR], 0.62; 95% credible interval [CrI], 0.35 to 1.25). Based on these outcomes, the probability of noninferiority was greater than 99.9%. For the individual components of the primary outcome, cardiovascular/unexplained death and hemorrhagic stroke were higher in the warfarin group. In contrast, ischemic stroke was higher in the LAA closure group at 2.2 per 100 patient years compared with 1.6 per 100 patient years in the warfarin group (RR=1.34; 95% CrI, 0.60 to 4.29).

The primary safety outcome occurred more commonly in the LAA closure group, at a rate of 7.4 per 100 patient years compared with 4.4 per 100 patient years in the warfarin group (RR=1.69; 95% CrI, 1.01 to 3.19). The excess in adverse event rates for the LAA closure group was primarily the result of early adverse events associated with placement of the device. The most frequent type of complication related to LAA closure device placement was pericardial effusion requiring intervention, which occurred in 4.8% of patients (22/463).

Longer term follow-up from the PROTECT AF study was reported by Reddy (2013).<sup>[11]</sup> At a mean follow-up of 2.3 years, the results were similar to the initial report. The relative risk for the composite primary outcome in the WATCHMAN™ group compared with anticoagulation was 0.71, and this met noninferiority criteria with a confidence of greater than 99%. Complications were more common in the WATCHMAN™ group, with an estimated rate of 5.6%/year in the WATCHMAN™ group compared with 3.6%/year in the warfarin group. Outcomes through four years of follow-up were reported by Reddy et al in 2014.<sup>[12]</sup> Mean follow-up was 3.9 years in the LAA closure group and 3.7 years in the warfarin group. In the LAA closure group, warfarin was discontinued in 345 of 370 patients (93.2%) by the 12 month follow-up evaluation. During the follow-up period, the relative risk for the composite primary outcome in the WATCHMAN™ group compared with anticoagulation was 0.60 (8.4% in the

device group vs 13.9% in the anticoagulation group; 95% CrI, 0.41 to 1.05), which met the noninferiority criteria with a confidence of greater than 99.9%. Fewer hemorrhagic strokes occurred in the WATCHMAN™ group (0.6% vs 4.0%; RR=0.15; 95% CrI, 0.03 to 0.49), and fewer cardiovascular events occurred in the WATCHMAN™ group (3.7% vs 0.95%; RR=0.40; 95% CrI, 0.23 to 0.82). Rates of ischemic stroke did not differ significantly between groups, but WATCHMAN™ group patients had lower all-cause mortality than anticoagulation group patients (12.3% vs 18.0%; HR=0.66; 95% CI, 0.45 to 0.98; p=0.04).

Alli (2013) reported quality-of-life parameters, as measured by change in scores on the Short-Form 12-Item Health Survey from baseline to 12-month follow-up, for a subset of 547 subjects in the PROTECT AF study.<sup>[13]</sup> For the subset of PROTECT AF subjects included in the present analysis, at baseline, control group subjects had a higher mean CHADS2 score (2.4 vs 2.2; p=0.052) and were more likely to have a history of coronary artery disease (49.5% vs 39.6%; p=0.028). For subjects in the WATCHMAN™ group, the total physical score improved in 34.9% and was unchanged in 29.9%; for those in the warfarin group, the total physical score improved in 24.7% and was unchanged in 31.7% (p=0.01).

A second RCT, the PREVAIL trial, was conducted after the 2009 FDA decision on the WATCHMAN™ device to address some of the limitations of the PROTECT AF study, including its inclusion of patients with low stroke risk (CHADS2 scores of 1) and generally poor compliance with warfarin therapy in the control group. Results from the PREVAIL trial were initially presented in FDA documentation, and published in peer-reviewed form by Holmes et al in 2014.<sup>[9]</sup> In the PREVAIL trial, 461 subjects enrolled at 41 sites were randomized in a 2:1 fashion to either the WATCHMAN™™ device or control, which consisted of either initiation or continuation of warfarin therapy with a target international normalized ratio (INR) of 2.0 to 3.0. Subjects had nonvalvular AF and required treatment for prevention of thromboembolism based on a CHADS2 score of two or higher (or ≥1 with other indications for warfarin therapy based on American College of Cardiology/American Heart Association/European Society of Cardiology guidelines) and were eligible for warfarin therapy. In the device group, warfarin and low-dose aspirin were continued until 45 days postprocedure; if a follow-up echocardiogram at 45 days showed occlusion of the LAA, warfarin therapy could be discontinued. Subjects who discontinued warfarin were treated with aspirin and clopidogrel for six months post device implantation and with 325 mg aspirin indefinitely after that.

Three noninferiority primary efficacy end points were specified: (1) occurrence of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and systemic embolism (18-month rates); (2) occurrence of late ischemic stroke and systemic embolization (beyond seven days postrandomization, 18-month rates); and (3) occurrence of all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention (eg, pseudoaneurysm repair, arteriovenous fistula repair, or other major endovascular repair) occurring within seven days of the procedure or by hospital discharge, whichever was later. The 18-month event rates were determined using Bayesian statistical methods to integrate data from the PROTECT-AF study. All patients had a minimum follow-up of six months. For randomized subjects, mean follow-up was 11.8 months and median follow-up was 12.0 months (range, 0.03-25.9 months).

The first primary end point, the 18-month modeled RR between the device and control groups was 1.07 (95% CrI, 0.57 to 1.89). Because the upper bound of the 95% CrI was above the preset noninferiority margin of 1.75, the noninferiority criteria were not met. For the second primary end point of late ischemic stroke and systemic embolization, the 18-month RR

between the device and control groups was 1.6 (95% CrI, 0.5 to 4.2), with an upper bound of the 95% CrI above the preset noninferiority margin of 2.0. The rate difference between the device and control groups was 0.005 (95% CrI, -0.019 to 0.027). The upper bound of the 95% CrI was lower than the noninferiority margin of 0.0275, so the noninferiority criterion was met for the rate difference. For the third primary end point, major safety issues, the noninferiority criterion was met.

Reddy (2017) published a study on the five-year outcomes after left atrial appendage closure, for patients who participated in the PREVAIL and/or PROTECT AF trials.<sup>[14]</sup> When evaluating the five-year findings the authors stated that if procedure related strokes are excluded, ischemic stroke and systemic embolism differences did not vary significantly (HR: 1.40; 95% CI: 0.76 to 2.59;  $p = 0.28$ ). But, hemorrhagic stroke was significantly reduced with left atrial appendage closure (HR: 0.20; 95% CI: 0.07 to 0.56;  $p = 0.0022$ ). The authors go on to state patients enrolled in the studies had to be able to take oral anticoagulants; thus, the results do not tell you anything about patients unable to take oral anticoagulants. Since the PREVAIL and/or PROTECT AF trials, novel oral anticoagulants have become routinely prescribed and have not been compared to left atrial appendage closure. They stated additional studies are needed to compare left atrial appendage closure to other oral anticoagulants and to determine outcomes for patients unable to take oral anticoagulants. There are studies underway. It is important to note that there is potential conflict of interest with several authors.

### **Nonrandomized Studies**

Saw (2017) evaluated safety and effectiveness of the WATCHMAN™ for 106 patients who cannot take anticoagulants and who had nonvalvular atrial fibrillation.<sup>[15]</sup> 97.2% of the patients had successful LAA closure, with one device embolization, one implant being placed too deep, and one cardiac perforation requiring repair prior to device implantation. The major combined safety event rate was 1.9% (one death and one device embolization). Follow-up occurred  $210 \pm 182$  days, noting two transient ischemic events. The authors stated that their early experience is that the WATCHMAN™ is safe and effective for patients who cannot be on anticoagulation therapy, but that there were study limitations including a small sample size, varied antithrombotic therapy and device surveillance, and both the device and events were not adjudicated. Additional studies must evaluate how the Watchman™ device impacts healthcare outcomes.

Main (2016) evaluated follow-up transesophageal (TEE) studies for how often device related thrombus (DRT) occurred in patients in the PROTECT-AF trial.<sup>[16]</sup> In all, 93 follow-up TEEs in 35 patients (33 at 45-day follow-up, 33 at six-month follow-up, and 27 at one-year follow-up) were assessed. The assessment process included a three-phase adjudication (an interactive training program, an interpretation process, development of DRT criteria, and a final determination of DRTs related to the Watchman™ device). This assessment found device related DRTs in 5.7% of the patients, with DRTs not as common at 45 days, when patients continued on Warfarin. The authors noted study limitations, including but not limited the fact that event adjudication studies tend to underestimate events that occur, the TEE studies varied in clinical quality, and anticoagulant routine data was not completely documented. In addition, there is potential conflict of interest identified in the article.

A number of small published case series are primarily intended to establish safety and feasibility of the device.<sup>[17-21]</sup> A larger case series of 143 patients from Europe was published in 2011.<sup>[19]</sup> The case series reported successful implantation in 96% (137/143) of patients and

serious complications in 7.0% of patients (10/143). Complications included stroke (n=3), device embolization (n=2), and pericardial effusion (n=5). Another larger case series was reported by Reddy et al<sup>[20]</sup>, primarily focusing on the adverse event rate from a registry of 460 patients who received the WATCHMAN™ device. Serious pericardial effusion occurred in 2.2% of patients, and there were no deaths or periprocedural strokes reported. Matsuo et al reported results from a case series of 179 patients who underwent LAA closure at a single center, most (n=172) of whom received a WATCHMAN™ device.<sup>[22]</sup> Device deployment was successful in 98.9% of patients. The overall complication rate was 11.2%; major complications occurred in 3.3% (tamponade in two cases; possible transient ischemic attack [TIA] in one case; device dislocation in three cases). At 45-day follow-up, 99.4% of patients (164/166) had closure of the LAA.

Reddy (2016) evaluated adverse events for the WATCHMAN™ since it was FDA approved.<sup>[23]</sup> Adverse events were identified by procedural data collected by the manufacturer clinical specialist present during surgery. Implantation was deemed successful in 95% of consecutive cases (3,653 out of 3,822 total). The complications included 39 pericardial tamponades (1.02%; 24 treated percutaneously, 12 surgically and 3 fatal), three procedure-related strokes (0.078%), nine device embolizations (0.24%; 6 requiring surgical removal), and three procedure-related deaths (0.078%).

Bonnet published safety and efficacy data for the WATCHMAN™ device from a small single center registry study.<sup>[24]</sup> There were 23 total patients (mean CHA2DS2-VASc score: 5). The procedural success rate was 95.7% (95% confidence interval: 77.3-100.0) and the reported efficacy was 90.9% (95% confidence interval: 71.0-98.7). No adverse events were reported during or after hospitalization.

Figini (2016) published retrospective results from a single center in Italy between 2009 and 2015.<sup>[25]</sup> The study included 165 patients in which 99 received the Amplatzer Cardiac Plug (ACP) and 66 the WATCHMAN™ system. The mean follow-up was 15 months. A total of five patients died and one patient had an ischemic attack. There were no episodes of definitive stroke recorded or reported. However, there were twenty-six leaks  $\geq 1$  mm detected (23%) and were not found to correlate with clinical events. The authors noted that further investigation is warranted for the small peri-device flow.

There is uncertainty about the role of the WATCHMAN™ device in patients with AF who have absolute contraindications to oral anticoagulants. Reddy et al<sup>[7]</sup> conducted a multicenter, prospective, nonrandomized trial to evaluate the safety and efficacy of LAA closure with the WATCHMAN™ device in patients with nonvalvular AF with a CHADS2 score 1 or higher who were considered ineligible for warfarin. Postimplantation, patients received 6 months of clopidogrel or ticlopidine and lifelong aspirin therapy. Thirteen patients (8.7%) had a procedure- or device-related serious adverse event, most commonly pericardial effusion (three patients). Over a mean 14.4 months of follow-up, all-cause stroke or systemic embolism occurred in four patients.

Chun (2013) compared the WATCHMAN™ device with the Amplatzer cardiac plug among patients with nonvalvular AF in a prospective cohort study, who were at high risk for stroke and had a contraindication to or were not willing to accept oral anticoagulants.<sup>[26]</sup> Eighty patients were assigned to LAA occlusion with the WATCHMAN™ or the Amplatzer device. After device implantation, either preexisting oral anticoagulation therapy or dual platelet inhibition with aspirin and clopidogrel was continued for six weeks. A follow-up transesophageal

echocardiogram was performed at six weeks postprocedure; if a device-related thrombus had formed, patients received intensive antithrombotic therapy for six weeks. Aspirin was continued indefinitely for all patients. The primary end point of successful device implantation occurred in 98% of patients. There were no statistically significant differences in procedure time, fluoroscopy time, or major safety events between the two groups. At a median 364 days of follow-up, there were no cases of stroke/TIA or other bleeding complications.

The EWOLUTION WATCHMAN™ registry is intended to evaluate procedural success, long-term outcomes, and adverse events in real-world settings. This registry compiles data from patients receiving the WATCHMAN™ device at 47 centers in 13 countries. A publication from the EWOLUTION registry in 2016 reported on 30-day outcomes of device implantation in 1,021 patients.<sup>[27]</sup> The overall population had a risk of bleeding that was substantially higher than that for patients in the RCTs. Over 62% of patients included in the registry were deemed ineligible for anticoagulation by their physicians. Approximately one-third of patients had a history of major bleeding, and 40% had HAS-BLED scores of 3 or greater, indicating moderate-to-high risk of bleeding. Procedural success was achieved in 98.5% of patients, and 99.3% of implants demonstrated no blood flow or minimal residual blood flow postprocedure. Serious adverse events due to the device or procedure occurred at an overall rate of 2.8% (95% CI, 1.9% to 4.0%) at 7 days and 3.6% (95% CI, 2.5% to 4.9%) at 30 days. The most common serious adverse event was major bleeding.

## Network Analyses

Sahay (2017) performed a network meta-analysis to evaluate the safety and effectiveness of LAAC versus other strategies to prevent stroke in AF patients.<sup>[28]</sup> Nineteen RCTs with 87,831 patients were evaluated. The authors stated that although LAAC was found to be better than anticoagulant therapy and similar to novel anticoagulants, the results should be carefully analyzed.

Bajaj (2016) conducted a network meta-analysis of published RCTs evaluating multiple novel oral anticoagulants and left atrial appendage closure devices (WATCHMAN™) which have been tested against dose-adjusted vitamin K antagonists for stroke prophylaxis in non-valvular atrial fibrillation.<sup>[29]</sup> At the time of the analysis, there were no direct comparisons of these strategies from RCTs. Six RCTs were included in the analysis (N=59,627). Safety and efficacy outcomes were evaluated for six treatment strategies. The analysis showed that all prophylaxis strategies had similar rates of ischemic stroke. The authors also reported that in a cluster analyses, assessing safety and efficacy, apixaban, edoxaban and dabigatran ranked best followed by vitamin K antagonists and rivaroxaban, whereas the WATCHMAN™ left atrial appendage closure device ranked last. All of these strategies had different safety outcomes. The authors concluded that more RCTs are needed that directly compare treatment strategies.

Tereshchenko (2016) published a network meta-analysis that included 21 RCTs (96,017 nonvalvular AF patients; median age, 72 years; 65% males; median follow-up, 1.7 years) in which the safety and efficacy of novel oral anticoagulants (NOACs) (apixaban, dabigatran, edoxaban, and rivaroxaban); vitamin K antagonists (VKA); aspirin; and the WATCHMAN™ device were evaluated.<sup>[30]</sup> The primary efficacy outcome was the combination of stroke and systemic embolism and the primary safety outcome was the combination of major extracranial bleeding and intracranial hemorrhage. The authors concluded that “in comparison to placebo/control, use of aspirin (odds ratio [OR], 0.75 [95% CI, 0.60-0.95]), VKA (0.38 [0.29-0.49]), apixaban (0.31 [0.22-0.45]), dabigatran (0.29 [0.20-0.43]), edoxaban (0.38 [0.26-0.54]),

rivaroxaban (0.27 [0.18-0.42]), and the WATCHMAN™ device (0.36 [0.16-0.80]) significantly reduced the risk of any stroke or systemic embolism in nonvalvular AF patients, as well as all-cause mortality (aspirin: OR, 0.82 [0.68-0.99]; VKA: 0.69 [0.57-0.85]; apixaban: 0.62 [0.50-0.78]; dabigatran: 0.62 [0.50-0.78]; edoxaban: 0.62 [0.50-0.77]; rivaroxaban: 0.58 [0.44-0.77]; and the WATCHMAN™ device: 0.47 [0.25-0.88]).”

## Section Summary

The evidence for the use of the WATCHMAN™ device for stroke prevention in patients with nonvalvular atrial fibrillation who are candidates for oral anticoagulation mainly includes two noninferiority RCTs (PROTECT-AF and PREVAIL) and patient-level meta-analysis of these trials. Both RCTs compare the WATCHMAN™ device to anticoagulation and report on composite outcomes. The first RCT reported noninferiority between the two groups for a composite outcome of stroke, cardiovascular/unexplained death, or systemic embolism up to four years of follow-up. However, there are documented issues with patient selection criteria (i.e. population low risk for stroke), losses to follow-up, and inconsistency between the two groups in the use of other treatments that may have impacted the findings. The second RCT did not demonstrate noninferiority for the same composite outcome as the first trial (stroke, cardiovascular/unexplained death, or systemic embolism). However, the trial reported noninferiority of the WATCHMAN™ device to warfarin for late ischemic stroke and systemic embolization. The meta-analysis of the two trials reported a periprocedural risk of ischemic stroke with the WATCHMAN™ device and a lower risk of hemorrhagic stroke over the long term.

The published RCTs and meta-analysis report mixed results for the primary composite outcome and risk of safety events. In addition, the two RCTs have methodological limitations that may impact not only the RCT but also the meta-analysis findings which includes unblinding, differing stroke risk among study participants, loss of patients to follow-up, and poor compliance to Warfarin in the comparison groups. The current evidence base does not consistently demonstrate a net improvement in health outcomes (balance of benefit and harms) compared with established treatments for preventing stroke in patients with AF who are eligible to receive systemic anticoagulation.

The evidence for patients where the use of oral anticoagulants is not feasible consists of small nonrandomized studies with methodological limitations. These studies report on the placement of the device but many of them do not report on the *comparative* efficacy and safety of LAA closure in preventing strokes in this population. More high quality, comparative evidence is needed.

## LARIAT® DEVICE

The available evidence on the efficacy of the Lariat device for LAA closure consists of a number of small case series.

Litwinowicz (2018) published a non-randomized, non-comparative single-center study of 139 patients undergoing LAAC with the LARIAT® device.<sup>[31]</sup> The study’s primary outcomes were risk of thromboembolism, severe bleeding, and mortality with an average follow-up time of 4.2 years. The results of the study indicated that the rate of thromboembolisms is 0.6% and the severe bleeding rate was 0.8%. The reported mortality rate was 1.6%. The authors concluded that LAAC using this device is a safe and effective treatment for stroke prevention and bleed risk reduction in this population. The authors also noted the significant limitations with this

study including the lack of control group, variability in post-procedure anticoagulation, and relying on calculated stroke or bleeding risks for analyses.

Gianni (2016) published a retrospective multicenter study of 98 patients who underwent LAA ligation with the LARIAT® device.<sup>[32]</sup> How many times and what the clinical implications of a leak were assessed. A transesophageal echocardiography assessed leaks during the procedure, at six and 12 months and after thromboembolic events. Leaks were detected in 5%, 15%, and 20% respectively in patients at the three evaluation periods. The authors stated that because incomplete occlusion can occur, appropriate long-term surveillance should be performed, along with the addition of anticoagulant therapy or percutaneous transcatheter closure as needed.

A SR of published studies on the Lariat device was published in 2016.<sup>[33]</sup> No RCTs were identified. Five case series were selected, with a total of 309 patients (range, 4-154 patients) treated. The combined estimate of procedural success was 90.3%. One (0.3%) death was reported and seven (2.3%) patients required urgent cardiac surgery. The reviewers also searched the MAUDE database for adverse events and found 35 unique reports. Among the 35 reported complications, there were five deaths and 23 cases of emergency cardiac surgery.

Individual case series continue to be published, including a large case series of 712 consecutive patients from 18 U.S. hospitals.<sup>[34]</sup> This series reported a procedural success rate of 95% and complete closure in 98%. There was one death and emergent cardiac surgery was required in 1.4%.

A large case series was reported by Price (2014) in a retrospective multicenter study of early outcomes after use of the Lariat device.<sup>[35]</sup> This study included 154 patients with a median CHADS2 score of 3. Device success, defined as suture deployment and a residual shunt less than 5 mm, was achieved in 94% of patients. Procedural success, defined as device success and no major complication (death, MI, stroke, major bleeding, or emergency surgery) at hospital discharge, was achieved in 86% of patients. Fifteen patients (10%) had at least one major periprocedural complication, and 10% had significant pericardial effusion. Of the 134 patients (87%) who had out-of-hospital outcome data available, the composite out-of-hospital outcome of death, MI, or stroke occurred in four patients (2.9%).

Gianni (2016) published a retrospective, multicenter study including 98 consecutive patients which evaluated the incidence and clinical implications of leaks (acute incomplete occlusion, early and late reopening) following LAA ligation with the LARIAT device.<sup>[32]</sup> Leaks were detected in 5 (5%), 14 (15%), and 19 (20%) patients at the three time points. A total of five patients developed neurological events (four strokes and one transient ischemic attack). Three occurred late and were associated with small leaks (< 5mm). The authors concluded that “incomplete occlusion of the LAA after LARIAT ligation is relatively common and may be associated with thromboembolic events.

Bartus (2013) reported results of a case series that enrolled 89 patients with AF and either a contraindication to warfarin or previous warfarin failure.<sup>[36]</sup> A total of 85 of 89 (96%) had successful left atrial ligation, and 81 of 89 (91%) had complete closure immediately. There were three access-related complications, two cases of severe pericarditis postoperatively, one late pericardial effusion, and two cases of unexplained sudden death. There were two late strokes, which the authors did not attribute to an embolic source. At 1-year follow-up, complete closure was documented by echocardiography in 98% of available patients (n=65). In a smaller, earlier series from the same research group,<sup>[37]</sup> 13 patients were treated with the

Lariat device, 11 of whom were treated as part of percutaneous radiofrequency ablation for AF. One of the 11 procedures was terminated due to unsuccessful placement, and the other 10 procedures were successful, with complete closure verified on echocardiography. There was one procedural complication in which the snare could not be removed and were retrieved by thoracoscopy.

Stone (2013) reported outcomes for 27 patients with AF, a high stroke risk (CHADS2 score  $\geq 2$ ), and contraindications or intolerance to anticoagulation who underwent percutaneous LAA ligation with the Lariat device.<sup>[38]</sup> Acute procedural success was 92.6%; periprocedural complications included 3 cases of pericarditis and 1 periprocedural stroke associated with no long-term disability. A follow-up transesophageal echo was performed in 22 patients at an average of 45 days postprocedure, which demonstrated successful LAA exclusion in all 22. Follow-up was for an average of four months, during which time one stroke and no deaths occurred.

Massumi (2013)<sup>[39]</sup> reported on 21 patients with AF and contraindications to anticoagulation. A total of 20 of 21 patients had successful atrial closure, which was documented by echocardiography to be intact at a mean follow-up of 96 days. No patients had a stroke during a mean follow-up of approximately one year. Complications were reported in 5 of 21 patients. One patient had right ventricular perforation and tamponade requiring surgical intervention. One patient developed pleuropericarditis that required multiple drainage procedures. Three additional patients developed pericarditis within 30 days of the procedure.

## Section Summary

The current studies on the Lariat device are limited to small nonrandomized studies. While these studies report high procedural success, interpretation is limited due to methodological limitations such as small sample size, lack of randomized treatment allocation, and lack of a control group for comparison. Larger-scaled trials are needed to confirm the efficacy and safety of the Lariat device.

## AMPLATZER® CARDIAC PLUG DEVICE

The available evidence on use of the Amplatzer device for left atrial occlusion consists of a number of case series, most of which included less than 40 patients.<sup>[17,40-44]</sup> The largest case series, Nietlispach et al., attempted LAA occlusion in 152 patients from a single institution.<sup>[45]</sup> Amplatzer Cardiac Plugs were used in 120 patients and nondedicated devices were used in 32 patients. Short-term complications occurred in 9.8% of patients (15/152). Longer-term adverse outcomes occurred in 7% of patients including two strokes, one peripheral embolization, and four episodes of major bleeding. Device embolization occurred in 4.6% (7/152) of patients.

Berti (2016) evaluated consecutive, high-risk patients (n=110) with non-valvular atrial fibrillation and contraindications to oral anticoagulants.<sup>[46]</sup> There was a mean follow-up of 30 $\pm$ 12 months. Procedures were performed using the Amplatzer Cardiac Plug or Amulet. Berti reports procedural success (technical success without major procedure-related complications) was achieved in 96.4%. The rate of major procedural complications was 3.6% (three cases of pericardial tamponade requiring drainage and one case of major bleeding). The annual rate of ischemic stroke and other thromboembolic events were 2.2% and 0%, respectively. The annual rate for major bleeding was 1.1%.

Additional case series of patients treated with the Amplatzer device were published including patients from different countries.<sup>[17,25,40,41,47-49]</sup> Many of the case series reported high procedural success, as well as various complications such as vascular complications, air embolism, esophageal injury, cardiac tamponade, and device embolization.

Several studies have reported the use of the Amplatzer device in patients with a contraindication to oral anticoagulation therapy. The largest study reported outcomes, up to four years postprocedure, for 134 patients with nonvalvular AF and a long-term contraindication to oral anticoagulation treated with the Amplatzer device.<sup>[50]</sup> Patients had a median CHA2DS2-VASc score of 4 and were generally considered at high risk for bleeding complications. Postprocedural antithrombotic therapy was tailored to the patient's individual risk profile, but the authors described that, generally, short-term dual antiplatelet therapy (1-2 months) and subsequent indefinite single antiplatelet therapy were prescribed after successful device implantation. Procedural success occurred in 93.3%, and three major procedure-related complications (two cases of cardiac tamponade, one case of pericardial effusion requiring drainage or surgery) occurred. Over a mean follow-up of 680 days, observed annual rates of ischemic strokes and any thromboembolic events were 0.8% and 2.5%, respectively.

Meerkin (2013) reported outcomes for 100 patients with AF, a CHADS2 score of 2 or higher, and a contraindication to oral warfarin who were treated with the Amplatzer device at a single institution.<sup>[51]</sup> All patients were treated with heparin during the procedure; they were maintained on clopidogrel for one month postprocedure and daily aspirin indefinitely. Successful deployment occurred in all patients. There were two significant periprocedural complications, including one pericardial effusion with tamponade and one case of acute respiratory distress with pulmonary edema.

Wiebe (2014) reported results of a retrospective cohort of 60 patients with nonvalvular AF who had a CHADS2-VASc score of at least 1 and contraindications to warfarin anticoagulation who underwent percutaneous LAA closure with the Amplatzer device.<sup>[43]</sup> Contraindications to warfarin included contraindications as defined in the warfarin product label, a history of severe bleeding while receiving anticoagulant therapy, as well as a history of bleeding tendencies in the absence of anticoagulation or blood dyscrasia, along with patients who were unable to maintain a stable INR and those with a known hypersensitivity to warfarin or a high-risk of falling who were also included. Patients received heparin during the closure procedure; they were maintained on clopidogrel for 3 months postprocedure and daily aspirin indefinitely. Device implantation was successful in 95% of patients. Over a median follow-up of 1.8 years, no patients experienced a stroke. The rate of major bleeding complications was 1.9%/year of follow-up.

Urena (2013) reported results from a similar cohort of 52 patients with nonvalvular AF who had a CHADS2-VASc score of at least 2 and contraindication to oral anticoagulation therapy who underwent percutaneous LAA closure with the Amplatzer device.<sup>[44]</sup> Device implantation was successful in all but one patient. There were no periprocedural strokes or death. Over the follow-up period (mean, 20 months), rates of death, stroke, and systemic embolism were 5.8% (3/52), 1.9% (1/52), and 0%, respectively.

Figini (2016) published retrospective results from a single center in Italy between 2009 and 2015.<sup>[25]</sup> The study included 165 patients in which 99 received the Amplatzer Cardiac Plug (ACP) and 66 the WATCHMAN™ system. The mean follow-up was 15 months. A total of five patients died and one patient had an ischemic attack. There were no episodes of definitive

stroke recorded or reported. However, there were twenty-six leaks  $\geq 1$  mm detected (23%) and were not found to correlate with clinical events. The authors noted that further investigation is warranted for the small peri-device flow.

Other smaller case series of patients with contraindication to oral anticoagulation include studies by Danna et al,<sup>[40]</sup> which included 37 patients and reported a 1-year stroke rate of 2.94%, and Horstmann et al,<sup>[52]</sup> which included 20 patients and reported no episodes of strokes over a mean follow-up of 13.6 months.

Gloekler (2015)<sup>[53]</sup> compared outcomes for nonvalvular AF patients treated with the first-generation Amplatzer cardiac plug (n=50) and those treated with the second-generation Amulet device (n=50) in a retrospective analysis of prospectively collected data. There were no significant differences between devices in terms of safety outcomes.

### **Section Summary**

All of the nonrandomized studies report high procedural success, but also report various complications such as vascular complications, air embolism, esophageal injury, cardiac tamponade, and device embolization. Well designed, large RCTs are needed to confirm the efficacy and safety of this device.

### **PLAATO DEVICE**

Bayard (2010) reported on 180 patients with nonrheumatic atrial fibrillation and a contraindication to warfarin and who were treated with the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device.<sup>[54]</sup> Placement was successful in 90% of patients. Two patients died within 24 hours of the procedure (1.1%), and six patients had cardiac tamponade (3.3%), with two required surgical drainage. During a follow-up of 129 patient-years, three strokes were reported for a rate of 2.3% per year. Other case reports and small case series report complications, including multiple reports of thrombus formation at the site of device placement.<sup>[54,55]</sup>

### **Section Summary**

The nonrandomized studies report high procedural success, but also report various complications. Well designed, large RCTs are needed to confirm the efficacy and safety of this device.

### **ATRICLIP DEVICE**

Ad (2015) reported on 24 patients that received the Atriclip PRO. Ninety five percent of patients had nonparoxysmal AF.<sup>[56]</sup> The clip did not deploy in one patient but the procedural success was 95%. Another study reported on 30 procedures for the Atriclip.<sup>[57]</sup> The device was successfully placed in 28 of the 30 patients and the study didn't report any adverse events at follow-up. A multicenter study reported on a total of 71 patients receiving the Atriclip device.<sup>[58]</sup> Safety of the device was assessed at 30 days and there was a three month follow-up for efficacy. One patient was not able to receive the Atriclip device but procedural success was confirmed in 67 of 70 patients. Significant adverse events were reported in 34 of 70 patients. There was no adverse events from the device itself and no perioperative mortality. At the three month follow-up, one patient passed away and 60 of 61 patients still had successful occlusion.

### **Section Summary**

Nonrandomized studies report high procedural success, but also report various complications. Well designed, large RCTs are needed to confirm the efficacy and safety of this device.

## EVALUATIONS OF MULTIPLE DEVICES

Hanif (2017) published a SR of RCTs to compare the risk of stroke in patients with left atrial appendage occlusion (LAAO) versus anticoagulant, antiplatelet, or placebo therapy.<sup>[59]</sup> The impact on operative time, major bleeding, and mortality were assessed. Although LAAO was found to be better than anticoagulant therapy for stroke and mortality, the authors stated the evidence had methodological limitations.

Health Quality Ontario (2017) performed a SR evaluating both clinical and cost effectiveness of left atrial appendage closure devices versus novel anticoagulants e.g. dabigatran or versus Warfarin.<sup>[60]</sup> Five studies compared novel anticoagulants to Warfarin and two compared left atrial appendage closure to Warfarin. The authors concluded that moderate quality evidence indicates left atrial appendage closure is as effective as novel oral anticoagulants for patients with nonvalvular AF, but is cost effective only for patients who cannot take anticoagulants.

Lempereur (2017) published a SR evaluating device associated thrombosis (DAT) for the Watchman™, Amplatzer™ Cardiac Plug (ACP), and Amulet devices from 2008-2015.<sup>[61]</sup> Thirty studies were included. The mean frequency of DAT after LAAO was 3.9% for all devices (82/2118). The reported frequency of DAT six weeks after implant was similar for WM and ACP/Amulet (2.0 versus 2.6%, respectively,  $P = 0.60$ ). The reported frequency of events did not appear to change over time. The conclusion was that DAT was an infrequent complication of LAAO as it occurs mostly in the early post procedure, and there is a low rate of neurological complications. But, the authors stated their review had limitations including lack of a standard definition for DAT amongst studies and that the review was based only on published data. Therefore unpublished, underreported and/or underdiagnosed DATs would impact the review outcomes. Additional larger multicenter studies are needed to determine risks, complications, and treatment efficacy of LAAO.

Wei (2016) published a SR evaluating two RCTs (PROTECT AF and PREVAIL) and 36 observational studies on the safety and effectiveness of left atrial appendage occlusion (LAAO) devices.<sup>[62]</sup> The systems mainly involved in the studies included PLAATO, the Amplatzer® Cardiac Plug device, and WATCHMAN™. Other devices such as nondedicated Amplatzer® occluders, and WaveCrest® were also reviewed. Procedure failure was 0.02 (95% CI: 0:02-0.03), with no heterogeneity amongst studies. All-cause mortality was 0.03 (95% CI: 0.02-0.03) and cardiac/neurological mortality was 0 (95% CI: 0.00-0.01), with low pooled results and no heterogeneity amongst studies. The frequency of stroke/transient ischemic attack was 0.01 (95% CI: 0.01-0.01), with no heterogeneity amongst studies. The frequency of thrombus on devices was 0.01 (95% CI: 0.01-0.02), with no heterogeneity amongst studies. Major hemorrhagic event complications were 0.01 (95% CI: 0.00-0.01), with no heterogeneity amongst studies. Of the devices, most did not differ in the frequency of events except all-cause mortality and cardiac/neurological mortality was higher for the PLAATO group and thrombus occurred more often in the ACP group and less often in the PLATTO group. The authors stated LAAO is safe and effective and there is a low rate of failure, for patients not able to be on long-term anticoagulant therapy. However, the authors stated their study had limitations, including but not limited to the definition of safety and effectiveness varied amongst studies, there were only two RCTs, two large studies did not report cardiac or neurological death frequencies, and the data on specific devices was not always easy to assess.

Li (2016) published a SR to report how effective and safe LAAO devices were for greater than one year, when compared to novel oral anticoagulants (NOACs).<sup>[63]</sup> They evaluated six RCTs and 27 observational studies. The authors stated the RCTs showed that LAAO was not better than NOACs for stroke prevention (odds ratio 0.86), but did show LAAO patients had less hemorrhagic events at follow-up. An analysis of the observational studies showed that LAAO patients had a lower rate of both thromboembolic events (1.8 per 100 patient-years versus 2.4 events per 100 patient-years) and major bleeding (2.2 events per 100 patient-years versus 2.5 events per 100 patient-years). During longer follow-up periods patients with LAAO had less thromboembolic events (2.1, 1.8, and 1.0 events per 100 person-years for 1, 1-2, and > 2 years respectively). The authors stated the SR had limitations, including but not limited to different follow-up durations between LAAO and NOAC groups and number of patients who received LAAO was less than those receiving NOACs. They stated additional studies with consistent homogeneity could assess healthcare outcomes and assist in confirming this study's findings.

Xu conducted a comprehensive literature search for studies evaluating patients after receiving an occlusion device.<sup>[23]</sup> Studies were included if they had at least 10 patients followed for at least six months. Twenty five total studies were included with only two RCTs and the rest were cohort studies (N= 2,779). Xu performed a meta-analysis of stroke events and adverse events after patients received an occlusion device. Xu reported that the adjusted incidence rate of stroke was 1.2/100 person-years (PY) (95% confidence interval [CI], 0.9-1.6/100 PY) and the ischemic and hemorrhagic stroke rates were 1.1/100 PY (95% CI, 0.8-1.4/100 PY) and 0.2/100 PY (95% CI, 0.1-0.3/100 PY), respectively. Additionally, the combined efficacy outcomes (stroke or transient ischemic attacks [TIAs], systemic embolism, or cardiovascular death) was 2.7/100 PY (95% CI, 1.9- 3.4/100 PY). The most common adverse events were major bleeding and pericardial effusions at a rate of 2.6% (95% CI, 1.5%-3.6%) and 2.5% (95% CI, 1.8%-3.2%), respectively.

Sahay conducted a SR of the evidence with a network meta-analysis of all RCTs (N=19) with a total of 87,831 patients.<sup>[64]</sup> The network analysis evaluated the safety and efficacy of left atrial appendage closure compared to other strategies for stroke prevention in atrial fibrillation.<sup>[64]</sup> The network meta-analysis includes direct and indirect comparisons for these various treatment strategies. The analysis compared treatment strategies to warfarin as a common comparator group. The authors reported that "...using warfarin as the common comparator revealed efficacy benefit favoring LAAC as compared with placebo (mortality: HR 0.38, 95% CI 0.22 to 0.67, p<0.001; stroke/SE: HR 0.24, 95% CI 0.11 to 0.52, p<0.001) and APT (mortality: HR 0.58, 95% CI 0.37 to 0.91, p=0.0018; stroke/SE: HR 0.44, 95% CI 0.23 to 0.86, p=0.017) and similar to NOAC (mortality: HR 0.76, 95% CI 0.50 to 1.16, p=0.211; stroke/SE: HR 1.01, 95% CI 0.53 to 1.92, p=0.969)." The rates for major bleeding were comparable. The authors further note that caution should be taken in interpreting these results as more studies are needed to further substantiate the findings especially in light of the wide confidence intervals.

Betts (2016) evaluated the feasibility and long term efficacy of LAAO using a retrospective multicenter registry (July 2009-November 2014).<sup>[65]</sup> The devices included the WATCHMAN™ (63%), Amplatzer™ Cardiac Plug (34.7%), Lariat (1.7%) and Coherex WaveCrest (0.6%). A total of 371 patients were included and the overall procedure success was 92.5% with major adverse events in 3.5% of patients. The authors reported "an annual 90.1% relative risk reduction (RRR) for ischemic stroke, an 87.2% thromboembolic events RRR, and a 92.9% major bleeding RRR were observed, if compared with the predicted annual risks based on CHADS2, CHA2DS2-Vasc, and HAS-BLED scores, respectively, over a follow-up period of

24.7 ± 16.07 months. In addition, the authors reported higher success rates and a reduction in acute major complications in the second half of recruitment.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN COLLEGE OF CARDIOLOGY, HEART RHYTHM SOCIETY, AND SOCIETY FOR CARDIOVASCULAR ANGIOGRAPHY AND INTERVENTIONS

In 2015, the American College of Cardiology (ACC), Heart Rhythm Society (HRS), and Society for Cardiovascular Angiography and Interventions published an overview of the integration of percutaneous LAA closure devices into the clinical practice of patients with AF.<sup>[66]</sup> The overview was organized around questions related to the sites of care delivery for LAA closure devices, training for proceduralists, necessary follow-up data collection, identification of appropriate patient cohorts, and reimbursement. The statement provides general guidelines for facility and operator requirements, including the presence of a multidisciplinary heart team, for centers performing percutaneous LAA closures. The statement does not provide specific recommendations about the indications and patient populations appropriate for percutaneous LAA closure.

### AMERICAN COLLEGE OF CARDIOLOGY, THE AMERICAN HEART ASSOCIATION, AND HEART RHYTHM SOCIETY<sup>[3,67]</sup>

The 2019 ACC/AHA/HRS focused update of the 2014 guidelines on the management of patients with AF recommends surgical occlusion of the LAA with the WATCHMAN device as an alternative to long-term anticoagulation therapy (Class IIB, Level of Evidence: B-NR).

### AMERICAN COLLEGE OF CHEST PHYSICIANS (ACCP)

In 2012, the American College of Chest Physicians published evidence-based clinical best practice guidelines on the use of antithrombotic therapy for prevention of stroke in AF.<sup>[1]</sup> In relation to the use of LAA closure devices, the guidelines states “At this time, we make no formal recommendations regarding LAA closure devices, pending more definitive research in this field.”

## SUMMARY

There is enough research to show that the WATCHMAN device for left atrial appendage closure results in improved health outcomes for the prevention of stroke in patients with atrial fibrillation. Clinical guidelines based on evidence recommend the use of the WATCHMAN device for left atrial appendage closure in certain patients. Therefore, the use of the WATCHMAN device for left atrial appendage closure may be considered medically necessary for the prevention of stroke in patients with atrial fibrillation who are at an increased risk of stroke.

There is not enough research for the use of other left atrial appendage closure devices (e.g., PLAATO, Lariat, Amplatzer, Atriclip) to conclude improved health outcomes and there have been some safety concerns reported. No evidence-based practice guidelines recommend the use of these devices. Therefore, the use of left atrial appendage closure devices is

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investigational when policy criteria are not met including the use of devices other than the WATCHMAN device.

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68. BlueCross BlueShield Association Medical Policy Reference Manual "Left-Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation." Policy No. 2.02.26

## CODES

Codes	Number	Description
CPT	33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation
	93799	Unlisted cardiovascular service or procedure
HCPCS	None	

**Date of Origin:** December 2011

## ***Ablation of Primary and Metastatic Liver Tumors***

**Effective:** March 1, 2020

**Next Review:** November 2020

**Last Review:** January 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Ablation is a method of locoregional therapy used to treat cancerous lesions, including hepatocellular carcinoma and hepatic metastases from other primary cancers.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy addresses locoregional therapies, specifically, percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation for primary and metastatic liver tumors. Please see Cross References for other ablative techniques and indications.

- I. Percutaneous ethanol injection, cryoablation, radiofrequency and microwave local ablative techniques may be considered **medically necessary** for treatment of liver tumors when either of the following (A. or B.) are met:
  - A. In patients *not* currently awaiting liver transplantation, and one or more of the following criteria are met:
    1. Unresectable primary liver tumors [hepatocellular carcinoma] when **all** of the following criteria (a.-c.) are met:
      - a. The tumor(s) is 5 cm or less in diameter; and

- b. There are no more than 3 hepatic lesions; and
      - c. There is documentation that the tumor(s) is unresectable (e.g., due to comorbidities or an estimate of inadequate liver volume following resection).
    - 2. Hepatic metastases from colorectal tumors, including but not limited to adenocarcinoma when **all** of the following criteria (a.-d.) are met
      - a. The metastatic tumor(s) is 5 cm or less in diameter; and
      - b. There are no more than 5 hepatic lesions; and
      - c. There is documentation that the tumor(s) is unresectable (e.g., due to comorbidities, or an estimate of inadequate liver volume following resection; and
      - d. No extrahepatic metastatic disease is present.
    - 3. Hepatic metastases from neuroendocrine tumors when **all** of the following criteria (a.-c.) are met:
      - a. The disease is symptomatic; and
      - b. Systemic therapy has failed to control symptoms; and
      - c. There is documentation that the tumor(s) is unresectable (e.g., due to comorbidities or an estimate of inadequate liver volume following resection)
  - B. As a bridge to liver transplantation when the intent is to prevent tumor progression or decrease tumor size to achieve or maintain a patient's candidacy for liver transplant.
- II. Percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation are considered **investigational** as a treatment for all other benign or malignant liver tumors that do not meet the medical necessity criteria above, including but not limited to the following:
- A. More than 3 hepatocellular carcinoma tumors; more than 5 metastatic colorectal tumors in the liver; or metastatic or primary liver tumors larger than 5 cm in diameter
  - B. Metastases to the liver from organ tumors other than colorectal, asymptomatic neuroendocrine tumors, or neuroendocrine tumors with symptoms controlled by systemic therapy

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

## POLICY GUIDELINES

### NEUROENDOCRINE TUMORS

Neuroendocrine tumors are rare, slow-growing, hormone-secreting tumors that may occur in numerous locations in the body.<sup>[1]</sup> Neuroendocrine tumors include the following:

- Carcinoid Tumors

- Islet Cell Tumors (also known as Pancreatic Endocrine Tumors)
- Neuroendocrine Unknown Primary
- Adrenal Gland Tumors
- Pheochromocytoma/paraganglioma
- Poorly Differentiated (High Grade or Anaplastic)/Small Cell
- Multiple Endocrine Neoplasia, Type 1 (also known as MEN-1 syndrome or Wermer's syndrome)
- Multiple Endocrine Neoplasia, Type 2 a or b (also known as pheochromocytoma and amyloid producing medullary thyroid carcinoma, PTC syndrome, or Sipple syndrome)

Neuroendocrine tumors may also be referred to by their location (e.g., pulmonary neuroendocrine tumors; gastroenteropancreatic neuroendocrine tumors).

Some appendiceal carcinoids, also called adenocarcinoids, goblet cell carcinoids, or crypt cell carcinoids, have mixed histology, including elements of adenocarcinoma. While these biphasic tumors have both neuroendocrine and adenocarcinoma components, the National Comprehensive Cancer Network (NCCN) recommends they be managed according to colon cancer guidelines.

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION

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

1. Specific description of the tumor(s) targeted for treatment including the following:
  - Tumor type (primary vs. metastatic; primary tumor type)
  - The location of tumor(s)
  - The number and size(s) of lesion(s) being treated
2. Rationale for the determination that the patient is not a surgical candidate or the tumor is unresectable
3. Whether the goal of treatment is curative or palliative
4. Comorbidities and any contraindicated treatments (e.g., surgery; radiation therapy)
5. Prior treatments, if any, and tumor response
6. Documentation of whether this treatment is to preserve organ function
7. Include documentation of the presence or absence of extra-hepatic disease

## CROSS REFERENCES

1. [Radioembolization, Transarterial Embolization \(TAE\), and Transarterial Chemoembolization \(TACE\)](#), Medicine, Policy No. 140
2. [Radiofrequency Ablation \(RFA\) of Tumors Other than Liver](#), Surgery, Policy No. 92
3. [Cryosurgical Ablation of Miscellaneous Solid Tumors](#), Surgery, Policy No. 132
4. [Magnetic Resonance \(MR\) Guided Focused Ultrasound \(MRgFUS\) and High Intensity Focused Ultrasound \(HIFU\) Ablation, Surgery](#), Policy No. 139
5. [Microwave Tumor Ablation](#), Surgery, Policy No. 189
6. [Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites](#), Surgery, Policy No. 214

### ABLATIVE TECHNIQUES

#### THERMAL ABLATION

##### Radiofrequency Ablation

Radiofrequency ablation (RFA) is one of a number of locoregional thermal ablation therapies to treat various benign or malignant tumors. RFA kills cells (cancerous and normal) by applying a heat-generating rapidly alternating radiofrequency current through probes inserted into the tumor. The cells killed by RFA are not removed but are gradually replaced by fibrosis and scar tissue. If there is local recurrence, it occurs at the edge of this scar tissue and, in some cases, may be retreated. RFA can be performed as an open surgical procedure, laparoscopically, or percutaneously with ultrasound or computed tomography (CT) guidance. The goals of RFA may include 1) controlling local tumor growth and preventing recurrence; 2) palliating symptoms; and 3) extending survival duration for patients with certain cancerous tumors.

Reports have been published on use of RFA to treat renal cell carcinomas, breast cancer, pulmonary (including primary and metastatic lung tumors), bone, and other tumors including those that are non-cancerous (benign). Well-established local or systemic treatment alternatives are available for each of these tumor types.

Radiofrequency ablation (RFA) has been investigated as a treatment for unresectable hepatic tumors, both as primary treatment and as a bridge to liver transplant. In the latter setting, RFA is being tested to determine whether it can reduce the incidence of tumor progression in patients awaiting transplantation and thus maintain patients' candidacy for liver ablation, transhepatic arterial chemoembolization, microwave coagulation, percutaneous ethanol injection, and radioembolization (yttrium-90 microspheres).

##### Microwave Ablation

Microwave ablation (MWA) is a technique in which the use of microwave energy induces an ultra-high speed, 915 MHz or 2.450 MHz (2.45 GHz), alternating electric field which causes water molecule rotation and the creation of heat. This results in thermal coagulation and localized tissue necrosis. In MWA, a single microwave antenna or multiple antennas connected to a generator are inserted directly into the tumor or tissue to be ablated; energy from the antennas generates friction and heat. The local heat coagulates the tissue adjacent to the probe, resulting in a small, approximately 2-3 cm elliptical area (5 x 3 cm) of tissue ablation. In tumors greater than 2 cm in diameter, 2-3 antennas may be used simultaneously to increase the targeted area of MWA and shorten operative time. Multiple antennas may also be used simultaneously to ablate multiple tumors. Tissue ablation occurs quickly, within one minute after a pulse of energy, and multiple pulses may be delivered within a treatment session depending on the size of the tumor. The cells killed by MWA are typically not removed but are gradually replaced by fibrosis and scar tissue. If there is local recurrence, it occurs at the edges. Treatment may be repeated as needed. MWA may be used to: 1) control local tumor growth and prevent recurrence; 2) palliate symptoms; and 3) extend survival duration.

Complications from MWA are usually considered mild and may include pain and fever. Other potential complications associated with MWA include those caused by heat damage to

normal tissue adjacent to the tumor (e.g., intestinal damage during MWA of the kidney or liver), structural damage along the probe track (e.g., pneumothorax as a consequence of procedures on the lung), liver enzyme elevation, liver abscess, ascites, pleural effusion, diaphragm injury or secondary tumors if cells seed during probe removal. MWA should be avoided in pregnant patients since potential risks to the patient and/or fetus have not been established and in patients with implanted electronic devices such as implantable pacemakers that may be adversely affected by microwave power output.

MWA is an ablative technique similar to radiofrequency or cryosurgical ablation; however, MWA may have some advantages. In MWA, the heating process is active, which produces higher temperatures than the passive heating of radiofrequency ablation and should allow for more complete thermal ablation in a shorter period of time. The higher temperatures reached with MWA (over 100° C) can overcome the “heat sink” effect in which tissue cooling occurs from nearby blood flow in large vessels potentially resulting in incomplete tumor ablation. MWA does not rely on the conduction of electricity for heating, and therefore, does not have electrical current flow through patients and does not require grounding pads be used during the procedure to prevent skin burns. Unlike radiofrequency ablation, MWA does not produce electric noise, which allows ultrasound guidance to occur during the procedure without interference. Finally, MWA can be completed in less time than radiofrequency ablation since multiple antennas can be used simultaneously.

### Regulatory Status

There are several devices cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for MWA. Covidien’s (a subsidiary of Tyco Healthcare) Evident Microwave Ablation System has 510(k) clearance for soft tissue ablation, including partial or complete ablation of non-resectable liver tumors. The following devices have 510(k) clearance for MWA of (unspecified) soft tissue:

- BSD Medical Corporation’s MicroThermX® Microwave Ablation System (MTX-180);
- Valleylab’s (a subsidiary of Covidien) VivaWave® Microwave Ablation System;
- Vivant’s (acquired by Valleylab in 2005) Tri-Loop™ Microwave Ablation Probe;
- MicroSurgeon Microwave Soft Tissue Ablation Device;
- Microsulis Medical’s Acculis Accu2i; and
- NeuWave Medical’s Certus 140™

FDA determined that these devices were substantially equivalent to existing radiofrequency and MWA devices. FDA product code: NEY.

### **CRYOSURGICAL ABLATION**

Cryosurgical ablation (also called cryosurgery, cryotherapy, or cryoablation) kills cells (cancerous and normal) by freezing target tissues, most often by inserting a probe into the tumor through which coolant is circulated. Cryosurgery may be performed as an open surgical technique or as a closed procedure under laparoscopic or ultrasound guidance.

The goals of cryosurgery may include the following:

- Destruction or shrinkage of tumor tissue
- Controlling local tumor growth and preventing recurrence
- Palliating symptoms

- Extending survival duration for patients with certain tumors.

Potential complications associated with cryosurgery in any organ include the following:

- Hypothermic damage to normal tissue adjacent to the tumor (e.g., nerve damage)
- Structural damage along the probe track
- Secondary tumors if cancerous cells are seeded during probe removal.

## Regulatory Status

There are several cryoablation devices cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for use in open, minimally invasive or endoscopic surgical procedures in the areas of general surgery, urology, gynecology, oncology, neurology, dermatology, proctology, thoracic surgery and ear, nose and throat. Examples include:

- Cryocare® Surgical System by Endocare;
- CryoGen Cryosurgical System by Cryosurgical, Inc.;
- CryoHit® by Galil Medical;
- IceRod® CX, IcePearl® 2.1 CX and IceFORCE® 2.1 CX Cryoablation Needles by Galil Medical;
- SeedNet™ System by Galil Medical;
- Visica® System by Sanarus Medical;
- Visual-ICE® Cryoablation System by Galil;
- ERBECRYO 2® Cryosurgical Unit, ERBE USA Incorporated

## PERCUTANEOUS ETHANOL INJECTION

Using a needle, percutaneous ethanol injection (PEI) delivers an injection of 95 percent ethanol directly into a tumor. Multiple treatment sessions may be performed in order to achieve tumor destruction. Prior to RFA, PEI was the most widely accepted, minimally invasive method to treat hepatocellular carcinoma. Like other local ablative techniques, PEI is most successful in small HCC tumors when resection is not an option.

## LIVER (HEPATIC) TUMORS

Hepatic tumors can arise either as primary liver cancer (such as hepatocellular carcinoma, HCC) or by metastasis to the liver from other primary cancer sites. Local therapy for hepatic metastasis may be indicated when there is no extrahepatic disease, which rarely occurs for patients with primary cancers other than colorectal carcinoma or certain neuroendocrine malignancies. At present, surgical resection with adequate margins or liver transplantation constitutes the only treatments available with demonstrated curative potential. Partial liver resection, hepatectomy, is considered the gold standard. However, the majority of hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, or underlying liver reserve.

Locoregional therapies are proposed as a treatment for unresectable hepatic tumors, both as primary treatment, palliative treatment, and as a bridge to liver transplant. In the case of liver transplants, it is hoped that locoregional ablative techniques will reduce the incidence of tumor progression while awaiting transplantation and thus maintain a patient's candidacy for liver transplant during the wait time for a donor organ.

## MULTIPLE ABLATIVE TECHNIQUES

## Systematic Reviews

Glassberg (2019) performed a systematic review and meta-analysis comparing MWA and RFA for the treatment of liver cancer.<sup>[2]</sup> A total of 28 RCTs and observational studies met inclusion criteria. The overall quality of the studies was rated as acceptable and most studies had low or unclear risk of bias across most domains. The meta-analysis indicated that local tumor progression was significantly reduced in patients treated with MWA as compared to RFA, whether the analysis included all studies (30% reduction, RR=0.70, p=0.02) or RCTs only (45% reduction, RR=0.55, p=0.007). No other efficacy or safety outcomes were found to be significantly different between groups.

Di Martino (2019) compared local ablative therapies for resectable colorectal liver metastases in a systematic review and meta-analysis.<sup>[3]</sup> Therapies evaluated included RFA, MWA, cryoablation and electroporation. A total of 20 studies with 860 patients met inclusion criteria. Surgical resection was superior to local ablative therapies with respect to disease-free survival, tumor progression, and overall survival. Compared to surgical resection, RFA reduced one-year disease-free survival (RR 0.83, 95%CI 0.71-0.98), three-year disease-free survival (RR 0.5, 95%CI 0.33-0.76), 5y-DFS (RR 0.53, 95%CI 0.28-0.98) and five-year OS (RR 0.76, 95%CI 0.58-0.98).

Majumdar (2017) published a Cochrane review and network meta-analysis of the management of early and very early-stage HCC.<sup>[4]</sup> Reviewers included 14 RCTs (total N=2533 patients) of nonsurgical treatments compared with each other, sham, or no intervention in patients with unresectable HCC. The quality of the evidence was rated as low or very low for all outcomes. Follow-up ranged from 6 to 37 months. Compared with RFA, mortality was higher for percutaneous acetic acid injection (HR=1.8; 95% CI 1.1 to 2.8; one trial; n=125) and PEI (HR=1.49; 95% CI 1.2 to 1.9; five trials; n=882). No trials reported health-related quality of life.

In 2016, Lan published a network meta-analysis comparing different interventional treatments for early stage HCC.<sup>[5]</sup> A total of 21 RCTs were included that compared transhepatic arterial chemoembolization (TACE), RFA, percutaneous ethanol injection (PEI), and hepatic resection, or combinations of treatments. These studies were all rated at a low-to-moderate risk of bias, with lack of blinding being the most substantial limitation. The primary outcome measures were overall survival (OS) at one, three, and five years posttreatment. The treatments and combinations of treatments were rank-ordered by results on OS. At each time point, the combination of RFA plus TACE was the number one ranked treatment. The combination of RFA plus TACE ranked second highest at one and three years, and was third highest at five years, with hepatic resection ranked second at five years. RFA alone was ranked as the fourth highest treatment at one year and the fifth highest treatment at three and five years.

In 2016, Facciorusso reported results from a systematic review and meta-analysis of one RCT and six retrospective studies (n=774) comparing RFA and MWA for the treatment of unresectable hepatocellular carcinoma (HCC).<sup>[6]</sup> The authors found a non-significant trend of higher complete response rates in the patients treated with MWA (odds ratio (OR) = 1.12, 95% confidence interval (CI) 0.67 to 1.88, p = 0.67]. Overall local recurrence was similar between the two treatment groups (OR 1.01, 95% CI 0.53-1.87, p = 0.98) but MWA outperformed RFA in

cases of larger nodules (OR 0.46, 95% CI 0.24-0.89,  $p = 0.02$ ). Three-year survival was higher after RFA without statistically significant difference (OR 0.95, 95% CI 0.58-1.57,  $p = 0.85$ ). Major complications were more frequent, although not significantly, in MWA patients (OR 1.63, 95% CI 0.88-3.03,  $p = 0.12$ ).

Chinnaratha published a meta-analysis of randomized controlled trials (RCTs) and observational studies that compared the effectiveness and safety of radiofrequency ablation (RFA) to MWA in patients with primary hepatocellular carcinoma (HCC).<sup>[7]</sup> MEDLINE, EMBASE, and Cochrane Central databases were searched between January 1980 and May 2014 for human studies comparing the two technologies. The primary outcome was the risk of local tumor progression (LTP); secondary outcomes were complete ablation, overall survival (OS), and major adverse events. Odds ratios (ORs) were combined across studies using a random-effects model. Ten studies (two prospective, eight retrospective) were included. The overall LTP rate was 14% (176/1298). There was no difference in LTP rates between RFA and MWA (OR=1.01; 95% CI, 0.67 to 1.50;  $p=0.9$ ). The complete ablation rate, one- and three-year OS, and major adverse events were similar between the two modalities ( $p>0.05$  for all). Subgroup analysis showed LTP rates were lower with MWA for treatment of larger tumors (OR=1.88; 95% CI 1.10 to 3.23;  $p=0.02$ ). No significant publication bias was detected nor was interstudy heterogeneity ( $I^2<50%$ ,  $p>0.1$ ) observed for any measured outcomes.

In a 2013 Cochrane review, Weis reviewed studies on RFA for HCC versus other interventions.<sup>[8]</sup> Moderate-quality evidence demonstrated hepatic resection had superior survival outcomes compared with RFA; however, resection might have greater rates of complications and longer hospital stays. Other systematic reviews and meta-analyses have also found superior survival with hepatic resection but higher rates of complications than RFA.<sup>[9-12]</sup> This finding reinforces the use of RFA only for unresectable HCC. The Cochrane review also reported finding moderate quality evidence demonstrating superior survival with RFA over PEI.<sup>[8]</sup> Evidence on RFA versus acetic acid injection, microwave ablation, or laser ablation was insufficient to draw conclusions.<sup>[8]</sup>

A systematic review of randomized trials for HCC treated with percutaneous ablation therapies was conducted by Cho.<sup>[13]</sup> The authors identified four RCTs (total N=652 patients) that compared RFA with PEI. The reviewers concluded that RFA demonstrated significantly improved three-year survival in patients with HCC compared with ethanol injections. Most patients in these studies had one tumor, and more than 75% of the tumors were 3 cm or smaller in size. The three-year survival with RFA ranged from 63% to 81%.

In a 2013, Shen reported on a systematic review of four RCTs and quasi-RCTs (total N=766 patients), to compare RFA with PEI for treatment of HCC nodules up to 3 cm.<sup>[14]</sup> OS was significantly longer for RFA than for PEI at three years (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.48 to 0.90;  $p=0.009$ ), and local recurrence risk was lower with RFA (HR=0.38; 95% CI, 0.15 to 0.96,  $p=0.040$ ). However, there was no difference in distant intrahepatic recurrence, and RFA resulted in more complications.

In a 2013 meta-analysis comparing RFA with cryoablation for HCC, Huang evaluated three prospective studies and one retrospective study.<sup>[15]</sup> Included in the studies were 180 RFA and 253 cryoablation patients. RFA was significantly superior to cryoablation in rates of complications (OR=2.80; 95% CI, 1.54 to 5.09), local recurrence of patient (OR=4.02; 95% CI, 1.93 to 8.39), and local recurrence of tumor (OR=1.96, 95% CI, 1.12 to 3.42). However, mortality did not differ significantly (OR=2.21; 95% CI, 0.45 to 10.8) between groups.

Tiong (2011) conducted a systematic review of the literature from 2000 to 2010 and a meta-analysis of survival and disease recurrence after RFA for HCC.<sup>[16]</sup> Studies reporting on patients with HCC who were treated with RFA, either in comparison to or in combination with other interventions (e.g., surgery, PEI), were eligible for inclusion. Outcome data collected were OS, disease-free survival (DFS), and disease recurrence rates. Only RCTs, quasi-RCTs, and nonrandomized comparative studies with more than 12 months of follow-up were included. Forty-three articles, including 12 RCTs, were included in the review. Most articles reported the use of RFA for unresectable HCC, often in combination with other treatments (e.g., PEI, TACE, surgery). Meta-analysis of five RCTs showed that RFA was better than PEI, with higher OS and DFS rates. Data on RFA compared with microwave ablation were inconclusive. The reviewers concluded that RFA can achieve good clinical outcomes for unresectable HCC.

A 2011 systematic review by Pathak assessed the long-term outcome and complication rates of various ablative therapies used in the management of colorectal liver metastases.<sup>[17]</sup> The literature search was from 1994 to 2010, and study inclusion criteria were minimum one-year follow-up and more than 10 patients. In all, 226 studies were identified, 75 of which met inclusion criteria. Most studies were single-arm, single-center, retrospective, and prospective. There was wide variability in patient groups, adjuvant therapies, and management approaches within individual studies. Several studies combined results for colorectal and non-colorectal metastases, often reporting combined outcomes. End points were not always reported uniformly, with varying definitions of survival time, recurrence time, and complication rates. Cryotherapy (26 studies) had local recurrence rates of 12% to 39%, with mean one-, three-, and five-year survival rates of 84%, 37%, and 17%, respectively. The major complication rate ranged from 7% to 66%. Microwave ablation (13 studies) had a local recurrence rate of 5% to 13%, with a mean one-, three-, and five-year survival of 73%, 30%, and 16%, respectively, and a major complication rate ranging from 3% to 16%. RFA (36 studies) had a local recurrence rate of 10% to 31%, with a mean one-, three-, and five-year survival of 85%, 36%, and 24%, respectively, with major complication rate ranging from 0% to 33%. The authors concluded that ablative therapies offer significantly improved survival compared with palliative chemotherapy alone, with five-year survival rates of 17% to 24%, and that complication rates of commonly used techniques are low.

## RADIOFREQUENCY ABLATION

### RFA AS A PRIMARY TREATMENT OF HEPATOCELLULAR CANCER

#### Systematic Reviews

Li (2019) performed a systematic review and meta-analysis to compare the effectiveness of laparoscopic hepatectomy and RFA.<sup>[18]</sup> A total of 10 studies met inclusion criteria. This included 1570 HCC patients treated with laparoscopic hepatectomy or RFA. The pooled five-year OS rate was significantly higher in the hepatectomy group (OR=0.53, 95% CI=0.40, 0.69,  $p<0.001$ ) analyzed as a whole and in a subgroup analysis of small HCCs (OR=0.47, 95% CI=0.33, 0.66,  $p<0.001$ ). The hepatectomy group also had better one- and three-year disease-free survival rate and a lower recurrence rate, but additionally a higher complication rate (OR=0.64, 95% CI=0.46, 0.89,  $p=0.008$ ).

Si (2019) reported results of a systematic review and meta-analysis of minimally invasive liver surgery compared to RFA for the treatment of small HCC nodules.<sup>[19]</sup> A total of six studies met inclusion criteria, including 313 RFA-treated and 284 surgically treated patients. Three-year OS rates were significantly higher in the surgically treated patients (OR 0.55; 95% CI 0.36 to

0.84), as were three-year disease-free survival rates (OR 0.63; 95% CI 0.41 to 0.98). RFA-treated patients experienced significantly higher rates of local intrahepatic recurrence (OR 2.24; 95% CI 1.47 to 3.42), lower incidence of postoperative complications (OR 0.34; 95% CI 0.22 to 0.53), and shorter operation (OR - 145.31, 95% CI - 200.24 to - 90.38) and hospitalization (OR - 4.02, 95% CI - 4.94 to - 3.10) durations.

Another systematic review comparing surgery to RFA, this one of early HCC, was reported by Tan (2019).<sup>[20]</sup> A total of 11 studies met inclusion criteria. These included 1691 patients undergoing hepatic resection or RFA. The hepatic resection group had statistically significantly higher three- and five-year OS, as well as three-year disease-free survival. This group also had a lower local recurrence rate that did not reach statistical significance. Patients undergoing laparoscopic radiofrequency ablation had higher three- and five-year OS than other minimally invasive ablation techniques.

In 2012, Xu reported on a meta-analysis of 13 studies that compared RFA with surgical resection for early HCC.<sup>[21]</sup> Only two studies were RCTs. Surgical resection was done in 1233 patients and RFA was used in 1302 patients. Surgical resection patients had significantly longer OS rates at one, three, and five years than RFA patients (odds ratio [OR], 0.60; 95% CI, 0.42 to 0.86, OR=0.49; 95% CI, 0.36 to 0.65; OR=0.60; 95% CI, 0.43 to 0.84), respectively. When only HCC tumors of 3 cm or less were analyzed, resection still had significantly better OS than RFA at one, three, and five years. Recurrence rates were also significantly lower in the surgical resection group at one, three, and five years than in the RFA group (OR=1.48; 95% CI, 1.05 to 2.08; OR=1.76; 95% CI, 1.49 to 2.08; OR=1.68; 95% CI, 1.21 to 2.34; all respectively). Local recurrence rates did not differ significantly between procedures. Complication rates were higher with resection than with RFA (OR=6.25; 95% CI, 3.12 to 12.52;  $p=0.000$ ), but, in a subanalysis of HCC 3 cm or less, complication rates were significantly lower with resection than RFA.

### **Randomized Controlled Trials**

Giorgio (2016) conducted an RCT comparing RFA plus chemotherapy with chemotherapy alone in 99 patients who had unresectable HCC invading the portal vein.<sup>[22]</sup> The HCC nodules ranged in size from 2.1 to 6.5 cm. The primary outcome was OS at three years. The OS rates at 1, 2, and three years were 60%, 35%, and 26% in the combined therapy group and 37% and 0% at one and two years in the chemotherapy-alone arm (HR=2.87; 95% CI, 1.61 to 5.39), respectively.

### **Nonrandomized Studies**

A large body of case series, meta-analyses, and retrospective evidence has been published on RFA as a treatment of unresectable primary liver tumors.<sup>[23-29]</sup> These articles reported disease-free survival rates consistent with those reported in the randomized controlled trials.

## **RFA AS A PRIMARY TREATMENT OF INTRAHEPATIC CHOLANGIOCARCINOMAS**

Cholangiocarcinomas are tumors that originate in the bile duct epithelium; 90% are adenocarcinomas. Intrahepatic cholangiocarcinomas (ICC) are located within the hepatic parenchyma. They may also be referred to as peripheral cholangiocarcinomas. Extrahepatic cholangiocarcinomas (ECC) are more common than intrahepatic cholangiocarcinoma and are located within the extrahepatic bile duct. ECC are reviewed under Complete resection with negative margin is potential curative, though recurrence is common and most cases are

unresectable due to advanced disease when diagnosed. For unresectable or metastatic cholangiocarcinomas at any location, the primary treatment may include chemotherapy, treatment within a clinical trial, or best supportive care. RFA and other locoregional therapies may be an option. Biliary drainage with biliary stenting may be warranted for unresectable or metastatic extrahepatic disease. Liver transplantation is potentially curative in carefully selected patients with lymph node negative, nondisseminated locally advanced hilar cholangiocarcinomas and otherwise normal biliary and hepatic function or underlying liver disease precluding surgery.

A number of small ( $n < 20$ ) retrospective analyses and case series have been published for ablation of ICC.<sup>[30-38]</sup> These studies consistently reported high technical effectiveness with early tumor necrosis, and a low rate of major adverse effects.

## **RFA AS A PRIMARY TREATMENT OF UNRESECTABLE LIVER METASTASES OF COLORECTAL AND NEUROENDOCRINE ORIGIN**

### **Colon Cancer**

More than half of patients with colorectal cancer (CRC) will develop liver metastases, generally with a poor prognosis.<sup>[39]</sup> A median survival of 21 months has been observed in patients with a single CRC liver metastasis; those with several unilobar lesions have median survival of 15 months; and those with disseminated metastases have median survival of less than one year. A number of first-line systemic chemotherapy regimens have been used to treat metastatic CRC, with a two-year survival rate of 25% for those treated with 5-fluorouracil (5-FU) or 5-FU plus leucovorin.<sup>[39]</sup> With the introduction of newer agents (eg, irinotecan, oxaliplatin) and targeted drugs (eg, cetuximab, bevacizumab), two-year survival rates have increased to between 30% and 39%, with marked improvement in OS. Because the liver is often the only site of metastases from CRC, however, locoregional therapies have been investigated. Surgical resection is considered the criterion standard for treatment of CRC liver metastases, with five-year actuarial survival rates that historically range from 28% to 38%, but may reach 58% in appropriately selected, resectable patients without widely disseminated disease.<sup>[40,41]</sup> However, only 10% to 25% of patients with CRC metastases are eligible for surgical resection because of the extent and location of the lesions within the liver or because of the presence of comorbid conditions or disseminated disease. Unresectable cases or those for whom surgery is contraindicated typically are treated with systemic chemotherapy, with poor results and considerable adverse effects.

Alternatively, RFA has been proposed to treat metastatic CRC in the liver. Early clinical experience with RFA comprised case series to establish feasibility, safety, tolerability, and local therapeutic efficacy in short-term follow-up. A 2006 literature review encompassing six case series (total  $N = 446$  patients) showed that RFA of unresectable CRC metastases was associated with one-, two-, and three-year survival rates that ranged from 87% to 99%, 69% to 77%, and 37% to 58%, respectively.<sup>[40]</sup> While these results suggested RFA may have clinical benefit in this setting, a primary caveat is the definition of the term “unresectable” in the different series and that different surgeons may have different opinions on this issue. Further, differences in lesion size, number, distribution, prior treatments, RFA technology, and physician experience may affect results, making it difficult to compare results of different studies.

### **Systematic Reviews**

A 2017 systematic review with meta-analyses by van Amerongen compared the RFA to surgery as a curative treatment for patients with colorectal liver metastases.<sup>[42]</sup> Authors found that all studies included had risk of patient selection bias.

A 2012 systematic review by Cirocchi analyzed 17 nonrandomized studies and a meeting abstract of an RCT on RFA for CRC liver metastases.<sup>[43]</sup> The RCT reported PFS was significantly higher in 60 patients receiving RFA plus chemotherapy than in 59 patients receiving only chemotherapy. The RCT did not report OS. This Cochrane review found different types of vulnerability in all reviewed studies. Of main concern was the imbalance in patient characteristics across studies reviewed, as well as heterogeneity in the interventions, comparisons, and outcomes. Therefore, the reviewers concluded the evidence was insufficient to recommend RFA for CRC liver metastasis. In a 2014 Health Technology Assessment, Loveman also found insufficient evidence to draw conclusions on the clinical effectiveness of ablative therapies, including RFA, for liver metastases.<sup>[44]</sup>

In 2012, Weng reported a meta-analysis comparing RFA with liver resection for the treatment of CRC liver metastases.<sup>[45]</sup> One prospective study and 12 retrospective studies were included in the analysis. OS at three and five years was significantly longer in liver resection than in RFA (relative risk [RR], 1.377; 95% CI, 1.246 to 1.522; RR=1.474; 95% CI, 1.284 to 1.692, respectively). DFS was also significantly longer in liver resection than RFA at three and five years (RR=1.735; 95% CI, 1.483 to 2.029; RR=2.227; 95% CI, 1.823 to 2.720, respectively). While postoperative morbidity with liver resection was significantly higher than with RFA (RR=2.495; 95% CI, 1.881 to 3.308), mortality did not differ significantly between treatments. Liver resection also performed significantly better than RFA when data were analyzed in three subgroups: tumors less than 3 cm, solitary tumor, and open or laparoscopic approach. However, hospital stays were significantly shorter (9.2 days vs 3.9 days,  $p<0.01$ ) and rates of complications lower (18.3% vs 3.9%,  $p<0.01$ ) with RFA than liver resection. Interpretation of the meta-analysis is limited by the retrospective nature of most studies.

A review by Guenette in 2010 summarized the literature on the use of RFA for colorectal hepatic metastases.<sup>[46]</sup> Approximately 17 studies with more than 50 patients treated with RFA for colorectal hepatic metastases reported survival. Average tumor size, reported in 15 studies, ranged from 2.1 to 4.2 cm. Five-year OS, reported in 12 studies, ranged from 2% to 55.3% (mean, 24.5%). The largest study series (Lencioni, 2004) included in the review consisted of 423 patients, with average tumor size of 2.7 cm, four or fewer metastases, each 5 cm or less in greatest dimension, and no extrahepatic disease.<sup>[41]</sup> OS in the Lencioni study at one, three, and five years was 86%, 47%, and 24%, respectively. Guenette concluded that 5-year survival rates following RFA were similar to those following resection but that long-term data associated with RFA and colorectal hepatic metastases were sparse, randomized trials have failed recruitment, and patients with resectable disease should undergo resection if possible. However, given the efficacy of RFA compared with chemotherapy alone, they noted that RFA should be considered as a primary treatment option in patients with unresectable disease.

### Randomized Controlled Trials

In 2012 and 2017, Ruers published the results of a multicenter RCT that compared RFA plus systemic treatment with systemic treatment alone for unresectable colorectal liver metastases.<sup>[47,48]</sup> This RCT, originally designed as a phase 3 study, was completed as a phase 2 study due to slow accrual (N=119 patients). To be included in the trial, patients had to have nonresectable liver metastases with fewer than 10 nodes and without extrahepatic disease. In

the experimental arm, RFA, with or without additional resection, was given in combination with systemic therapy. The primary end point was a 30-month survival higher than 38% in the experimental arm with intention-to-treat analysis. At three years, OS did not differ significantly between groups. However, there was a significant improvement in progression-free survival (HR=0.74; 95% CI, 0.42 to 0.95; p=0.025), which corresponded to a difference in progression-free survival at three years from 10.6% in the systemic therapy arm to 27.6% in the combined treatment arm. At a median follow-up of 9.7 years, 39 (65%) of 60 patients in the combined treatment arm had died compared with 53 (89.8%) of 59 in the systemic treatment arm (HR=0.58; 95% CI, 0.38 to 0.88; p=0.01).

### Nonrandomized Studies

Nonrandomized studies in which RFA was compared to resection or systemic chemotherapy in patients with localized CRC metastases and no evidence of additional metastatic disease have been conducted. In 2016, Hof compared outcomes from RFA or hepatic resection in patients with hepatic metastases from CRC.<sup>[49]</sup> There were 431 patients included from an institutional database. All patients underwent locoregional treatment for hepatic metastases from CRC. Initial treatment was either hepatic resection (n=261), open RFA (n=26), percutaneous RFA (n=75), or a combination of resection plus RFA (n=69). Mean follow-up was 38.6 months. The overall recurrence rate was 83.5% (152/182) in patients treated with RFA compared to 66.6% (201/302) in patients treated with hepatic resection (p<0.001). The five-year OS estimate by Kaplan-Meier analysis was 51.9% for RFA and 53.0% for hepatic resection (p=0.98).

Abdalla examined recurrence and survival rates for clinically similar patients treated with hepatic resection only (n=190), resection plus RFA (n=101), RFA only (n=57, open laparotomy by hepatobiliary surgeon), and systemic chemotherapy alone (n=70).<sup>[50]</sup> In the key relevant comparison, RFA versus chemotherapy in chemotherapy-naive patients with nonresectable CRC metastases (median, one lesion per patient; range, 1-8; median tumor size, 2.5 cm), OS at four years was 22% in the RFA group and 10% in the chemotherapy group (p=0.005). Median survival was estimated at 25 months in the RFA group and 17 months in the chemotherapy group (p not reported). Recurrence at a median follow-up of 21 months was 44% in the RFA group and 11% in the resection-only group (p<0.001), although the proportion of patients with distant recurrence as a component of failure was similar (41% resection vs 40% RFA, p=NS).

In a second trial, a consecutive series of well-defined, previously untreated patients (N=201) without extrahepatic disease underwent laparotomy to determine therapeutic approach.<sup>[51]</sup> Three groups were identified: those amenable to hepatic resection (n=117); those for whom resection plus local ablation were indicated (RFA, n=27; cryoablation, n=18); and those deemed unresectable and unsuitable for local ablation (n=39) who received systemic chemotherapy. Median OS was 61 months (95% CI, 41 to 81 months) in resected patients (median, one tumor per patient; range, 1-9; median diameter, 3.8 cm), 31 months (95% CI, 20 to 42 months) in locally ablated patients (median, four tumors per patient; range, 1-19; median diameter, 3 cm per lesion), and 26 months (95% CI, 17 to 35 months) in the chemotherapy patients (median, four tumors per patient; range, 1-17; median diameter, 4 cm per lesion; p=NS, ablated vs chemotherapy). Results from two validated quality-of-life instruments (EuroQol-5D, EORTC QLQ C-30) showed that patients treated by local ablation returned to baseline values within three months, whereas those treated with chemotherapy remained significantly lower (ie, worse quality of life) than baseline over 12 months posttreatment (p<0.05).

In 2011, Van Tilborg reported long-term results in 100 patients with unresectable colorectal liver metastases who underwent a total of 126 RFA sessions (237 lesions).<sup>[52]</sup> Lesion size ranged from 0.2 to 8.3 cm (mean 2.4 cm). Mean follow-up time was 29 months (range, 6-93 months). Major complications (including abscess, hemorrhage, grounding pad burns, and diaphragm perforation) occurred in eight patients. Factors that determined the success of the procedure included lesion size and the number and location of the lesions. Local tumor site recurrence was 5.6% for tumors less than 3 cm, 19.5% for tumors 3 to 5 cm, and 41.2% for those greater than 5 cm. Centrally located lesions recurred more often than peripheral, at 21.4% versus 6.5%, respectively (p=0.009). Mean survival time from the time of RFA was 56 months (95% CI, 45 to 67 months).

## **Neuroendocrine Cancer**

Unlike the above liver tumors, the treatment benefit for RFA of neuroendocrine metastases in the liver is related to symptom control rather than survival or local recurrence. Therefore, patient selection and outcome measures in related studies focused on the level of symptoms rather than lesion size, number, and location. The primary treatment of symptomatic neuroendocrine tumor (NET) metastases is chemotherapy.

### Systematic Reviews

Most reports of RFA treatment for neuroendocrine liver metastases include small numbers of patients or subsets of patients in reports of more than one ablative method or very small subsets of larger case series of patients with various diagnoses. A systematic review of RFA as treatment for unresectable metastases from neuroendocrine tumors was published in 2015.<sup>[53]</sup> Seven unique studies (total N=301 patients) included in the review, all were retrospective case series from a single institution. The most common tumor type was carcinoid (59%), followed by nonfunctional pancreatic tumors (21%) and functional pancreatic tumors (13%). There were two periprocedural deaths (rate, 0.7%), and the overall rate of complications was 10% (including hemorrhage, abscess, viscus perforation, bile leak, biliopleural fistula, transient liver insufficiency, pneumothorax, grounding pad burn, urinary retention, pneumonia, pleural effusion). Improvement in symptoms was reported in 92% (117/127) of symptomatic patients, with a median duration of symptom relief ranging from 14 to 27 months. There was a high degree of variability in the length of follow-up and surveillance used for follow-up, and a wide range of local recurrence rates, from less than 5% to 50%. The reported 5-year survival rates ranged from 57% to 80%.

### Randomized Controlled Trials

No randomized controlled trials of RFA as a treatment for neuroendocrine metastases in the liver were identified.

### Nonrandomized Studies

Fairweather (2017) compared OS in patients with neuroendocrine liver metastases (N=649) from a large prospective database.<sup>[54]</sup> Primary treatment modalities included: systemic therapy (n=316), chemoembolization (n=130), observation (n=117), surgical resection (n=58), and RFA (n=28). The most favorable 10-year OS estimates were achieved with surgical resection (70%), followed by RFA (55%), systemic therapy (31%), chemoembolization (28%), and observation (20%).

Berber analyzed a large series of liver tumors treated with RFA.<sup>[55]</sup> Of 1032 tumors in the study, 295 were neuroendocrine tumor metastases. The mean number of lesions treated was 5.6 (range, 1-16) and mean lesion size was 2.3 cm (range, 0.5-10.0 cm). Local recurrence rates were lower in patients with neuroendocrine tumors than in patients with other tumor types: neuroendocrine tumors (19/295 [6%]), colorectal metastases (161/480 [24%]), non-colorectal, non-neuroendocrine metastases (28/126 [22%]), and HCC (23/131 [18%]). In patients with neuroendocrine tumors, 58% of the recurrences were evident at one year and 100% at two years versus 83% at one year and 97% at two years for colorectal metastases. Eight neuroendocrine tumors were eligible for repeat RFA; seven were retreated, and one was not. Symptom control and survival were not reported.

Mazzaglia reported on a series gathered over 10 years for 63 patients with neuroendocrine metastases who were treated with 80 sessions of LRFA.<sup>[56]</sup> Tumor types were 36 carcinoid, 18 pancreatic islet cell, and nine medullary thyroid cancer. Indications for study enrollment were liver metastases from neuroendocrine tumors, enlarging liver lesions, worsening of symptoms, and/or failure to respond to other treatment modalities and predominance of disease in the liver; patients with additional minor extrahepatic disease were not excluded. RFA was performed 1.6 years (range, 0.1-7.8 years) after diagnosis of liver metastases. Fourteen patients had repeat sessions for disease progression. The mean number of lesions treated at the first RFA session was six and the mean tumor size was 2.3 cm. One week after surgery, 92% of patients had at least partial symptom relief and 70% had complete relief. Symptom control lasted 11 months. Median survival times were 11 years postdiagnosis of the primary tumor, 5.5 years postdiagnosis of the neuroendocrine hepatic metastases, and 3.9 years after the first RFA treatment.

Elias reported on 16 patients who underwent a one-step procedure comprising a combination of hepatectomy and RFA for treatment of gastroenteropancreatic endocrine tumors.<sup>[57]</sup> A mean of 15 liver tumors per patient were surgically removed, and a mean of 12 were ablated using RFA. Three-year survival and DFS rates were similar to those observed in the authors' preliminary series of 47 patients who had hepatectomy with a median of seven liver tumors per patient. Venkatesan reported on six patients treated for pheochromocytoma metastases.<sup>[58]</sup> Complete ablation was achieved in six of seven metastases. Mean follow-up was 12.3 months (range, 2.5-28 months).

## **RFA AS A PRIMARY TREATMENT OF UNRESECTABLE LIVER METASTASES OF OTHER ORIGIN**

### **Breast Cancer**

A number of case series have reported on use of RFA to treat breast cancer liver metastases. In 2014, Veltri analyzed 45 women treated with RFA for 87 breast cancer liver metastases (mean size, 23 mm).<sup>[59]</sup> Complete ablation was seen on initial follow-up in 90% of tumors, but tumor recurrence occurred in 19.7% within eight months. RFA did not impact OS, which at one year was 90% and at three years was 44%.

In a retrospective review, Meloni assessed local control and intermediate- and long-term survival in 52 patients.<sup>[60]</sup> Inclusion criteria were fewer than five tumors, maximum tumor diameter of 5 cm, and disease confined to the liver or stable with medical therapy. Complete tumor necrosis was achieved in 97% of tumors. Median time to follow-up from diagnosis of liver metastasis and from RFA was 37.2 and 19.1 months, respectively. Local tumor progression occurred in 25% of patients, and new intrahepatic metastases developed in 53%.

Median OS, from the time of first liver metastasis diagnosis, was 42 months, and five-year survival was 32%. Patients with tumors 2.5 cm in diameter or larger had worse prognoses than those with smaller tumors. The authors concluded that these survival rates were comparable to those reported in the literature for surgery or laser ablation. In another series of 43 breast cancer patients with 111 liver metastases, technical success (tumor ablation) was achieved in 107 (96%) metastases.<sup>[61]</sup> During follow-up, local tumor progression was observed in 15 metastases. Estimated median OS was 58.6 months. Survival was significantly lower among patients with extrahepatic disease, with the exception of skeletal metastases.

A series of 19 patients was reported by Lawes.<sup>[62]</sup> Eight patients had disease confined to the liver, with 11 also having stable extrahepatic disease. At the time of the report, seven patients, with disease confined to the liver at presentation, were alive, as were six with extrahepatic disease; median follow-up after RFA was 15 months (range, 0-77 months). Survival at 30 months was 41.6%. RFA failed to control hepatic disease in three patients.

## **Sarcoma**

Jones evaluated RFA in a series of patients with sarcoma.<sup>[63]</sup> Thirteen gastrointestinal stromal tumor (GIST) patients and 12 with other histologic subtypes received RFA for metastatic disease in the liver: 12 responded to the first RFA procedure and one achieved stable disease. Two GIST patients received RFA on two occasions for separate lesions within the liver, and both responded to the second RFA procedure. Of the other subtypes, seven underwent RFA to liver lesions, five of whom responded to RFA, one progressed, and one was not assessable at the time of analysis. RFA was well-tolerated in this series of sarcoma patients. RFA may have a role in patients with GIST who have progression in a single metastasis but stable disease elsewhere. The authors advised conducting further larger studies to better define the role of this technique in this patient population.

A case series of 66 patients who underwent hepatic resection (n=35), resection and RFA (n=18), or RFA alone (n=13) was reported by Pawlik.<sup>[64]</sup> After a median follow-up of 35.8 months, 44 patients had recurrence (intrahepatic only, n=16; extrahepatic only, n=11; both, n=17). The one-, three-, and five-year OS rates were 91.5%, 65.4%, and 27.1%, respectively. The authors recommended that patients with metastatic disease who can be rendered surgically free of disease be considered for potential hepatic resection.

## **RFA AS A TREATMENT OF UNRESECTABLE HCC TUMORS IN THE TRANSPLANT SETTING**

The goal of RFA prior to transplantation is to maintain a patient's eligibility for liver transplant by either downsizing a large tumor or by preventing progression of a smaller tumor. The literature related to locoregional therapy for HCC in the transplant setting can be divided into three objectives:

- Prevention of tumor progression while on the waiting list
- Downgrading HCC prior to transplantation
- To reduce risk of post-transplantation tumor recurrence in patients with T3 tumors

Assessment of the effects of pre-transplantation RFA on these objectives would, ideally, include clinical trials that compare the recurrence-free survival of patients who received pretransplant locoregional therapies with those who did not and to study recurrence-free

survival in patients who received locoregional therapies to downsize larger tumor(s) or to prevent progression of smaller tumor(s) in order to meet transplant waiting list criteria.

The current published evidence is limited to case series and retrospective reviews which are considered unreliable due to methodologic limitations such as lack of randomization and lack of a control group for comparison.<sup>[65-74]</sup> In addition to these limitations, current studies targeted only a subset of candidates for liver transplant to treat HCC. Because only patients with adequate liver reserves were offered treatment, it cannot be determined whether any reported increase in recurrence-free survival was related to the pretransplant locoregional therapy or liver reserve status. It is unknown whether patients with adequate liver reserves have improved outcomes regardless of pretransplant management.

### **United Network for Organ Sharing policy**

The United Network for Organ Sharing (UNOS) recognizes pretransplant locoregional therapies including RFA as a component of patient management during the waiting period for a donor liver.<sup>[75]</sup> In allocating donor organs, UNOS sought to balance risk of death on the waiting list against risk of recurrence after transplant. For HCC, part of this balance included tumor size and number of nodules as follows:

T1: 1 nodule 1.9 cm or smaller

T2: 1 nodule between 2.0–5.0 cm, or 2 or 3 nodules each smaller than 3.0 cm

T3: 1 nodule larger than 5.0 cm, or 2 or 3 nodules with at least 1 larger than 3.0 cm

Patients with T1 lesions were considered at low risk of death on the waiting list, while those with T3 lesions were considered at high risk of post-transplant recurrence. Patients with T2 tumors were considered to have an increased risk of dying while on the waiting list compared with T1 lesions, and an acceptable risk of post-transplant tumor recurrence. Therefore, the UNOS criteria prioritized T2 HCC. In addition, patients could be removed from the waiting list if they were determined to be unsuitable for transplantation based on progression of HCC. Thus these criteria provide incentives to use locoregional therapies to maintain T2 classification.

The UNOS allocation system provides incentives to use locoregional therapies in two different settings:

To downsize T3 tumors to T2 status to meet the UNOS criteria for additional allocation points; or to prevent progress of T2 tumors while on the waiting list to maintain the UNOS allocation points.

These two indications are discussed further here. It should be noted that the UNOS policy addresses the role of locoregional therapy in the pretransplant setting as follows:

Organ Procurement and Transplant Network (OPTN) Class 5T (Treated) nodules are defined as any OPTN Class 5 or biopsy-proven HCC lesion that was automatically approved upon initial application or extension and has subsequently undergone locoregional treatment. OPTN Class 5T nodules qualify for continued priority points predicated on the pre-treatment classification of the nodule(s) and are defined as:

- Past loco-regional treatment for HCC (OPTN class 5 lesion or biopsy proven prior to ablation).

- Evidence of persistent/recurrent HCC such as nodular or crescentic extra-zonal or intra-zonal enhancing tissue on late arterial imaging (relative to hepatic parenchyma) may be present.

OPTN guidelines also indicate “candidates whose tumors have been ablated after previously meeting the criteria for additional MELD/PELD points (OPTN Class 5T) will continue to receive additional MELD/PELD points (equivalent to a 10-percentage point increase in candidate mortality) every 3 months without RRB review, even if the estimated size of residual viable tumor falls below stage T2 criteria.”

Candidates with HCC not meeting transplant criteria, “including those with downsized tumors whose original or presenting tumor was greater than a stage T2, must be referred to the applicable RRB [Regional Review Board] for prospective review in order to receive additional priority.”<sup>[75]</sup>

## ADVERSE EVENTS

Complication rates for RFA of liver tumors are reported in approximately 7% of patients, as compared with that of open liver resection which may be as high as 22%.<sup>[76]</sup>

Specific complications reported in the literature to date include the following:<sup>[52,55,76-79]</sup>

1. Hemorrhage
2. Liver Abscess
3. Liver infarction
4. Liver failure
5. Cutaneous burn
6. Diaphragm perforation
7. Bowel perforation
8. Seeding of the needle tract with cancer cells
9. Hydrothorax or hemothorax requiring drainage
10. Bile duct injury
11. Death

## MICROWAVE ABLATION

### MWA AS A TREATMENT OF HEPATOCELLULAR CARCINOMA

#### Systematic Reviews

Glassberg (2019) conducted a systematic review of MWA compared to resection in patients with HCC or metastatic liver cancer. One RCT (Xu 2015)<sup>[80]</sup> was included; the other studies (n=15) were observational (2 prospective, 13 retrospective).<sup>[81]</sup> Patients who received MWA had significantly higher risk of LTR compared to those who received resection (RR=3.04; p<0.001). At one year, overall survival did not differ between MWA and resection, but three- and five-year overall survival was significantly higher in patients who had received resection. Overall complications and major complications were lower with MWA compared to resection. Additionally, operative time, intraoperative blood loss, and hospital length of stay were significantly lower with MWA. Some studies included patients that were nonresectable in the MWA treatment arm, but due to limited reporting and patient preference affecting which treatment was performed, the reviewers were not able to calculate the number of patients who

were nonresectable or to conduct subgroup analyses by resectable vs unresectable tumors. Microwave ablation was typically selected for patients with smaller and/or deeper tumors, more comorbidities, and a preference for a less invasive procedure. The reviewers concluded that MWA can be an effective and safe alternative to HR in patients or tumors that are not amenable to resection, but more studies are needed to determine the target population that would benefit most from MWA.

In 2017, Zhang reported results from a systematic review and meta-analysis comparing hepatic resection with microwave ablation as a treatment of hepatocellular carcinoma.<sup>[82]</sup> Nine studies with follow-up time of three years or greater were included overall, totalling 1,480 participants. For overall survival (seven reports), studies were not found to have statistical bias, and overall heterogeneity amongst studies was not significant ( $I^2 = 0.0\%$ ,  $p=0.749$ ), however, heterogeneity amongst studies included for meta-analysis of disease-free survival (five reports) was significant ( $I^2 = 71.1\%$ ,  $p=0.008$ ). No difference was found comparing MWA to resection for OS and DFS (HR =0.98, 95% CI 0.76 to 1.26,  $p=0.878$ , and HR =1.16, 95% CI 0.79 to 1.71,  $p=0.442$ , respectively). Meta-analysis demonstrated that MWA was associated with shorter operation time (standardized mean difference [SMD]  $-1.37$ , 95% CI  $-1.92$  to  $-0.81$ ,  $p=0.000$ ), less amount of blood loss in operation (SWD  $-1.19$ , 95% CI  $-1.76$  to  $-0.61$ ,  $p=0.000$ ), and less complications (OR 0.22, 95% CI 0.12 to 0.40,  $p=0.000$ ) than resection. The authors concluded that MWA may be superior given there were no differences identified in OS and DFS, but demonstrated fewer complications and improved intraoperative outcomes.

In 2011, Bertot conducted a systematic review evaluating mortality and complication rates of ablation techniques for primary and secondary liver tumors.<sup>[83]</sup> This review included two studies using MWA totaling 1,185 patients.<sup>[84,85]</sup> The pooled mortality rate for MWA was 0.23% (95% confidence interval [CI]: 0.0 to 0.58%). Major complication rates were 4.6% for MWA (calculated by using a random effects model since there was significant heterogeneity). The authors concluded that percutaneous ablation techniques, including MWA, are safe and have acceptable complication rates for the treatment of liver tumors.

In 2009, Ong conducted a systematic review of studies on MWA for primary and secondary liver tumors.<sup>[86]</sup> Based on the results from 25 clinical studies, the authors concluded that MWA was an effective and safe technique for liver tumor ablation with low complication rates and survival rates comparable to hepatic resection. However, rates of local recurrence after MWA were noted to be higher than hepatic resection. In most studies of MWA, hepatocellular carcinoma recurrence rates were approximately 10% but were also noted to be as high as 50%, which the authors indicated could be addressed with further ablation. Survival rates in the studies on MWA for hepatocellular carcinoma were as high as 92% at three years and 72% at five years, which was noted to be comparable to radiofrequency ablation (RFA) and percutaneous ethanol injections. Pain and fever were the most frequently reported complications, but complications increased when there were more tumors, larger tumors, and more microwave antennas used. The authors concluded that MWA may be a promising option for the treatment of HCC tumors but should be reserved for patients not amenable to hepatic resection. The authors also noted further randomized clinical trials are warranted to compare MWA to other ablation procedures.

## Randomized Controlled Trials

Fang (2019) randomized hepatic carcinoma patients to receive conventional surgical excision (n=47) or ultrasound-guided microwave ablation (n=47).<sup>[87]</sup> Statistically significant differences (p<0.05) between groups were reported for duration of operation (shorter for MWA), quantities of intraoperative bleeding and blood transfusions (lower for surgical excision), effective rate of treatment (higher for MWA), occurrence rate of complications (lower for MWA). In addition significantly higher albumin and total bilirubin and lower alanine aminotransferase and aspartate transaminase were reported for the MWA group (p<0.05).

An RCT by Vietti Violi (2018) compared the effectiveness of RFA and microwave ablation (MWA) on treating inoperable HCC in 152 patients with up to three lesions of 4 cm or smaller.<sup>[88]</sup> At two years, 6% (6/98) of lesions treated with MWA had local tumor progression vs 12% (12/104) of lesions treated with RFA (RR1.62; 95% CI: 0.66 to 3.94; P=0.27). Few complications and no treatment-related deaths were reported for either group. OS at two years was not significantly different between the groups. Because some patients did not receive the allocated treatment or were lost to follow-up, the analyses were per-protocol rather than intention-to-treat. In addition, the investigators had planned to assess the effects of the treatments on larger lesions, but only a few patients had lesions of nearly 4 cm, making a detailed analysis impossible. A five-year follow-up is planned for this study.

Yu conducted an open-label RCT of MWA compared to RFA ablation in patients with HCC.<sup>[89]</sup> Results were reported in a letter to the editor instead of a full publication. There were no significant differences between groups in rates of tumor progression, overall survival, or progression-free survival at one, three, or five years of follow-up. There were no differences in tumor progression rates according to tumor size or high-risk location. MWA showed higher tumor inactivation than RFA for tumors over 3 cm (6.7% vs 13.0%), but the difference was not statistically significant. Survival outcomes were not reported by tumor size. In addition to its open-label design, this study is limited because it did not report randomization and allocation concealment methods, baseline characteristics, and information on any patients lost to followup or with missing data.

Older RCTs are included in the SRs above.

## Nonrandomized Studies

In addition to the studies noted above, a number of nonrandomized studies have been published on the use of MWA in patients with hepatocellular carcinoma. Several examples are cited, below. The results of these studies should be interpreted with caution due to the following limitations:

- Results from small sample sizes (n<100), limit the ability to rule out the role of chance as an explanation of study findings.<sup>[90-97]</sup>
- Results from studies with short-term follow-up (<one year) are not adequate to determine the durability of the treatment effect.<sup>[90,98,99]</sup>
- A lack of comparison group, without which it is not possible to account for the many types of bias that can affect study outcomes.<sup>[84,85,96-105]</sup>

Given the limitations noted above, nonrandomized studies do not provide reliable data to demonstrate the efficacy of MWA treatment in patients with HCC.

## MWA AS A TREATMENT OF HEPATIC METASTASIS

The literature search identified several systematic reviews<sup>[17,44,83,86,106]</sup> on MWA for hepatic metastases and a single RCT.

### Systematic Reviews

A 2014 Health Technology Assessment<sup>[44]</sup> and a 2013 Cochrane review<sup>[106]</sup> also identified only one RCT on ablation for liver metastasis, Shibata.<sup>[107]</sup> The reviewers found insufficient evidence to determine any benefits of MWA for liver metastasis over surgical resection.

In 2013, Vogl reviewed evidence regarding RFA, laser-induced thermotherapy (LITT) and MWA treatment of breast cancer liver metastasis.<sup>[108]</sup> Local tumor response, progression and survival rates were evaluated. Authors reported positive response rates of 63 % to 97 % in RF-ablated lesions, 98.2 % in LITT-treated lesions and 34.5-62.5 % in MWA lesions. Median survival was 10.9-60 months with RFA, 51-54 months with LITT and 41.8 months with MWA. Five-year survival rates were 27-30 %, 35 % and 29 %, respectively. Local tumour progression ranged from 13.5 % to 58 % using RFA, 2.9 % with LITT and 9.6 % with MWA. The authors called for additional, large RCTs to further explore the benefits of ablation therapies.

In the Ong review described above<sup>[86]</sup>, local recurrence rates for liver metastases after treatment with MWA averaged approximately 15% but varied between 0 and 50% in the seven studies reviewed that addressed liver metastases. As noted above, Ong concluded MWA may be a promising treatment option for the treatment of liver tumors but should be reserved for patients not amenable to hepatic resection.

In 2011, Pathak also conducted a systematic review of ablation techniques for colorectal liver metastases, which included 13 studies on MWA, totaling 406 patients with a minimum of 1-year follow-up.<sup>[17]</sup> Mean survival rates were 73%, 30% and 16% and ranged from 40–91.4%, 0–57% and 14–32% at one-, three-, and five-years' follow-up, all respectively. Minor and major complication rates were considered acceptable and ranged from 6.7–90.5% and 0–19%, respectively. Local recurrence rates ranged from 2-14%. The authors acknowledged limitations in the available studies but concluded survival rates for MWA are more favorable than for palliative chemotherapy alone.

### Randomized Controlled Trials

Only one RCT comparing the use of MWA for hepatic metastases to the gold standard of surgical resection was identified. In 2000, Shibata reported on a trial of 30 patients with hepatic metastases from colorectal cancer randomly assigned without stratification to treatment with either MWA after laparotomy (n=14) or hepatectomy (n=16).<sup>[107]</sup> The study began with 40 patients, but 10 patients were excluded because the researchers discovered intraoperatively that these patients did not meet study criteria due to having extensive metastasis or equal to or greater than 10 tumors. The treatment groups of MWA vs. hepatectomy were not significantly different in age (mean age 61 in both groups) number of tumors (mean 4.1 vs. 3.0, respectively) or tumor size (mean 27 mm vs. 34 mm, respectively). The authors reported no significant differences in survival rates following MWA or hepatectomy (27 months vs. 25 months, respectively) and mean disease-free survival (11.3 vs. 13.3 months, respectively). However, intraoperative blood loss was significantly lower and no blood transfusions were

required in the MWA group whereas six patients in the hepatectomy group required blood transfusions. Complications in the microwave group consisted of one hepatic abscess and one bile duct fistula. In the hepatectomy group, complications were one intestinal obstruction, one bile duct fistula and one wound infection.

## Nonrandomized Studies

Several nonrandomized trials regarding MWA treatment in patients with liver metastases were identified; however, these studies were limited by a lack of comparison group,<sup>[109-111]</sup> short-term follow-up<sup>[109,110]</sup> and small sample size.<sup>[109,111]</sup> These limitations preclude reaching a conclusion regarding MWA treatment in this patient population.

## CRYOSURGICAL ABLATION

### CRYOSURGICAL ABLATION AS A TREATMENT OF HEPATOCELLULAR CARCINOMA

The evidence regarding cryoablation as a treatment for hepatocellular carcinoma (HCC) remains controversial. However, use of cryotherapy for HCC became a standard of care and published research increased through the late 1990's and early 2000's. Awad published a systematic Cochrane Review in 2009, noting that the literature consisted of two prospective cohort studies and two retrospective cohort studies.<sup>[112]</sup> Overall, the Review concluded that the evidence is not sufficient to evaluate potential harms and benefits; large well-designed randomized clinical trials (RCTs) are feasible and necessary to define the role of cryotherapy in the treatment of HCC.

Since the 2009 Cochrane Systematic Review, Wang (2015) reported results from one RCT comparing the safety and efficacy of cryotherapy vs RFA.<sup>[1]</sup> One hundred eighty participants were randomized to each group, with no significant differences found at baseline between the arms, with the exception of number of tumors – 10.56% of the cryo group participants had two tumors at enrollment, compared to 5% in the RFA group. Participants were followed for five years, and there were no differences in local recurrence, new recurrence, overall survival, or tumor-free survival. At the end of follow-up, 52 patients (28.9%) in the CRYO group and 55 patients (30.6%) in the RFA group died. The causes of death included HCC progression in 44 (24.4%), hepatic failure in five (2.8%), and variceal bleeding in three (1.7%) in the CRYO group, and HCC progression in 47 (26.1%), hepatic failure in four (2.2%), variceal bleeding in two (1.1%), and refractory ascites-induced renal failure in two (1.1%) in the RFA group. Overall, the authors concluded that patients with Child-Pugh class A-B cirrhosis and HCC lesions less than or equal to 4cm and no more than two lesions in total, percutaneous cryoablation and RFA are equally safe and effective ablation treatments. For HCC 3.1-4.0 cm, cryoablation was associated with a lower rate of local tumor progression than RFA.

### CRYOSURGICAL ABLATION AS A TREATMENT OF LIVER METASTASES

A 2019 Cochrane SR was published by Bala evaluation the use of cryotherapy for the treatment of liver metastases.<sup>[113]</sup> The selection criteria included RCTs assessing effects of cryotherapy and its comparators for liver metastases. One RCT was identified. It compared cryotherapy with conventional surgery for patients with liver metastases from the following primary sites: colon and rectum (66.6%), stomach (7.3%), breast (6.5%), skin (4.9%), ovaries (4.1%), uterus (3.3%), kidney (3.3%), intestines (1.6%), pancreas (1.6%), and unknown (0.8%). The SR authors were not able to calculate the risk of bias of the randomization

process, allocation concealment, presence of blinding, incomplete outcome data, or selective outcome reporting bias due to insufficient reporting by the RCT authors. Follow-up was five months to 10 years. The trial reported mortality at 10 years (81% vs. 92% for cryotherapy vs. conventional therapy) and the SR authors calculated the relative risk (RR=0.88, 95% CI 0.77 to 1.02). The evidence regarding mortality was rated as low-certainty. The SR authors also calculated chance of recurrence in the liver, which was 86% in the cryotherapy group and 95% in the conventional surgery group (RR 0.90, 95% CI 0.80 to 1.01; low-certainty evidence). The SR authors concluded that the evidence is limited and they cannot determine whether cryotherapy is beneficial or harmful compared to conventional surgery.

## PERCUTANEOUS ETHANOL INJECTION

Like RFA, percutaneous ethanol injection (PEI) is most often considered a treatment option for patients with small HCC lesions who are not resection candidates. RFA and PEI are the most commonly performed ablation therapies.

Weis (2015) published a Cochrane Systematic Review that evaluated the harms and benefits of percutaneous ethanol injection (PEI) and percutaneous acetic acid injection (PAI) in adults with early HCC defined by Milam criteria, i.e., one cancer nodule up to 5 cm in diameter or up to three cancer nodules up to 3 cm in diameter compared with no intervention, sham intervention, each other, other percutaneous interventions, or surgery.<sup>[114]</sup> One randomised trial compared PEI versus surgery; we included 76 participants in the analyses. There was no significant difference in the overall survival (HR 1.57; 95% CI 0.53 to 4.61) and recurrence-free survival (HR 1.35; 95% CI 0.69 to 2.63). No serious adverse events were reported in the PEI group while three postoperative deaths occurred in the surgery group. Given the data on PEI were available for only one RCT, the authors concluded there is insufficient evidence to determine whether PEI versus surgery was more effective for early HCC.

In a number of RCT's, the safety and efficacy of RFA and PEI have been investigated in the treatment of Child-Pugh class A patients with early stage HCC tumors.<sup>[115-121]</sup> Complication rates were relatively low for both methods.

## PRACTICE GUIDELINE SUMMARY

### National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for hepatobiliary cancers (v.4.2019) recommend ablation be considered in patients who are not candidates for surgical curative treatments, or as part of a strategy to bridge patients for other curative therapies. (category 2A)<sup>[122]</sup>

The NCCN guidelines for rectal (v.1.2020) and colon (v.1.2020) cancer metastatic to the liver state that "Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection."<sup>[123,124]</sup> (category 2A).

The NCCN guidelines for neuroendocrine tumors (v.1.2019) state that "...ablative therapies such as radiofrequency ablation (RFA) or cryoablation may be considered if near-complete treatment of tumor burden can be achieved (category 2B). For unresectable liver metastases, ... (arterial embolization, chemoembolization, or radioembolization [category 2B]) is recommended."<sup>[125]</sup>

### AMERICAN COLLEGE OF RADIOLOGY (ACR)

The 2014 ACR Appropriateness Criteria® for metastatic rectal cancer states that RFA “yields excellent local control of small (<3 cm) CRC liver metastases.”<sup>[126]</sup>

The 2011 ACR Appropriateness Criteria® considered RFA by percutaneous, open, or laparoscopic methods effective for treatment of small ( $\leq 5$  cm) HCC tumors.<sup>[127]</sup> While ablative therapy is most effective for these small HCCs, moderate success has also been described with tumors  $\leq 7$  cm. With larger tumor number and/or size, “the operator may want to focus on arterial-based therapies and adjuvant or neoadjuvant therapy.” The 2016 guidelines were consistent with the previous recommendations.<sup>[128]</sup>

## AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD)

The 2011 update of the practice guideline from the American Association for the Study of Liver Diseases (AASLD) considered RFA a safe and effective therapy for unresectable HCC or as a bridge to liver transplantation.<sup>[129]</sup>

## SUMMARY

For primary tumors of the liver, and hepatic metastases from colorectal tumors or neuroendocrine tumors, there is limited research regarding locoregional ablative therapies, however, treatment options are limited in this population. Clinical practice guidelines based on research recommend ablative therapies in carefully selected patients. Therefore, percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation may be considered medically necessary when policy criteria are met. Due to a lack of research and clinical practice guidelines, percutaneous ethanol injection, cryoablation, radiofrequency and microwave ablation are considered investigational when the policy criteria are not met.

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132. BlueCross BlueShield Association Medical Policy Reference Manual "Microwave Tumor Ablation." Policy No. 7.01.133

## CODES

Codes	Number	Description
CPT	47370	Laparoscopy, surgical, ablation of one or more liver tumor(s); radiofrequency
	47371	Laparoscopy, surgical, ablation of 1 or more liver tumor(s); cryosurgical
	47380	Ablation, open, of one or more liver tumor(s); radiofrequency
	47381	Ablation, open, of 1 or more liver tumor(s); cryosurgical
	47382	Ablation, 1 or more liver tumor(s), percutaneous, radiofrequency
	47383	Ablation, 1 or more liver tumor(s), percutaneous, cryoablation
	47399	Unlisted procedure, liver
HCPCS	None	

**Date of Origin:** June 2017

## ***Implantable Peripheral Nerve Stimulation for Chronic Pain of Peripheral Nerve Origin***

**Effective:** July 1, 2020

**Next Review:** January 2021

**Last Review:** May 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Implantable peripheral nerve stimulation (PNS) for chronic pain of *peripheral nerve origin* is a type of neuromodulation therapy that involves the surgical implantation of electrodes that target *peripheral nerves considered to be the origin of pain*. This procedure differs from other forms of PNS, because the origin of pain is from a peripheral nerve and the electrical impulses are delivered to the nerve versus surrounding tissues or the spine.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy only addresses implantable peripheral nerve stimulation (PNS) (e.g., StimRouter) for chronic pain of peripheral nerve origin. Please refer to the Cross References below for other specific neuromodulation or stimulation therapies.

Implantable peripheral nerve stimulation (PNS) for chronic pain of peripheral nerve origin is considered **investigational**.

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

## POLICY GUIDELINES

Peripheral nerve stimulation (PNS) systems vary from other electrical stimulation therapies.

- Transcutaneous electrical nerve stimulation (TENS) delivers impulses across the skin to alleviate pain. PNS is similar to TENS, except PNS requires electrodes to be inserted under the skin and targets a nerve considered to be the origin of the pain.
- Percutaneous neuromodulation therapy (PNT) is an electrical stimulation therapy in which fine filament electrodes are temporarily placed in the tissues near the area causing pain. PNS is similar to PNT, except PNS requires electrodes to be inserted under the skin and targets a nerve considered to be the origin of the pain.
- Peripheral subcutaneous field stimulation (PSFS) is similar to PNS, except PSFS involves electrical stimulation via electrodes implanted under the skin over the area of maximal pain, rather than targeting the nerve thought to be the origin of the pain, as is done in PNS. PNS devices (e.g. the Sprint PNS System) are sometimes used off-label for PSFS.

## CROSS REFERENCES

1. [Percutaneous Neuromodulation Therapy \(PNT\)](#), Surgery, Policy No. 44
2. [Spinal Cord and Dorsal Root Ganglion Stimulation](#), Surgery, Policy No. 45
3. [Deep Brain Stimulation](#), Surgery, Policy No. 84
4. [Occipital Nerve Stimulation](#), Surgery, Policy No. 174
5. [Peripheral Subcutaneous Field Stimulation](#), Surgery, Policy No. 188

## BACKGROUND

Implantable peripheral nerve stimulation (PNS) is a type of neuromodulation that delivers electrical impulses *directly to a nerve*.

Implantable PNS therapies have been around since the 1960s.<sup>[1]</sup> There are several implantable PNS neuromodulation therapies that use electrical stimulation for pain.<sup>[2]</sup> Examples include, but are not limited to: occipital nerve stimulation (ONS) and spinal cord stimulation (SCS). The StimRouter, an implantable PNS system, is being marketed specifically for chronic pain of *peripheral nerve origin* i.e. upper/lower limb pain, entrapment syndromes, intercostal neuralgias and other peripheral injuries or diseases.<sup>[3]</sup> Although SCS addresses pain in the trunk and limbs, the electrodes for SCS deliver electrical stimulation to the spine versus directly to the peripheral nerve pain site like the StimRouter.<sup>[4]</sup>

## REGULATORY STATUS

In July 2018, the SPRINT Peripheral Nerve Stimulation System (SPR Therapeutics, Inc) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K181422).<sup>[5]</sup>

The Bioness® StimRouter Neuromodulation System™ received FDA 510(k) approval in February 2015<sup>[6]</sup> and in October 2019.<sup>[7]</sup>

In March of 2016, the StimQ Peripheral Nerve Stimulator (PNS) System received FDA 510(k) approval.<sup>[8]</sup>

## EVIDENCE SUMMARY

The principal outcomes associated with treatment of pain due to any cause may include: relief of pain, improved functional level, and return to work. Relief of pain can be a subjective outcome associated with a placebo effect. Therefore, data from adequately powered, blinded, randomized controlled trials (RCT) are required to control for the placebo effect and determine if an implanted peripheral nerve stimulation (PNS) system for chronic pain of peripheral nerve origin provides a significant advantage over placebo.

Treatment with an implanted PNS system to treat chronic pain of peripheral nerve origin must also be evaluated in general groups of patients against the existing standard of care for the condition being treated. For example, in patients with pain symptoms, treatment with an implanted PNS system to treat chronic pain of peripheral nerve origin should be compared to other forms of conservative therapy such as rest, non-steroidal anti-inflammatory medications, physical therapy, or steroid injection.

### Systematic Reviews

There were no systematic reviews identified.

### Randomized Controlled Trials

Deer (2015) published a multicenter, randomized, double-blinded, partial crossover study addressing the safety and efficacy of the StimRouter™ neuromodulation system for 94 patients with chronic pain of peripheral nerve origin (upper or lower extremity or trunk).<sup>[9]</sup> The patients were assigned to the StimRouter™ group (n=45) or the control group (n=49). Efficacy was evaluated for three months and safety for one year. Primary outcomes included pain relief and safety. At three months the StimRouter™ group reported 27.2% pain reduction vs. the control group 2.3%. Fifty-one percent of patients did not follow-up at one year. No serious adverse events were reported related to the device. A significant limitation of the study is the small sample size and large loss to follow-up.

### Nonrandomized Studies

A multi-center, prospective case series published by Oswald (2019) evaluated outcomes in 39 patients implanted with the StimRouter™ on various isolated mononeuropathies.<sup>[10]</sup> The authors report 78% of the participants noted an improvement in pain, 72% noted improvement in activity, and 89% experienced a greater than 50% reduction in opioid consumption. This was not a controlled trial and no information comparing these outcomes to outcomes achieved through standard of care was provided. Future RCTs addressing these limitations are required.

Deer and Rosenfeld (2010) published the results of a single-center open-label study in which eight patients with carpal tunnel syndrome were evaluated for pain relief from the StimRouter™. Pain evaluation occurred before implant, during implant and after explant. The authors concluded the StimRouter™ was effective and safe for pain reduction from carpal tunnel syndrome, but the study had methodological limitations including a small sample size and no mention of follow-up after the StimRouter™ was explanted after five days of treatment.

## PRACTICE GUIDELINE SUMMARY

There are no evidence-based clinical practice guidelines that recommend the use of implanted percutaneous neuromodulation therapy for the treatment of pain of peripheral nerve origin.

## SUMMARY

There is not enough research to show that an implantable percutaneous neuromodulation stimulation (PNS) system for treatment of chronic pain of peripheral nerve origin improves health outcomes. There are no evidence-based clinical practice guidelines that recommend the use of an implantable PNS system for treatment of chronic pain of peripheral nerve origin. Therefore, the use of an implantable PNS system for treatment of chronic pain of peripheral nerve origin is considered investigational.

## REFERENCES

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## CODES

Codes	Number	Description
CPT	64555	Percutaneous implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
	64575	Incision for implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
	64585	Revision or removal of peripheral neurostimulator electrode array

	64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling
	64595	Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver
	64999	Unlisted procedure, nervous system
	95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulsewidth, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter, t programming by physician or other qualified health care professional
	95972	;with complex spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
	97014	Application of a modality to 1 or more areas; electrical stimulation (unattended)
	97032	Application of a modality to 1 or more areas; electrical stimulation (manual), each 15 minutes
HCPCS	C1778	Lead, neurostimulator (implantable)
	L8680	Implantable neurostimulator electrode, each
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver

**Date of Origin:** January 2018

## ***Phrenic Nerve Stimulation for Central Sleep Apnea***

**Effective:** October 1, 2020

**Next Review:** June 2021

**Last Review:** August 2020

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Central sleep apnea (CSA) is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. The goal of phrenic nerve stimulation treatment is to normalize sleep-related breathing patterns.

### **MEDICAL POLICY CRITERIA**

**Note:** This policy only addresses phrenic nerve stimulation for *central* sleep apnea (CSA). It does not address hypoglossal nerve stimulation for *obstructive* sleep apnea (OSA). See Cross References section below.

The use of phrenic nerve stimulation for central sleep apnea is considered **investigational**.

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

### **CROSS REFERENCES**

1. [Noninvasive Ventilators in the Home Setting](#), Durable Medical Equipment, Policy No. 87
2. [Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome](#), Surgery, Policy No. 166
3. [Hypoglossal Nerve Stimulation](#), Surgery, Policy No.215

## BACKGROUND

### CENTRAL SLEEP APNEA

Central sleep apnea (CSA) is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. CSA may be idiopathic or secondary (associated with Cheyne-Stokes breathing, a medical condition, drugs, or high altitude breathing). Cheyne-Stokes breathing is common among patients with heart failure or who have had strokes, and accounts for about half of the population with CSA. CSA is less common than obstructive sleep apnea (OSA). Based on analyses of a large community-based cohort in the Sleep Heart Health Study, the estimated prevalences of CSA and OSA are 0.9% and 47.6%, respectively.<sup>[1]</sup> Risk factors for CSA include age (>65 years), male gender, history of heart failure, history of stroke, other medical conditions (acromegaly, renal failure, atrial fibrillation, low cervical tetraplegia, and primary mitochondrial diseases), and opioid use. Individuals with CSA have difficulty maintaining sleep and therefore experience excessive daytime sleepiness, poor concentration, morning headaches, and are at higher risk for accidents and injuries.

### TREATMENT

The goal of treatment is to normalize sleep-related breathing patterns. Because most cases of CSA are secondary to an underlying condition, central nervous system pathology, or medication side effects, treatment of the underlying condition or removal of the medication, may improve CSA.

Treatment recommendations differ depending on the classification of CSA as either hyperventilation-related (most common, including primary CSA and those relating to heart failure or high altitude breathing) or hypoventilation-related (less common, relating to central nervous system diseases or use of nervous system suppressing drugs such as opioids).

For patients with hyperventilation-related CSA, continuous positive airway pressure (CPAP) is considered first-line therapy. Due to CPAP discomfort, patient compliance may become an issue. Supplemental oxygen during sleep may be considered for patients experiencing hypoxia during sleep or who cannot tolerate CPAP. Patients with CSA due to heart failure and with an ejection fraction >45% and who are not responding with CPAP and oxygen therapy, may consider bilevel positive airway pressure (BPAP) or adaptive servo-ventilation (ASV) as second-line therapy. BPAP devices have two pressure settings, one for inhalation and one for exhalation. ASV uses both inspiratory and expiratory pressure, and titrates the pressure to maintain adequate air movement. However, a clinical trial reported increased cardiovascular mortality with ASV in patients with CSA due to heart failure and with an ejection fraction <45%,<sup>[2]</sup> and therefore, ASV is not recommended for this group.

For patients with hypoventilation-related CSA, first-line therapy is BPAP.

Pharmacologic therapy with a respiratory stimulant may be recommended to patients with hyper- or hypoventilation CSA who do not benefit from positive airway pressure devices, though close monitoring is necessary due to the potential for adverse effects such as rapid heart rate, high blood pressure, and panic attacks.

### PHRENIC NERVE STIMULATION

Currently, there is one phrenic nerve stimulation device approved by the Food and Drug Administration (FDA), the remede System (Respicardia, Inc.). The remede System is an

implantable device that stimulates the phrenic nerve in the chest which sends signals to the diaphragm to restore a normal breathing pattern. A cardiologist implants the battery powered device under the skin in the right or left pectoral region. The procedure is conducted using local anesthesia. The device has two leads, one to stimulate a phrenic nerve (either the left pericardiophrenic or right brachiocephalic vein) and one to sense breathing. The device runs on an algorithm that activates automatically at night when the patient is in a sleeping position, and suspends therapy when the patient sits up. Patient-specific changes in programming can be conducted externally by a programmer.

## REGULATORY STATUS

In October 2017, the FDA granted approval for the remedē System (Respicardia, Inc; Minnetonka, MN) through the premarket approval application process. The approved indication is for treatment of moderate to severe central sleep apnea in adults. Product code: PSR.

## EVIDENCE SUMMARY

Outcomes of interest include sleep quality metrics and quality of life measures. The Apnea-Hypopnea Index (AHI) is the number of apnea and hypopnea (events per hour of sleep, in which the apnea events last at least 10 seconds and are associated with decreased blood oxygenation. In adults, the AHI scale is: <5 AHI (normal); 5<AHI<15 (mild); 15<AHI<30 (moderate); and >30 AHI (severe). Additional sleep metrics include central apnea index (CAI, number of central apnea events per hour of sleep) and obstructive apnea index (OAI, number of obstructive apnea events per hour of sleep).

Quality of life outcomes can be measured by the Epworth Sleepiness Scale (ESS) or a Patient Global Assessment. The ESS is a short self-administered questionnaire that asks patients how likely they are to fall asleep (0="no chance" to 3="high chance") in 8 different situations (e.g., watching TV, sitting quietly in a car, or sitting and talking to someone). The scores are added, ranging from 0 to 24, with scores over 10 indicating excessive sleepiness and recommendation to seek medical attention.

## SYSTEMATIC REVIEWS

Luni (2020) reported a meta-analysis of five studies (n=204) evaluating the efficacy of transvenous neurostimulation of the phrenic nerve for central sleep apnea.<sup>[3]</sup> An analysis of the pooled data demonstrated a reduction of mean AHI in the stimulation group compared to the control group by 26.7 events/hour (95% CI -31.99 to -21.46, p 0.00), and a mean AHI difference of -22.47. Compared with the control group, the mean reduction in the oxygen desaturation index of 4% or more was decreased in the stimulation group by -24.16 events/hour (95% CI -26.20 to -22.12, p 0.00).

## RANDOMIZED CONTROLLED TRIAL

Costanzo (2015) provided background and methodologic details of the remedē System Pivotal Trial.<sup>[4]</sup> The trial is a prospective, multicenter, randomized, open-label controlled trial comparing transvenous unilateral phrenic nerve stimulation with no stimulation in patients with CSA of various etiologies (Table 1). All patients received implantation of the phrenic nerve stimulation system, with activation of the system after one month in the intervention group (n=73) and activation after six months in the control group (n=78). Activation is delayed one month after implantation to allow for lead healing. The primary efficacy endpoint is percentage of patients

achieving a reduction in Apnea-Hypopnea Index (AHI) of 50%, as interpreted from polysomnography by an assessor blinded to treatment arm. The reduction of 50% was based on assessments showing that a 50% reduction in AHI is associated with reduced mortality risk and is therefore clinically meaningful. Secondary endpoints include mean reductions in CAI, AHI, arousal index, OD14, and Epworth Sleepiness Scale. Quality of life is measured by Patient Global Assessment (PGA), which consists of a 7-point scale (1="markedly improved" to 7="markedly worsened"). Of the 151 patients in the trial, 64% had heart failure, 42% had atrial fibrillation, and a mean left ventricular ejection fraction of 39.6. Six-month per protocol comparative results for the treatment and control groups were published in 2016 by Costanzo (Table 3).<sup>[5]</sup> Adverse events were reported in 9% of the intervention group and 8% of the control group (for example, implant site infection, implant site hematoma, and lead dislodgement). Non-serious therapy-related discomfort was reported in 27 (37%) of the intervention group, with all but one case resolved by system reprogramming.

Costanzo (2018) provided 12 months followup results for the intervention arm.<sup>[6]</sup> At six months followup, 15 of the 73 (21%) in the treatment group were excluded due to no six-month data (n=9: unrelated death, device explant, missed visit, study exit), failed inclusion criteria (n=3), unsuccessful implant (n=2), therapy programmed off (n=1). At 12 months followup, an additional four patients were lost due to unrelated death, device explant, patient refusal, and missed visit. Results from the remaining 54 patients in the intervention group are summarized in Table 3. Subgroup analyses showed consistent improvements in percent experiencing >50% AHI reductions from treatment across all of the following subgroups: age (<65, 65 to <75, and >75), gender, heart failure (yes/no), defibrillator (yes/no), AHI severity (moderate/severe), and atrial fibrillation (yes/no).

Another publication by Costanzo in 2018 provided 12-months follow-up results for the subgroup of patients in the Pivotal Trial who had heart failure.<sup>[7]</sup> Pooling of results was possible by using 6 and 12 month data from the intervention group and 12 and 18 month data from the control group (the phrenic nerve stimulator was activated in the control group six months after implantation). At baseline, 96 of the patients in the trial had heart failure. By the six-month followup, there had been four deaths, one explant, and five withdrew from the study. By the 12-month followup, there had been an additional five deaths, one implant, and one withdrawal, as well as four missing the final visit. Results at 6 and 12 months followup for the subgroup of patients with heart failure are summarized in Table 2.

Follow-up at 24 months was available for 42 patients in the treatment group, while 22 patients in the treatment group and 28 patients in the control arm had reached 36 month follow-up at the time of study closure.<sup>[8]</sup> Central apnea events remained low throughout follow-up with a median time to battery depletion of 39.4 months. Median AHI at 24 months and 36 months was 16 and 13, respectively. Serious adverse events related to the implant procedure, device, or delivered therapy occurred in 10% of patients through the 24-month visit. All were reported to be resolved with remedē System revisions or programming. Safety data will be collected through five years as part of the post-approval study.

An analysis of the pivotal trial data for safety and efficacy of TPNS in patients with concomitant cardiovascular implantable electronic devices (CIEDs) was reported by Nayak (2020).<sup>[9]</sup> Of the 151 initially enrolled patients, 64 had a concomitant CIED. There was no difference in safety or efficacy between patients with and without CIEDs.

## Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Intervention	Control
Costanzo (2015) <sup>[4]</sup>	Germany, Poland, United States	31	2013-2015	Adult patients with moderate to severe CSA of various etiologies confirmed by PSG <sup>a</sup> and medically stable <sup>b</sup>	Implanted phrenic nerve stimulator (remede system) activated at 1 month postprocedure (n=73)	Implanted phrenic nerve stimulator (remede system) activated at 6 months postprocedure (N=78)

<sup>a</sup> AHI>20 events/hr; CAI>50% of all apneas, with>30 central apnea events; OAI<20% of all AHI

<sup>b</sup> For 30 days prior to baseline testing: no hospitalizations for illness, no breathing mask-based therapy, and on stable medications and therapies.

AHI: apnea-hypopnea index; CSA: central sleep apnea; PSG: polysomnography.

**Table 2. Summary of Key RCT Results**

Study	Baseline	6-Month	Change from Baseline	Between Group Difference
<b>Costanzo (2018)<sup>[5]</sup></b>				
>50% AHI reduction				
Treatment, n=58	NA	51% (39% to 64%)	NA	
Control, n=73	NA	11% (5% to 20%)	NA	41% (25% to 54%)
AHI				
Treatment, n=58	49.7 ± 18.9	25.9 ± 20.5	-23.9 ± 18.6	
Control, n=73	43.9 ± 17.3	45.0 ± 20.3	1.1 ± 17.6	-25.0 ± 18.1
CAI				
Treatment, n=58	31.7 ± 18.6	6.0 ± 9.2	-25.7 ± 18.0	
Control, n=73	26.2 ± 16.2	23.3 ± 17.4	-2.9 ± 17.7	-22.8 ± 17.8
PGA				
Treatment, n=58	NA	60% (47% to 73%)	NA	
Control, n=73	NA	6% (2% to 14%)	NA	55% (40% to 68%)
ESS				
Treatment, n=58	10.7 ± 5.3	7.1 ± 4.1	-3.6 ± 5.6	
Control, n=73	9.3 ± 5.7	9.4 ± 6.1	0.1 ± 4.5	-3.7 ± 5.0
	<b>Baseline</b>	<b>6-Month</b>	<b>12-Month</b>	<b>Paired Change, Baseline to 12-Month Mean (95% CI)</b>
<b>Costanzo (2018)<sup>[6]</sup></b>				
<b>Treatment arm alone, N</b>	58	58	54	54
AHI	49.7 ± 18.9	25.9 ± 20.5	23.0 ± 21.9	-25.4 (-44.4 to -11.4)
CAI	31.7 ± 18.6	6.0 ± 9.2	3.4 ± 6.9	-26.0 (-40.2 to -14.6)
OAI	2.1 ± 2.2	6.3 ± 7.0	4.5 ± 5.1	0.9 (-0.5 to 4.4)
PGA <sup>b</sup>	NA	60% (47% to 72%)	60% (47% to 72%)	NA
ESS	10.7 ± 5.3	7.1 ± 4.1	6.5 ± 3.5	-4.0 (-7.0 to -1.0)
<b>Costanzo (2018)<sup>[7]</sup></b>				
<b>Pooled HF subgroup, N</b>	96	86	75	79
≥50% AHI reduction	NA	53% (42% to 64%)	57% (45% to 68%)	NA
AHI	47.1 ± 18.5	25.2 ± 14.2	3.5 ± 6.5	-19.9 (-34.6 to -11.8)

Study	Baseline	6-Month	Change from Baseline	Between Group Difference
CAI	26.2 ± 17.7	4.1 ± 6.0	3.4 ± 6.9	-26.0 (-40.2 to -14.6)
PGA <sup>b</sup>	NA	58% (NR)	55% (NR)	NA
ESS	8.9 ± 5.1	6.2 ± 4.1	6.1 ± 3.7	-2.0 (-5.0 to 0.0)

<sup>a</sup> Data are presented as either % (95% confidence intervals) or mean (standard deviation)

<sup>b</sup> Patients with marked or moderate improvement in 7-point quality of life scale

AHI: Apnea-Hypopnea Index; CAI: central apnea index; CI: confidence interval; ESS: Epworth Sleepiness Scale; HF: heart failure; NA: not applicable; NR: not reported; OAI: obstructive apnea index; PGA: Patient Global Assessment; RCT: randomized controlled trial; SD: standard deviation.

## NON-COMPARATIVE STUDIES

Abraham (2015)<sup>[10]</sup> and Jagielski (2016)<sup>[11]</sup> presented 6-month and 12 month results from a cohort of 47 patients with CSA of various etiologies who received phrenic nerve stimulation with the remedē system (Table 3). Sleep disorder parameters were measured by polysomnography, through 12 months, with an optional sleep testing at 18 months (Table 3). Quality of life was measured on a seven-point scale, with patients answering the question, "How do you feel today compared with how you felt before having your device implanted?" CSA etiologies included heart failure (79%), other cardiac (13%), and opiate use (4%). Three deaths occurred during the study period, none attributed to the intervention. Five experienced serious adverse events, three at the beginning of the study (two [hematoma, migraine] due to implantation procedure and one chest pain), and two during 12-month followup (pocket perforation and lead failure). A summary of sleep metric and quality of life results are presented in Table 4.

**Table 3. Summary of Non-Comparative Study Characteristics**

Study	Country	Participants	Follow-Up
Abraham (2015) <sup>[10]</sup> and Jagielski (2016) <sup>[11]</sup>	Germany, Italy, Poland, United States	Adult patients with a history of sleep apnea, predominantly CSA rather than OSA, and an AHI>20 events/hour	12 months (optional 18 months)

AHI: Apnea-Hypopnea Index; CSA: central sleep apnea; OSA: obstructive sleep apnea.

**Table 4. Summary of Non-Comparative Study Results<sup>[10,11]</sup>**

Outcome	Baseline (n=47) mean± SD	3 months (n=47) mean± SD	6 months (n=41) mean± SD	12 months (n=41) mean± SD	18 months (n=17) mean± SD
AHI, events/hour	49.9± 14.6	22.4± 13.6	23.8± 13.1	27.5± 18.3 <sup>b</sup>	24.9± 13.5 <sup>b</sup>
CAI, events/hour	28.0± 14.2	4.7± 8.6	4.6± 7.4	6.0± 9.2 <sup>b</sup>	4.8± 5.8 <sup>b</sup>
OAI, events/hour	3.0± 2.9	3.9± 4.7	3.9± 5.4	4.5± 6.0	5.6± 6.2
4% ODI, events/hour	45.2± 18.7	21.6± 13.7	23.1± 13.1	26.9± 18.0 <sup>b</sup>	25.2± 13.7 <sup>b</sup>
Arousal index, events/hour	36.2± 18.8	23.7± 10.6	25.1± 12.5	32.1± 15.2	26.8± 9.2
QOL, % improvement from baseline	NA	70.8%	75.6%	83.0%	NR

<sup>a</sup> Patients with marked or moderate improvement in 7-point quality of life scale

<sup>b</sup> p<0.006 compared to baseline

AHI: Apnea-Hypopnea Index; CAI: central apnea index; NA: not applicable; NR: not reported; OAI: obstructive apnea index; ODI: oxygen desaturation index; QOL: quality of life; RCT: randomized controlled trial; SD: standard deviation.

Fox (2017) presented data on long term durability of the remedē System, measuring battery lifetime, device exchangeability, lead position stability, and surgical accessibility.<sup>[12]</sup> Three consecutive patients, mean age 75.7 years, with CSA and HF with preserved ejection fraction were implanted with the remedē phrenic nerve stimulation device due to intolerability of conventional mask therapy. Implantation occurred in 2011 and the patients were followed for four years. Mean battery life duration was 4.2+ 0.2 years. Therapy was well tolerated by the patients, with improvements sustained in AHI, oxygen desaturation index, and quality of life (measured by ESS). Mean device replacement procedure time was 23 minutes, under local anesthesia, with a two-day hospital stay.

## SUMMARY OF EVIDENCE

For individuals with central sleep apnea who receive phrenic nerve stimulation, the evidence includes one randomized controlled trial (RCT) and observational studies. Relevant outcomes are change in disease status, functional outcomes, and quality of life. The RCT compared the use of phrenic nerve stimulation to no treatment among patients with central sleep apnea of various etiologies. All patients received implantation of the phrenic nerve stimulation system, with activation of the system after one month in the intervention group and activation after six months in the control group. Activation is delayed one month after implantation to allow for lead healing. At six months follow-up, the patients with the activated device experienced significant improvements in several sleep metrics and quality of life measures. At 12 months followup, patients in the activated device arm showed sustained significant improvements from baseline in sleep metrics and quality of life. A subgroup analysis of patients with heart failure combined 6 and 12 month data from patients in the intervention group and 12 and 18 month data from the control group. Results from this subgroup analyses showed significant improvements in sleep metrics and quality of life at 12 months compared with baseline. Results from observational studies supported the results of the RCT. No RCTs were identified in which phrenic nerve stimulation was compared with the current standard of care, positive airway pressure or respiratory stimulant medication. An invasive procedure would typically be considered appropriate only if non-surgical treatments had failed, but there is very limited data in which phrenic nerve stimulation was evaluated in patients who had failed the current standard of care, positive airway pressure or respiratory stimulant medication. The evidence is insufficient to determine the effects of the technology on health outcomes.

## PRACTICE GUIDELINE SUMMARY

No evidence-based clinical practice guidelines were identified with recommendations regarding the use of phrenic nerve stimulation for central sleep apnea.

## SUMMARY

There is not enough research to know if or how well phrenic nerve stimulation works to treat central sleep apnea. This does not mean that it does not work, but more research is needed to know. There are no clinical practice guidelines based on research that recommend phrenic nerve stimulation for this population. Therefore, the use of phrenic nerve stimulation for the treatment of central sleep apnea is considered investigational.

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13. BlueCross BlueShield Association Medical Policy Reference Manual "Phrenic Nerve Stimulation for Central Sleep Apnea." Policy No. 2.02.33

## CODES

Codes	Number	Description
CPT	0424T	Insertion or replacement of neurostimulator system for treatment of central

Codes	Number	Description
		sleep apnea; complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)
	0425T	;sensing lead only
	0426T	;stimulation lead only
	0427T	;pulse generator only
	0428T	Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only
	0429T	;sensing lead only
	0430T	;stimulation lead only
	0431T	Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only
	0432T	Repositioning of neurostimulator system for treatment of central sleep apnea; stimulation lead only
	0433T	;sensing lead only
	0434T	Interrogation device evaluation implanted neurostimulator pulse generator system for
	0435T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session
	0436T	;during sleep study
HCPCS	C1823	Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation leads

**Date of Origin:** December 2018

## Hypoglossal Nerve Stimulation

**Effective:** September 1, 2020

**Next Review:** June 2021

**Last Review:** July 2020

### IMPORTANT REMINDER

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

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

### DESCRIPTION

When patients with obstructive sleep apnea cannot tolerate positive airway pressure, or when continuous positive airway pressure (CPAP) treatment has failed, hypoglossal nerve stimulation may be considered.

### MEDICAL POLICY CRITERIA

**Note:** Contract language takes precedent over medical policy. Some member contracts have specific benefit limitations for orthognathic surgery.

- I. Hypoglossal nerve stimulation may be considered **medically necessary** in adults with obstructive sleep apnea when all of the criteria below (A.-E.) are met:
  - A. Age greater than or equal to 22 years (Note: Food and Drug Administration approved indication); and
  - B. AHI greater than or equal to 15 with less than 25% central apneas (see Policy Guidelines); and
  - C. CPAP failure (residual AHI greater than or equal to 20 or failure to use CPAP greater than or equal to 4 hr per night for greater than or equal to 5 nights per week) or inability to tolerate CPAP; and

- D. Body mass index less than or equal to 32 kg/m<sup>2</sup>; and
  - E. Non-concentric retropalatal obstruction on drug-induced sleep endoscopy. Note: Concentric collapse decreases the success of hypoglossal nerve stimulation and is an exclusion criterion from the Food and Drug Administration.
- II. Hypoglossal nerve stimulation may be considered **medically necessary** in adolescents or young adults with Down syndrome and obstructive sleep apnea when all of the criteria below (A.-E.) are met:
- A. Age 10 to 21 years; and
  - B. AHI greater than 10 and less than 50 with less than 25% central apneas after prior adenotonsillectomy (see Policy Guidelines); and
  - C. Have either tracheotomy or be ineffectively treated with CPAP due to noncompliance, discomfort, un-desirable side effects, persistent symptoms despite compliance use, or refusal to use the device; and
  - D. Body mass index less than or equal to 95th percentile for age; and
  - E. Non-concentric retropalatal obstruction on drug-induced sleep endoscopy. Note: Concentric collapse decreases the success of hypoglossal nerve stimulation and is an exclusion criterion from the Food and Drug Administration.
- III. Hypoglossal nerve stimulation is considered **investigational** for all other indications including but not limited to when policy Criteria I. or II. are not met.

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

## POLICY GUIDELINES

There is divergence on scoring rules for hypopneas between the recommendations of the American Academy of Sleep Medicine (AASM) and the Center for Medicare Services (CMS), the latter being more restrictive.<sup>[1]</sup> Policy Criteria are based on apnea-hypopnea index (AHI) scored with either the AASM or the CMS scoring rules,<sup>[2,3]</sup> either of which are acceptable in this medical policy.

The most recent (2012) AASM rules define apnea in adults as a drop in the peak signal excursion by  $\geq 90\%$  of pre-event baseline using an oronasal thermal sensor (diagnostic study), positive airway pressure (PAP) device flow (titration study), or an alternative apnea sensor, for  $\geq 10$  seconds. Hypopnea in adults is scored when the peak signal excursions drop by  $\geq 30\%$  of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative sensor, for  $\geq 10$  seconds in association with either  $\geq 3\%$  arterial oxygen desaturation or an arousal.

The Center for Medicare Services (CMS) scoring rules state that apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thoracoabdominal movement or airflow as compared to baseline, and with at least a 4% oxygen desaturation.

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION:

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

- History and physical/chart notes
- Current symptomology
- Conservative medical therapies failed
- CPAP Trial results
- Sleep Study results, including apnea-hypopnea index (AHI) scored either by the American Academy of Sleep Medicine (AASM) scoring rules or the Center for Medicare Services (CMS) scoring rules.
- Drug-induced sleep endoscopy (DISE) results

## CROSS REFERENCES

1. [Prefabricated Oral Appliances for Obstructive Sleep Apnea](#), Allied Health, Policy No. 36
2. [Orthognathic Surgery](#), Surgery, Policy No. 137
3. [Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome, Surgery](#), Policy No. 166
4. [Absorbable Nasal Implant for Treatment of Nasal Valve Collapse](#), Surgery, Policy No. 209

## BACKGROUND

### OBSTRUCTIVE SLEEP APNEA (OSA)

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction due to the collapse and obstruction of the upper airway during sleep. The hallmark symptom of OSA is excessive daytime sleepiness, and the typical clinical sign of OSA is snoring, which can abruptly cease and be followed by gasping associated with a brief arousal from sleep. The snoring resumes when the patient falls back to sleep, and the cycle of snoring/apnea/arousal may be repeated as frequently as every minute throughout the night.

Sleep fragmentation associated with the repeated arousal during sleep can impair daytime activity. For example, adults with OSA-associated daytime somnolence are thought to be at higher risk for accidents involving motorized vehicles (i.e., cars, trucks, heavy equipment). OSA in children may result in neurocognitive impairment and behavioral problems. In addition, OSA affects the cardiovascular and pulmonary systems. For example, apnea leads to periods of hypoxia, alveolar hypoventilation, hypercapnia, and acidosis. This, in turn, can cause systemic hypertension, cardiac arrhythmias, and cor pulmonale. Systemic hypertension is common in patients with OSA. Severe OSA is associated with decreased survival, presumably related to severe hypoxemia, hypertension, or an increase in automobile accidents related to overwhelming sleepiness.

A polysomnogram performed in a sleep laboratory and, in adults, home sleep apnea testing with a technically adequate device, are considered the gold standard test used to diagnose OSA.<sup>[4]</sup> Objective measures of OSA are compiled using polysomnography monitors, which document the number of apneic (cessation or near cessation of airflow) and hypopneic (reductions in airflow associated with certain physiological consequences) events per hour and combine them into the apnea-hypopnea index (AHI). AHI is a measure of severity of OSA. The American Academy of Sleep Medicine (AASM) provided an updated set of scoring rules in 2012.<sup>[2]</sup> Based on the 2012 AASM rules, apnea in adults is scored when there is a drop in the peak signal excursion by  $\geq 90\%$  of pre-event baseline using an oronasal thermal sensor

(diagnostic study), positive airway pressure (PAP) device flow (titration study), or an alternative apnea sensor, for  $\geq 10$  seconds. Hypopnea in adults is scored when the peak signal excursions drop by  $\geq 30\%$  of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative sensor, for  $\geq 10$  seconds in association with either  $\geq 3\%$  arterial oxygen desaturation or an arousal. The Center for Medicare Services (CMS) also published a set of scoring rules.<sup>[3]</sup> The CMS scoring rules state that apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thoracoabdominal movement or airflow as compared to baseline, and with at least a 4% oxygen desaturation. The respiratory disturbance index (RDI) may be defined as the number of apneas, hypopneas and respiratory effort-related arousals (RERAs) per hour of sleep.

The final diagnosis of OSA rests on a combination of objective and subjective criteria (e.g. AHI or RDI and excessive daytime sleepiness) that seek to identify those levels of obstruction which are clinically significant. When sleep onset and offset are unknown (e.g., in home sleep studies) the AHI or RDI may be calculated based on the number of apneas, hypopneas, and/or RERAs per hour of recording time.

An increase in mortality is associated with an AHI greater than 15. More difficult to evaluate is the clinical significance of patients with mild sleep apnea. Mortality has not been shown to be increased in these patients, and frequently the most significant manifestations reported by the patient are snoring, excessive daytime sleepiness, witnessed breathing interruptions, awakenings due to gasping or choking, nocturia, morning headaches, memory loss, irritability, or hypertension.<sup>[5,6]</sup> The hallmark clinical symptom of OSA is excessive snoring, although it is important to note that snoring can occur in the absence of OSA. Isolated snoring in the absence of medical complications, while troubling to the patient's bed partner, is not considered a medical problem requiring surgical intervention.

**Table 1. Definitions of Terms for Obstructive Sleep Apnea**

Terms	Definition
Apnea	The frequency of apneas and hypopneas is measured from channels assessing oxygen desaturation, respiratory airflow, and respiratory effort. In adults, apnea is defined as a drop in airflow by $\geq 90\%$ of pre-event baseline for at least 10 seconds. Due to faster respiratory rates in children, pediatric scoring criteria define an apnea as $\geq 2$ missed breaths, regardless of its duration in seconds.
Hypopnea	Hypopnea in adults is scored when the peak airflow drops by at least 30% of pre-event baseline for at least 10 seconds in association with either at least 4% arterial oxygen desaturation or an arousal. Hypopneas in children are scored by a $\geq 50\%$ drop in nasal pressure and either a $\geq 3\%$ decrease in oxygen saturation or an associated arousal.
Apnea/Hypopnea Index (AHI)	The average number of apneas or hypopneas per hour of sleep
Obstructive sleep apnea (OSA)	Repetitive episodes of upper airway obstruction due to the collapse and obstruction of the upper airway during sleep
Mild OSA	In adults: AHI of 5 to $<15$  In children: AHI $\geq 1.5$ is abnormal
Moderate OSA	AHI of 15 to $< 30$
Severe OSA	Adults: AHI $\geq 30$  Children: AHI of $\geq 15$

Terms	Definition
Continuous positive airway pressure (CPAP)	Positive airway pressure may be continuous (CPAP) or auto-adjusting (APAP) or Bi-level (Bi-PAP). CPAP is a more familiar abbreviation and will refer to all types of PAP devices.
CPAP Failure	Usually defined as an AHI greater than 20 events per hour while using CPAP
CPAP Intolerance	CPAP use for less than 4 h per night for 5 nights or more per week, or refusal to use CPAP. CPAP intolerance may be observed in patients with mild, moderate, or severe OSA

## IMPLANTABLE HYPOGLOSSAL NERVE STIMULATORS

Hypoglossal nerve stimulation involves the surgical implantation of a subcutaneous generator in the upper chest and an electrode tunneled from the generator to the hypoglossal nerve. The patient uses a hand-held remote to activate the device just prior to sleep and to turn it off upon waking. Some have sensors detect inspiratory efforts and the hypoglossal nerve is stimulated in a synchronized fashion. This stimulation is intended to maintain muscle tone of the tongue base to prevent airway occlusion.

Stimulation systems such as the Inspire II Upper Airway Stimulation System include respiratory sensing leads that permit intermittent stimulation during inspiration. Stimulation parameters are titrated during an in-laboratory polysomnography and can be adjusted by the patient during home use. The device is turned on only during sleep periods.

## REGULATORY STATUS

The *Inspire® II Upper Airway Stimulation System* (Inspire Medical Systems) received FDA approval in 2014 (P130008) for a subset of patients with moderate to severe obstructive sleep apnea. The original approval was for patients with an Apnea Hypopnea Index (AHI) of greater or equal to 20 and less than or equal to 65. In 2017, approval was granted to expand the AHI range to 15 to 65 events per hour (S021). Product code: MNQ

In 2014, ImThera™ Medical received FDA approval for an IDE trial with the aura6000® hypoglossal nerve stimulator system.

In 2011, Apex Medical received FDA approval to conduct a randomized investigational device exemption (IDE) trial for the Hypoglossal Nerve Stimulation (HGNS®) System. The trial was terminated and Apex Medical has ceased operations.

## EVIDENCE SUMMARY

Continuous positive airway pressure (CPAP) is the most widely accepted medical therapy for treatment of obstructive sleep apnea (OSA) and improvement of primary health outcomes such as cardiovascular disease, type 2 diabetes, and overall mortality associated with OSA. Hypoglossal nerve stimulation (HNS), sometimes referred to as upper airway stimulation, is being proposed as a second line treatment for patients who have failed CPAP.

## SYSTEMATIC REVIEWS

Costantino (2020) published a systematic review (SR) with meta-analysis of studies evaluating the clinical outcomes of HNS in the treatment of moderate to severe OSA.<sup>[7]</sup> The SR included 12 prospective studies, excluding redundant cohorts of the same studies with varied follow-up lengths such as the STAR Trial<sup>[8-11]</sup> and the German Post-Market studies<sup>[12,13]</sup> No randomized

controlled trials comparing HNS to CPAP or other surgical interventions were identified. Of the 350 patients (median age 54.3 [IQR 53-56.25] years), 239 were implanted with the Inspire® system, 59 were implanted with the ImThera™ system, and 52 were implanted with the Apnex system. All of the studies were considered to be of generally high quality, having satisfied at least six of the eight NICE quality assessment tool items. In all studies, the American Academy of Sleep Medicine (AASM) apnea and hypopnea definitions<sup>[2]</sup> were used, except that a 4% oxygen desaturation was required for a hypopnea to determine AHI. Analyses of long-term outcomes were conducted with data from the nine studies which had follow-up timepoints of six- and 12-months separately from the STAR trial data, which reported longer-term follow-up timepoints of 18-, 36-, and 60-months. At 12 months, the mean AHI difference was - 17.50 (Inspire; 95% CI: - 20.01 to - 14.98,  $p < 0.001$ ), - 24.20 (ImThera™; 95% CI: - 37.39 to 11.01,  $p < 0.001$ ), and - 20.10 (Apnex; 95% CI: - 29.62 to - 10.58,  $p < 0.001$ ). The mean AHI reduction after five years was - 18.00 (Inspire®, - 22.38 to - 13.62,  $p < 0.001$ ). The Epworth sleepiness scale (ESS) mean reduction was - 5.27 (Inspire®), - 2.90 (ImThera™), and - 4.20 (Apnex) at 12 months and - 4.40 (Inspire) at 60 months, respectively. Five-year serious device-related adverse events requiring surgical intervention in the STAR trial were 6% (8/126 patients), and the other studies included in the meta-analysis ( $n=195$ ) reported a comparable complication rate at six and 12 months. Among the nine studies included in the meta-analysis, the overall success rate at 12 months (defined as a 50% reduction in AHI and overall AHI less than 20), was 72.4% (Inspire®,  $n=211$ ), 76.9% (ImThera™,  $n=13$ ), and 55% (Apnex,  $n=31$ ).

A 2015 SR identified six case series with a total of 200 patients treated with HNS.<sup>[14]</sup> No controlled trials were identified. Two series were identified on the Inspire II System and included the STAR trial described below. Three series were identified with the HGNS system and included the study of 31 patients described above. One series of 13 patients was identified with the aura6000 System (ImThera Medical). When data were combined for meta-analysis, AHI and Oxygen Desaturation Index (ODI) improved by 50% (eg, AHI from 44 to 20, ODI from 21 to 10), and the ESS improved from 12 to 7. All of the included studies described minor complications such as tongue weakness, tongue soreness, pain/swelling at the neck incision, fever, and lack of tongue response to stimulation. Of the 200 patients, nine (4.5%) had serious device-related adverse events that led to removal of the stimulator.

## **RANDOMIZED CONTROLLED TRIALS**

No RCTs have been identified on HNS.

## **NONRANDOMIZED STUDIES**

### **Observational Comparative Studies**

Nonrandomized evidence consists of two comparative studies that compared HNS with historical controls treated with UPPP or a variant of UPPP (expansion sphincter pharyngoplasty, see Table 2). AHI success by the Sher criteria ranged from 87% to 100% in the HNS group compared with 40% to 64% in the UPPP group (see Table 3). Posttreatment ESS was below 10 in both groups. It is not clear from these studies whether the patients in the historical control group were similar to the subset of patients in the HNS group, particularly in regard to the pattern of palatal collapse and from patients who did not return for postoperative PSG (see Tables 4 and 5). UPPP may not be the most appropriate comparator for HNS, because UPPP is less effective for patients with obstruction arising primarily from the tongue base (the primary target for HNS).

**Table 2. Summary of Observational Comparative Study Characteristics**

Study	Study Type	Country	Dates	Participants	HNS	Traditional Surgery	Follow-Up
Shah (2018) <sup>[15]</sup>	Retrospective series with historical controls	U.S.	HNS 2015-2016  UPPP 2003-2012	40 OSA patients with AHI >20 and <65, BMI ≤32 kg/m <sup>2</sup> , failed CPAP, favorable pattern of palatal collapse <sup>a</sup>	35% had previously had surgery for OSA	UPPP 50% of patients had additional surgical procedures	2-13 mo
Huntley (2018) <sup>[16]</sup>	Retrospective series with historical controls	U.S.	HNS 2014-2016  Modified UPPP 2011-2016	Retrospective review included treated patients who had a postoperative PSG	75 patients age 61.67 y with a favorable pattern of palatal collapse	33 patients age 43.48 y treated by ESP	To post-operative PSG

BMI: body mass index; CPAP: continuous positive airway pressure; ESP: expansion sphincter pharyngoplasty; HNS: hypoglossal nerve stimulation; OSA: obstructive sleep apnea; PSG: polysomnography; UPPP: uvulopalatopharyngoplasty.

<sup>a</sup> A favorable pattern of palatal collapse is not concentric retropalatal obstruction on drug-induced sleep endoscopy.

**Table 3. Summary of Key Observational Comparative Study Results**

Header Row	Baseline AHI (SD)	Posttreatment AHI (SD)	AHI Success (%) Sher Criteria	Baseline ESS (SD)	Posttreatment ESS (SD)
Shah (2018) <sup>[15]</sup>					
HNS	38.9 (12.5)	4.5 (4.8) <sup>b</sup>	20 (100%)	13 (4.7)	8 (5.0) <sup>b</sup>
UPPP	40.3 (12.4)	28.8 (25.4) <sup>a</sup>	8 (40%)	11 (4.9)	7 (3.4) <sup>b</sup>
Huntley (2018) <sup>[16]</sup>					
HNS	36.8 (20.7)	7.3 (11.2)	86.7	11.2 (4.2)	5.4 (3.4)
ESP	26.7 (20.3)	13.5 (19.0)	63.6	10.7 (4.5)	7.0 (6.0)
p	0.003	0.003	0.008	0.565	NS

AHI: Apnea/Hypopnea Index; ESP: expansion sphincter pharyngoplasty; HNS: hypoglossal nerve stimulation; NS: not significant; Sher criteria: 50% decrease in AHI and final AHI <20; SD; standard deviation; UPPP: uvulopalatopharyngoplasty.

<sup>a</sup> Baseline vs posttreatment p<0.05.

<sup>b</sup> Baseline vs posttreatment p<0.001.

**Table 4. Relevance Gaps**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Shah (2018) <sup>[15]</sup>			2. UPPP may not be preferred treatment for patients with primarily lingual obstruction		
Huntley (2018) <sup>[16]</sup>	4. Study populations not comparable		1. Not clearly defined, few ESP patients had follow-up PSG		

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Steffen (2018) <sup>[12]</sup>			2.No comparator		
STAR trial <sup>[8-11,17,18]</sup>			2.No comparator		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. ESP: expansion sphincter pharyngoplasty; PSG: polysomnography; STAR: Stimulation Therapy for Apnea Reduction; UPPP: uvulopalatopharyngoplasty.

<sup>a</sup> 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.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> 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.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 5. Study Design and Conduct Gaps**

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>d</sup>	Power <sup>d</sup>	Statistical <sup>f</sup>
Shah (2018) <sup>[15]</sup>	1. Not randomized (retrospective)  4. Inadequate control for selection bias	1.-3. No blinding				4. Comparative treatment effects not calculated
Huntley (2018) <sup>[16]</sup>	1. Not randomized (retrospective)	1.-3. No blinding				
Steffen (2018) <sup>[12]</sup>	1. Not randomized	1.-3. No blinding				
STAR trial <sup>[8-11,17,18]</sup>	1. Not randomized	1.-3. No blinding				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. STAR: Stimulation Therapy for Apnea Reduction.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> 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).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

## Prospective Single Arm Studies

Results of prospective single-arm studies show success rates in 66% to 68% of patients who had moderate-to-severe sleep apnea and a favorable pattern of palatal collapse (see Tables 6 and 7). Mean AHI was 31 to 32 at baseline, decreasing to 14 to 15 at 12 months. ESS scores decreased to 6.5 to 7.0. All improvements were maintained through 5 years of follow-up. Discomfort due to the electrical stimulation and tongue abrasion were initially common but

were decreased when stimulation levels were reduced (see Table 8). In the post-market study, a normal ESS score (< 10) was obtained in 73% of patients. A FOSQ score of at least 19 was observed in 59% of patients compared to 13% at baseline. At the 12- month follow-up, 8% of bed partners regularly left the room due to snoring, compared to 75% of bed partners at baseline. The average use was 5.6 + 2.1 h per night. Use was correlated with the subjective outcomes, but not with AHI response.

**Table 6. Summary of Prospective Single-Arm Study Characteristics**

Study	Country	Participants	Treatment Delivery	Follow-Up
STAR trial <sup>[8-11,17,18]</sup>	EU, U.S.	126 patients with AHI >20 and <50, BMI ≤32 kg/m <sup>2</sup> , failed CPAP, favorable pattern of palatal collapse <sup>a</sup>	Stimulation parameters titrated with full PSG	5 y
Postmarket studies: Heiser (2017) <sup>[13]</sup>  Steffen (2018) <sup>[12]</sup>  Hasselbacher (2018) <sup>[19]</sup>  Withrow (2019) <sup>[20]</sup>	3 sites in Germany    Thirteen US hospitals and 3 German hospitals	60 patients with AHI ≥15 and ≤65 on home sleep study, BMI ≤35 kg/m <sup>2</sup> , failed CPAP; favorable pattern of palatal collapse <sup>a</sup>   600 adults with moderate to severe OSA (AHI, 15-65), <25% central and mixed apneas, CPAP nonadherence or intolerance, absence of concentric collapse		12 mo    12 mo

AHI: apnea/hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; STAR: Stimulation Therapy for Apnea Reduction.

<sup>a</sup> A favorable pattern of palatal collapse is non-concentric retropalatal obstruction on drug-induced sleep endoscopy.

**Table 7. Summary of Prospective Single-Arm Study Results**

Study	N	Percent of Patients with AHI Success (Sher criteria)	Mean AHI Score (SD)	Mean ODI Score (SD)	FOSQ Score (SD)	ESS Score (SD)
STAR trial <sup>[8-11,17,18]</sup>						
Baseline	126		32.0 (11.8)	28.9 (12.0)	14.3 (3.2)	11.6 (5.0)
12 months	124	66%	15.3 (16.1) <sup>d</sup>	13.9 (15.7) <sup>d</sup>	17.3 (2.9) <sup>d</sup>	7.0 (4.2) <sup>d</sup>
3 years	116 <sup>a</sup>	65%	14.2 (15.9)	9.1 (11.7)	17.4 (3.5) <sup>b</sup>	7.0 (5.0) <sup>b</sup>
5 years	97 <sup>c</sup>	63%	12.4 (16.3)	9.9 (14.5)	18.0 (2.2)	6.9 (4.7)
Postmarket studies:						

Study	N	Percent of Patients with AHI Success (Sher criteria)	Mean AHI Score (SD)	Mean ODI Score (SD)	FOSQ Score (SD)	ESS Score (SD)
Heiser (2017) <sup>[13]</sup> Steffen (2018) <sup>[12]</sup> Hasselbacher (2018) <sup>[19]</sup>						
Baseline	60		31.2 (13.2)	27.6 (16.4)	13.7 (3.6)	12.8 (5.3)
12 months	56 <sup>f</sup>	68%	13.8 (14.8) <sup>e</sup>	13.7 (14.9) <sup>e</sup>	17.5 (3) <sup>e</sup>	6.5 (4.5) <sup>e</sup>
Withdraw (2019) <sup>[20]</sup>						
age < 65	365					
Baseline			36.2 (34.6-37.8) <sup>f</sup>			12.3 (11.7-12.9) <sup>f</sup>
12 months			11.9 (9.9-13.9) <sup>f</sup>			7.1 (6.4-7.8)
age ≥ 65	235					
Baseline			36.1 (34.2-38.0) <sup>f</sup>			10.7 (9.9-11.5) <sup>f</sup>
12 months			7.6 (6.1-9.1) <sup>f</sup>			6.3 (5.4-7.2) <sup>f</sup>

AHI: Apnea/Hypopnea Index; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; ODI: Oxygen Desaturation Index; PSG: polysomnography; SD: standard deviation; STAR: Stimulation Therapy for Apnea Reduction.

<sup>a</sup> Ninety-eight participants agreed to undergo PSG at 36 months, of the 17 participants who did not undergo PSG at 36 months, 54% were nonresponders and their PSG results at 12 or 18 months were carried forward.

<sup>b</sup> The change from baseline was significant at  $p < 0.001$ .

<sup>c</sup> Seventy-one participants agreed to a PSG.

<sup>d</sup>  $p < 0.001$ .

<sup>e</sup>  $p < 0.05$ .

<sup>f</sup> Four patients lost to follow-up were analyzed as treatment failures.

<sup>g</sup> Range

**Table 8. Device-Related Adverse Events from Prospective Single-Arm Studies**

Header Row	N	Discomfort due to Electrical Stimulation <sup>a</sup>	Tongue Abrasion	Dry Mouth	Mechanical Pain from Device	Internal Device Usability	External Device Usability
STAR trial <sup>[11]</sup>							
0 to 12 months	126	81	28	10	7	12	11
12 to 24 months	124	23	12	5	2	8	11
24 to 36 months	116	26	4	2	3	1	8
36 to 48 months	97	7	3	0	1	3	9
> 48 months		5	3	3	1	1	6
Participants with event, n of 126 (%)		76 (60.3)	34 (27.0)	19 (15.1)	14 (11.1)	21 (16.7)	33 (26.2)

STAR: Stimulation Therapy for Apnea Reduction.

<sup>a</sup> Stimulation levels were adjusted to reduce discomfort

## PRACTICE GUIDELINE SUMMARY

### AMERICAN ACADEMY OF OTOLARYNGOLOGY - HEAD AND NECK SURGERY

In a position statement, the American Academy of Otolaryngology - Head and Neck Surgery (2019) supported hypoglossal nerve stimulation as an effective second-line treatment of moderate-to-severe obstructive sleep apnea in patients who are intolerant or unable to achieve benefit with positive pressure therapy.<sup>[2<sup>1</sup>]</sup>

## SUMMARY

Evidence for hypoglossal nerve stimulation (HNS) as a treatment of obstructive sleep apnea (OSA) is limited. However, HNS has become generally accepted in medical practice, and is recommended as an effective second-line treatment in a consensus statement by the American Academy of Otolaryngology - Head and Neck Surgery. Therefore, hypoglossal nerve stimulation may be considered medically necessary for some patients with OSA when policy criteria are met.

There is not enough research to know if or how well hypoglossal nerve stimulation (HNS) works to treat people with indications other than those listed in policy criteria. This does not mean that it does not work, but more research is needed to know. No clinical guidelines based on research address HNS for indications other than for those listed in the policy criteria. Therefore, hypoglossal nerve stimulation is considered investigational for all other indications not listed in policy criteria.

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  22. BlueCross BlueShield Association Medical Policy Reference Manual "Surgical Treatment of Snoring and Obstructive Sleep Apnea Syndrome." Policy No. 7.01.101

## CODES

Codes	Number	Description
CPT	64568	Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
	0466T	Insertion of chest wall respiratory sensor electrode or electrode array, including connection to pulse generator (List separately in addition to code for primary procedure)
	0467T	Revision or replacement of chest wall respiratory sensor electrode or electrode array, including connection to existing pulse generator
	0468T	Removal of chest wall respiratory sensor electrode or electrode array
HCPCS	None	

**Date of Origin:** June 2019

## ***Responsive Neurostimulation***

**Effective:** November 1, 2019

**Next Review:** September 2020

**Last Review:** September 2019

### **IMPORTANT REMINDER**

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

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

### **DESCRIPTION**

Responsive neurostimulation (RNS) provides cortical stimulation in response to detection of specific seizure-related electrical signals. RNS shares some features with deep brain stimulation, but is differentiated by its use of direct cortical stimulation and by its use in both monitoring and stimulation. RNS is used in individuals with refractory focal epilepsies to provide a treatment option that is an alternative to or an improvement on existing therapies.

### **MEDICAL POLICY CRITERIA**

- I. Responsive neurostimulation may be considered **medically necessary** for patients with focal epilepsy who meet ALL of the following criteria:
  - A. 18 years or older; and
  - B. Device is FDA approved (PMA or 510k only); and
  - C. Diagnosis of focal seizures with 1 or 2 localized seizure foci identified; and
  - D. Average of 3 or more disabling seizures (e.g., motor focal seizures, complex focal seizures, or secondary generalized seizures) per month for 3 consecutive months; and
  - E. Failed greater than or equal to 2 antiepileptic medications; and

- F. Not a candidate for focal resective epilepsy surgery (e.g., have an epileptic focus near the eloquent cerebral cortex; have bilateral temporal epilepsy); and
- G. Do not have any of the following contraindications for responsive neurostimulation device placement:
  - 1. 3 or more specific seizure foci
  - 2. Presence of primary generalized epilepsy
  - 3. Presence of a rapidly progressive neurologic disorder
- II. Responsive neurostimulation is considered **investigational** for all other indications, including but not limited to patients with focal epilepsy who do not meet the above Criteria.

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

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION:

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

- History and physical exam, including requirements as outlined by the policy criteria
- Number of seizure foci
- Documentation of seizure occurrence over the prior 3 months
- Clinical documentation demonstrating medicine-refractory symptoms
- Clinical documentation demonstrating that the patient is not a candidate for focal resective epilepsy surgery
- Presence of other conditions, such as a neurological disorder

## CROSS REFERENCES

1. [Vagus Nerve Stimulation](#), Surgery, Policy No. 74
2. [Deep Brain Stimulation](#), Surgery, Policy No. 84
3. [Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy of Intracranial, Skull Base, and Orbital Sites](#), Surgery, Policy No. 213

## BACKGROUND

Focal seizures (previously referred to as partial seizures) arise from a discrete area of the brain and can cause a range of symptoms, depending on the seizure type and the brain area involved.

Note that the term focal seizure in older literature may be referred to as “partial seizure.” A position paper from the International League Against Epilepsy (2017) outlined updated terminology for seizure and epilepsy subtypes.<sup>[1]</sup> For example, focal-onset seizures are subdivided based on the associated level of consciousness, and subsequently into whether they are motor or non-motor-onset.

Seizure disorders may be grouped into epileptic syndromes based on a number of factors, including the types of seizures that occur and their localization, the age of onset, patterns on electroencephalogram, associated clinical or neuroimaging findings, and genetic factors. Temporal lobe epilepsy is the most common syndrome associated with focal seizures. Of those with focal seizures, 30% to 40% have intractable epilepsy, defined as a failure to control seizures after two seizure medications have been appropriately chosen and used.<sup>[2]</sup>

## **EPILEPSY TREATMENT**

### **Medical Therapy for Seizures**

Standard therapy for seizures, including focal seizures, includes treatment with one or more of various antiepileptic drugs (AEDs), which include newer AEDs, like oxcarbazepine, lamotrigine, topiramate, gabapentin, pregabalin, levetiracetam, tiagabine, and zonisamide.<sup>[2]</sup> Currently, response to AEDs is less than ideal: one systematic review comparing newer AEDs for refractory focal epilepsy reported an overall average responder rate in treatment groups of 34.8%.<sup>[2]</sup> As a result, a substantial number of patients do not achieve good seizure control with medications alone.

### **Surgical Therapy for Seizures**

When a discrete seizure focus can be identified, seizure control may be achieved through resection of the seizure focus (epilepsy surgery). For temporal lobe epilepsy, a randomized controlled trial has demonstrated that surgery for epilepsy was superior to prolonged medical therapy in reducing seizures associated with impaired awareness and in improving quality of life.<sup>[3]</sup> Surgery for refractory focal epilepsy (excluding simple focal seizures) is associated with five-year freedom from seizure rates of 52%, with 28% of seizure-free individuals able to discontinue AEDs.<sup>[4]</sup> Selection of appropriate patients for epilepsy surgery is important, because those with nonlesional extratemporal lobe epilepsy have worse outcomes after surgery than those with nonlesional temporal lobe epilepsy.<sup>[5]</sup> Some patients are not candidates for epilepsy surgery if the seizure focus is located in an eloquent area of the brain or other region that cannot be removed without risk of significant neurologic deficit.

### **Neurostimulation for Neurologic Disorders**

Electrical stimulation at one of several locations in the brain has been used as therapy for epilepsy, either as an adjunct to or as an alternative to medical or surgical therapy. Vagus nerve stimulation (VNS) has been widely used for refractory epilepsy, following Food and Drug Administration (FDA) approval of a VNS device in 1997 and two randomized controlled trials evaluating VNS in epilepsy.<sup>[6]</sup> Although the mechanism of action for VNS is not fully understood, VNS is thought to reduce seizure activity through activation of vagal visceral afferents with diffuse central nervous system projections, leading to a widespread effect on neuronal excitability.

Stimulation of other locations in the neuroaxis has been studied for a variety of neurologic disorders. Electrical stimulation of deep brain nuclei (deep brain stimulation [DBS]) involves the use of chronic, continuous stimulation of a target. It has been most widely used in the treatment of Parkinson disease and other movement disorders, and has been investigated for treating epilepsy. DBS of the anterior thalamic nuclei was studied in a randomized control trial, the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy trial, but DBS is not currently approved by FDA for stimulation of the anterior thalamic nucleus.<sup>[7]</sup> Stimulation of the

cerebellar and hippocampal regions and the subthalamic, caudate, and centromedian nuclei have also been evaluated for the treatment of epilepsy.<sup>[6]</sup>

## **Responsive Neurostimulation for Epilepsy**

Responsive neurostimulation (RNS) shares some features with DBS, but is differentiated by its use of direct cortical stimulation and by its use in both monitoring and stimulation. The RNS system provides stimulation in response to detection of specific epileptiform patterns, while DBS provides continuous or intermittent stimulation at preprogrammed settings.

Development of the RNS system arose from observations related to the effects of cortical electrical stimulation for seizure localization. It has been observed that electrical cortical stimulation can terminate induced and spontaneous electrographic seizure activity in humans and animals.<sup>[8]</sup> Patients with epilepsy may undergo implantation of subdural monitoring electrodes for the purposes of seizure localization, which at times have been used for neurostimulation to identify eloquent brain regions. Epileptiform discharges that occur during stimulation for localization can be stopped by a train of neighboring brief electrical stimulations.<sup>[9]</sup>

In tandem with the recognition that cortical stimulation can stop epileptiform discharges was development of fast pre-ictal seizure prediction algorithms. These algorithms interpret electrocorticographic data from detection leads situated over the cortex. The RNS process thus includes electrocorticographic monitoring via cortical electrodes, analysis of data through a proprietary seizure detection algorithm, and delivery of electrical stimulation via both cortical and deep implanted electrodes in an attempt to halt a detected epileptiform discharge.

One device, the NeuroPace RNS System, is currently approved by FDA and is commercially available.

## **RNS FOR SEIZURE MONITORING**

Although the intent of the electrocorticography component of the RNS system is to provide input as a trigger for neurostimulation, it also provides continuous seizure mapping data (chronic unlimited cortical electrocorticography) that may be used by practitioners to evaluate patients' seizures. In particular, the seizure mapping data have been used for surgical planning of patients who do not experience adequate seizure reduction with RNS placement. Several studies have described the use of RNS in evaluating seizure foci for epilepsy surgery<sup>[10]</sup> or for identifying whether seizure foci are unilateral.<sup>[11,12]</sup>

This review does not further address use of RNS exclusively for seizure monitoring.

## **REGULATORY STATUS**

In November 2013, the NeuroPace RNS® System (NeuroPace) was approved by FDA through the premarket approval process for the following indication<sup>[13]</sup>:

“The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/ or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more

disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures.”

FDA product code: PFN.

## EVIDENCE SUMMARY

### RNS FOR TREATMENT OF REFRACTORY FOCAL EPILEPSY

The body of evidence addressing whether RNS is associated with improved health outcomes for patients with focal epilepsy includes an industry-sponsored RCT, which was used for the device’s U.S. Food and Drug Administration (FDA) approval, as well as multiple case series and case reports.

#### Pivotal Trial

RNS for epilepsy was evaluated in the RNS System Pivotal Trial, a multicenter, double-blinded, sham-controlled trial that served as the basis of FDA’s approval of the device.<sup>[14]</sup> Published by Morrell (2011), this RCT included 191 patients with medically intractable focal epilepsy who were implanted with the RNS device and randomized to treatment or sham control after a one-month postimplant period during which time no subjects had the device activated. Eligible patients were adults with focal seizures whose epilepsy had not been controlled with at least two trials of antiepileptic drugs (AEDs), who had at least three disabling seizures (motor focal seizures, complex focal seizures, or secondary generalized seizures) per month on average, and who had standard diagnostic testing that localized one or two epileptogenic foci. Thirty-two percent of those implanted had prior epilepsy surgery, and 34% had a prior vagal nerve stimulator.

Patients were randomized to active stimulation (n=97) or sham stimulation (n=94). After the four-week postoperative period, patients received either sham or active stimulation according to group assignment. There was a four-week stimulation optimization period, followed by a three-month blinded evaluation period. In the evaluation period, all outcome data were gathered by a physician blinded to group assignment, and the neurostimulator was managed by a nonblinded physician. One patient in each group did not complete the stimulus optimization period (one due to subject preference in the active stimulation group; one due to death in the sham stimulation group). An additional patient in each group did not complete the blinded evaluation phase due to emergent explant of the device. After the three-month blinded evaluation period, all patients received active stimulation during an open-label follow-up period. At the time of the Morrell publication, 98 subjects had completed the open-label period and 78 had not. Eleven patients did not complete the open-label follow-up period (five due to death, two to emergent explant, four to study withdrawal).

The trial’s primary effectiveness objective was to demonstrate a significantly greater reduction in the frequency of total disabling seizures in the treatment group compared with the sham group during the blinded evaluation period relative to baseline (preimplant). The mean preimplant seizure frequency per month in the treatment group was 33.5 (range, 3-295) and 34.9 (range, 3-338) in the sham group.<sup>[13]</sup> Mean seizure frequency modeled using generalized estimating equations was significantly reduced in the treatment group compared with the sham group (p=0.012). During the blinded evaluation period, the mean seizure frequency in the treatment group was 22.4 (range, 0.0-227) and 29.8 (range, 0.3-447) in the sham group. The treatment group experienced a -37.9% change in seizure frequency (95% confidence interval

[CI], -46.7% to -27.7%), while the sham group experienced a -17.3% change in seizure frequency (95% CI, -29.9% to -2.3%).

By the third month of the blinded evaluation period, the treatment group had 27% fewer days with seizures while the sham group experienced 16% fewer days ( $p=0.048$ ). There were no significant differences between groups over the blinded evaluation period for secondary end points of responder rate (proportion of subjects who experienced a  $\geq 50\%$  reduction in mean disabling seizure frequency vs the preimplant period), change in average frequency of disabling seizures, or change in seizure severity.

During the open-label period, subjects in the sham group demonstrated significant improvements in mean seizure frequency compared with the preimplant period ( $p=0.04$ ). For all subjects (treatment and sham control), the responder rate at one-year postimplant was 43%. Overall quality of life scores improved for both groups compared with baseline at one year ( $p=0.001$ ) and two years postimplant ( $p=0.016$ ).

For the study's primary safety end point, the significant adverse event rate over the first 28 days postimplant was 12%, which did not differ significantly from the prespecified literature-derived comparator of 15% for implantation of intracranial electrodes for seizure localization and epilepsy surgery. During the implant period and the blinded evaluation period, the significant adverse event rate was 18.3%, which did not differ significantly from the prespecified literature-derived comparator of 36% for implantation and treatment with deep brain stimulation for Parkinson disease. The treatment and sham groups did not differ significantly in terms of mild or serious adverse events during the blinded evaluation period. Intracranial hemorrhage occurred in 9 (4.7%) of 191 subjects; implant or incision site infection occurred in 10 (5.2%) of 191 subjects, and the devices were explanted from 4 of these subjects.

### **Follow-Up Analyses to the Pivotal Trial Subjects**

In a follow-up to the RNS System Pivotal Trial, Heck (2014) compared outcomes at one and two years postimplant with baseline for patients in both groups (sham and control) who had the RNS stimulation device implanted during the RNS System Pivotal Trial.<sup>[15]</sup> Of the 191 subjects implanted, 182 subjects completed follow-up to one year postimplant and 175 subjects completed follow-up to two years postimplant. Six patients withdrew from the trial, four underwent device explantation due to infection, and five died, with one due to sudden unexplained death in epilepsy. During the open-label period, at two years of follow-up, median percent reduction in seizures was 53% compared with the preimplant baseline ( $p<0.001$ ), and the responder rate was 55%.

Loring (2015) analyzed one of the trial's prespecified safety end points (neuropsychologic function) during the trial's open-label period.<sup>[16]</sup> Neuropsychological testing focused on language and verbal memory, measured by the Boston Naming Test and the Rey Auditory Verbal Learning Test. One hundred seventy-five subjects had cognitive assessment scores at baseline and at one or two years or both and were included in this analysis. The authors used reliable change indices (RCIs) to identify patients with changes in test scores beyond that attributed to practice effects or measurement error in the test-retest setting, with 90% RCIs used for classification. Overall, no significant group-level declines in any neuropsychological outcomes were detected. On the Boston Naming Test, 23.5% of subjects demonstrated RCI improvements while 6.7% had declines; on the Rey Auditory Verbal Learning Test, 6.9% of subjects demonstrated RCI improvements and 1.4% demonstrated declines.

Meador (2015) reported on quality of life and mood outcomes for individuals in the RNS pivotal trial.<sup>[17]</sup> At the end of the blinded study period, both groups reported improvements in Quality of Life in Epilepsy Inventory-89 (QOLIE-89) scores, with no statistically significant differences between groups. In analysis of those with follow-up to two years post-enrollment, implanted patients had statistically significant improvements in QOLIE-89 scores from enrollment to one- and two-year follow-up. Mood, as assessed by the Beck Depression Inventory and the Profile of Mood States, did not worsen over time.

## Systematic Reviews

Cox (2014) reported on a systematic review of implantable neurostimulation devices, including RNS, along with vagus nerve stimulation and deep brain stimulation for refractory epilepsy.<sup>[18]</sup> The evidence on RNS in this review was primarily from the pivotal RCT<sup>[14]</sup> described previously. Reviewers concluded that RNS is “promising,” but that improvements in the accuracy of the seizure prediction method and standardization of electrical stimulation parameters were needed.

Gooneratne (2016) performed a systematic review comparing neurostimulation technologies in refractory focal epilepsy.<sup>[19]</sup> They performed a literature search for studies with long-term efficacy data ( $\geq 5$  years) and at least 30 patients evaluating vagus nerve stimulation, cortical responsive stimulation, or deep brain stimulation in refractory focal or focal epilepsy through November 2015. No direct comparisons of the technologies were found. The previously described pivotal trial of RNS was the only RNS study included. Indirect comparisons of the technologies were limited by differences in RCT inclusion criteria, definitions of response, and methods of data collection between studies. Reviewers concluded that all three neurostimulation technologies showed long-term efficacy, with progressively better seizure control over time.

## Noncomparative Studies

Before and during conduct of the pivotal RCT to evaluate the RNS system, short- and long-term outcomes following the use of the device have been described in case series.

The Long-Term Treatment (LTT) Study was a seven-year, multicenter, prospective, open-label study to evaluate the RNS system’s long-term efficacy and safety in individuals who participated in device’s feasibility or pivotal trials. Bergey (2015) reported on follow-up for 191 participants in the LTT Study (of a total of 230 originally enrolled in the LTT Study) for a median 5.4 years.<sup>[20]</sup> Of those who discontinued, three were lost to follow-up, 28 patients withdrew (nine to pursue other treatments, five due to insufficient efficacy, five decided not to replace the RNS system after expected battery depletion, five after infection resolved, three for noncompliance, one for elective explant, one due to ongoing suicidality/noncompliance), four underwent emergent explant, and four died. For follow-up at years three and six, the median percent reductions in seizures were 60% and 66%, respectively. Statistically significant quality of life improved at four years, with a trend toward improvement at five years. The most common adverse events were implant site infection ( $n=24$  [9.4%]) and increase in complex focal seizures ( $n=20$  [7.8%]).

Since device approval, a single-center study by Lee (2015) has reported on outcomes after RNS implantation (40 surgeries) in 10 patients.<sup>[21]</sup> In this series, one patient had an implant site infection requiring device explantation and another had multiple lead breakages.

Earlier studies have reported that the RNS implant was well-tolerated in small numbers of patients. Anderson (2008) reported on procedural details and clinical outcomes for four patients treated with the RNS device (as part of the device's pivotal clinical trial) and noted that the device implant was well-tolerated and qualitatively reduced the frequency of seizures.<sup>[9]</sup> Kossoff (2004) reported qualitative reduction in seizure frequency in four patients with intractable seizures who received neurostimulation with an external RNS (a precursor to the FDA-approved implantable RNS device) during intracranial monitoring to localize seizure onset for surgery mapping.<sup>[8]</sup>

Cases in which chronic (i.e., not responsive to detected seizure activity) focal cortical stimulation was used to treat medically refractive epilepsy have also been described.<sup>[22]</sup> In these cases, cortical electrodes were placed during planned neurosurgical intervention for seizure mapping and were connected to a pulse generator.

### **Section Summary: RNS for Treatment of Refractory Focal Epilepsy**

The most direct and rigorous evidence related to the effectiveness of RNS in the treatment of refractory focal seizures is from the RNS System Pivotal Trial, in which patients who had focal epilepsy refractory to at least two medications and received RNS treatment demonstrated a significantly greater reduction in their rates of seizures compared with sham-control patients. Although this single RCT was relatively small (97 patients in the treatment group), it was adequately powered for its primary outcome and all patients were treated with the device during the open-label period (97 in the original treatment group, 94 in the original sham group) and demonstrated a significant improvement in seizure rates compared with baseline. However, there were no differences in the percentage of patients who responded to RNS, and no difference on most of the other secondary outcomes. Follow-up has been reported to five years postimplantation, without major increases in rates of adverse events.

### **ADVERSE EVENTS WITH THE RNS SYSTEM**

As a surgical procedure, implantation of the RNS system is associated with the risks that should be balanced against the risks of alternative treatments, including AEDs and other invasive treatments (vagal nerve stimulator and epilepsy surgery), and the risks of uncontrolled epilepsy. During the RNS System Pivotal Trial, rates of serious adverse events were relatively low: 3.7% of patients had implant site infections, 6% had lead revisions or damage, and 2.1% percent had intracranial hemorrhages during initial implantation.<sup>[15]</sup>

FDA's summary of safety and effectiveness data for the RNS system summarized deaths and adverse events. As reported in the safety and effectiveness data, as of October 24, 2012, there were 11 deaths in the RNS System trials, including the pivotal trial and the ongoing long-term treatment study. Two of the deaths were suicides (one each in the pivotal and LTT studies), one due to lymphoma and another to complications of status epilepticus, and seven were attributed to possible, probable, or definite sudden unexplained death in epilepsy. With 1195 patient implant years, the estimated sudden unexplained death in epilepsy rate is 5.9 per 1000 implant years, which is comparable with the expected rate for patients with refractory epilepsy.<sup>[13]</sup>

Additional safety outcomes have been reported to five years postimplantation through the device's LTT study (see above).

As of March 13, 2019, there were 203 reports in the FDA Manufacturer and User Facility Device Experience database for product code PFN. Five were labeled as event type “Malfunction,” one was extended hospitalization due to aphasia, and all remaining reports were labeled as “Injury.” Seven of the “Injury” event narratives mentioned hemorrhages, three stroke, six fluid leakage, 46 infection, five swelling or edema, and in five the device had become exposed.

## SUMMARY OF EVIDENCE

For individuals who have refractory focal epilepsy who receive RNS, the evidence includes an industry-sponsored RCT, which was used for Food and Drug Administration approval of the NeuroPace RNS System, as well as case series. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related mortality and morbidity. The pivotal trial was well-designed and well-conducted; it reported that RNS is associated with improvements in mean seizure frequency in patients with refractory focal epilepsy, with an absolute difference in change in seizure frequency of about 20% between groups, though the percentage of treatment responders with at least a 50% reduction in seizures did not differ from sham control. Overall, the results suggested a modest reduction in seizure frequency in a subset of patients. The number of adverse events reported in the available studies is low, although the data on adverse events were limited because small study samples. Generally, patients who are candidates for RNS are severely debilitated and have few other treatment options, so the benefits are likely high relative to the risks. In particular, patients who are not candidates for resective epilepsy surgery and have few treatment options may benefit from RNS. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

## PRACTICE GUIDELINE SUMMARY

The American Academy of Neurology has published guidelines on specific treatments for epilepsy.<sup>[23]</sup> It has not published any guidelines with recommendations regarding responsive neurostimulation.

## SUMMARY

It appears that in patients with refractory focal epilepsy, responsive neurostimulation (RNS) may improve health outcomes, including a reduction in seizure frequency in some patients. In particular, patients who are not candidates for resective epilepsy surgery and have few treatment options may benefit from RNS. Therefore, RNS may be considered medically necessary in patients with medication-refractory focal epilepsy when criteria are met.

There is not enough research to show that responsive neurostimulation (RNS) improves health outcomes for all other indications not meeting the criteria, including but not limited to patients with focal epilepsy who do not meet the criteria. Therefore, RNS is considered investigational when criteria are not met.

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## CODES

Codes	Number	Description
CPT	61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
	61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
	61863	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
	61864	;each additional array (List separately in addition to primary procedure)
	61880	Revision or removal of intracranial neurostimulator electrodes
	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61886	;with connection to 2 or more electrode arrays
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
	95970	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (ie, cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming
	95971	;simple spinal cord, or peripheral (ie, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming
HCPCS	L8680	Implantable neurostimulator electrode, each
	L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension

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<b>Codes</b>	<b>Number</b>	<b>Description</b>
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

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**Date of Origin:** September 2019

## Leadless Cardiac Pacemakers

**Effective:** January 1, 2020

**Next Review:** September 2020

**Last Review:** December 2019

### 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

Conventional pacemakers consist of two components: a pulse generator and electrodes (or leads). Although the efficacy and safety profile of conventional pacemakers are excellent, some patients are medically ineligible for conventional pacemakers due to lack of venous access and recurrent infection. Leadless pacemakers are single-unit devices that are implanted in the heart via femoral access.

### MEDICAL POLICY CRITERIA

**Notes:** See Policy Guidelines for contraindications for the Micra leadless pacemaker system.

- I. An FDA-approved leadless cardiac pacing system (e.g. the Micra transcatheter system) may be considered **medically necessary** in patients when both Criteria A and B below are met:
  - A. The patient has one or more of the following:
    1. Symptomatic paroxysmal or permanent high-grade arteriovenous block; or
    2. Symptomatic bradycardia-tachycardia syndrome; or

3. Sinus node dysfunction (sinus bradycardia or sinus pauses).
- B. The patient has a significant contraindication precluding placement of conventional single-chamber ventricular pacemaker leads, including but not limited to a history or high risk of infection, limited venous access, or presence of a bioprosthetic tricuspid valve.
- II. A leadless cardiac pacing system is considered **investigational** for all other indications when Criterion I. is not met, including but not limited to the use of non-FDA-approved devices.

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

## POLICY GUIDELINES

### MICRA SYSTEM CONTRAINDICATIONS

#### Devices

As per the FDA label, the Micra Model MC1VR01 pacemaker is contraindicated for patients who have the following types of devices implanted:

- An implanted device that would interfere with the implant of the Micra device in the judgment of the implanting physician
- An implanted inferior vena cava filter
- A mechanical tricuspid valve
- An implanted cardiac device providing active cardiac therapy which may interfere with the sensing performance of the Micra device

#### Conditions

As per the FDA label, the Micra Model MC1VR01 pacemaker is also contraindicated for patients who have the following conditions:

- Femoral venous anatomy unable to accommodate a 7.8 mm (23 French) introducer sheath or implant on the right side of the heart (for example, due to obstructions or severe tortuosity)
- Morbid obesity that prevents the implanted device to obtain telemetry communication within <12.5 cm (4.9 in)
- Known intolerance to titanium, titanium nitride, parylene C, primer for parylene C, polyether ether ketone, siloxane, nitinol, platinum, iridium, liquid silicone rubber, silicone medical adhesive, and heparin or sensitivity to contrast medical which cannot be adequately premedicated

#### Other Contraindications

As per the FDA label, the Micra Model MC1VR01 pacemaker should not be used in patients for whom a single dose of 1.0 mg dexamethasone acetate cannot be tolerated because the device contains a molded and cured mixture of dexamethasone acetate with the target dosage of 272 µg dexamethasone acetate. It is intended to deliver the steroid to reduce inflammation and fibrosis.

For the MRI contraindications for patients with a Micra MRI device, refer to the Medtronic MRI Technical Manual.

## LIST OF INFORMATION NEEDED FOR REVIEW

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

- History and Physical/Chart Notes
- Documentation of symptoms, associated diagnoses and treatments
- Name of FDA-approved leadless device
- Documentation that supports contraindication of placement of conventional single-chamber ventricular pacemaker leads

## CROSS REFERENCES

1. [Implantable Cardioverter Defibrillator](#), Surgery, Policy No. 17
2. [Intracardiac Ischemia Monitoring](#), Surgery, Policy No. 208

## BACKGROUND

### CONVENTIONAL PACEMAKERS

Pacemakers are intended to be used as a substitute for the heart's intrinsic pacing system to correct cardiac rhythm disorders. By providing an appropriate heart rate and heart rate response, cardiac pacemakers can reestablish effective circulation and more normal hemodynamics that are compromised by a slow heart rate. Pacemakers vary in system complexity and can have multiple functions as a result of the ability to sense and/or stimulate both the atria and the ventricles.

Transvenous pacemakers or pacemakers with leads (hereinafter referred as conventional pacemakers) consist of two components: a pulse generator (i.e., battery component) and electrodes (i.e., leads). The pulse generator consists of a power supply and electronics that can provide periodic electrical pulses to stimulate the heart. The generator is commonly implanted in the infraclavicular region of the anterior chest wall and placed in a pre-pectoral position; in some cases, a subpectoral position is advantageous. The unit generates an electrical impulse, which is transmitted to the myocardium via the electrodes affixed to the myocardium to sense and pace the heart as needed.

Conventional pacemakers are also referred to as single-chamber or dual-chamber systems. In single-chamber systems, only one lead is placed, typically in the right ventricle. In dual-chamber pacemakers, two leads are placed: one in the right atrium and the other in the right ventricle. Single-chamber ventricular pacemakers are more common.

Annually, approximately 200,000 pacemakers are implanted in the United States and one million worldwide.<sup>[1]</sup> Implantable pacemakers are considered life-sustaining, life-supporting class III devices for patients with a variety of bradyarrhythmias. Pacemaker systems have matured over the years with well-established, acceptable performance standards. As per the Food and Drug Administration (FDA), the early performance of conventional pacemaker systems from implantation through 60 to 90 days has usually demonstrated acceptable pacing capture thresholds and sensing. Intermediate performance (90 days through more than five

years) has usually demonstrated the reliability of the pulse generator and lead technology. Chronic performance (5 to 10 years) includes a predictable decline in battery life and mechanical reliability but a vast majority of patients receive excellent pacing and sensing free of operative or mechanical reliability failures.

Even though the safety profile of conventional pacemakers is excellent, they are associated with complications particularly related to leads. Most safety data on the use of conventional pacemakers comes from registries from Europe, particularly from Denmark where all pacemaker implants are recorded in a national registry. These data are summarized in Table 1. It is important to recognize that valid comparison of complication rates is limited by differences in definitions of complications, which results in a wide variance of outcomes, as well as by the large variance in follow-up times, use of single-chamber or dual-chamber systems, and data reported over more than two decades.<sup>[2]</sup> As such, the following data are contemporary and limited to single-chamber systems when reported separately.

In many cases when conventional pectoral approach is not possible, alternate approaches such as epicardial pacemaker implantation and trans-iliac approaches have been used<sup>[3]</sup>. Cohen (2001) reported outcomes from a retrospective analysis of 123 patients who underwent 207 epicardial lead implantations<sup>[4]</sup>. Congenital heart disease was present in 103 (84%) of the patients. Epicardial leads were followed for 29 months (range 1 to 207 months). Lead failure was defined as the need for replacement or abandonment due to pacing or sensing problems, lead fracture, or phrenic/muscle stimulation. The one-, two-, and five-year lead survival was 96%, 90%, and 74%, respectively. Epicardial lead survival in those placed by a subxiphoid approach was 100% at one year and at 10 years, by the sternotomy approach (93.9% at one year and 75.9% at 10 years) and lateral thoracotomy approach (94.1% at one year and 62.4% at 10 years).

Doll (2008) reported results of a randomized trial comparing epicardial implantation to conventional pacemaker implantation in 80 patients with indications for cardiac resynchronization therapy.<sup>[5]</sup> The authors reported that the conventional pacemaker group had significantly shorter intensive care unit stay, less blood loss, and shorter ventilation times while the epicardial group had less exposure to radiation and less use of contrast medium. The left ventricular pacing threshold was similar in the two groups at discharge but longer in the epicardial group during follow-up. Adverse events were also similar in the two groups. The following events were experienced by one (3%) patient each in the epicardial group: pleural puncture, pneumothorax, wound infection, acute respiratory distress syndrome, and hospital mortality.

As a less invasive alternate to epicardial approach, trans-iliac approach has also been utilized. Data using trans-iliac approach is limited. Multiple other studies with smaller sample size report a wide range of lead longevity.

Harake (2018) reported a retrospective analysis of five patients who underwent a transvenous iliac approach (median age 26.9 years)<sup>[6]</sup>. Pacing indications included AV block in three patients and sinus node dysfunction in two. After a median follow-up of 4.1 years (range 1.0-16.7 years), outcomes were reported for four patients. One patient underwent device revision for lead position-related groin discomfort; a second patient developed atrial lead failure following a Maze operation and underwent lead replacement by the iliac approach. One patient underwent heart transplantation six months after implant with only partial resolution of pacing-induced cardiomyopathy.

Tsutsumi (2010) reported a case series of four patients from Japan in whom conventional pectoral approach was precluded due to recurrent lead infections (n=1), superior vena cava obstruction following cardiac surgery (n=2) and a postoperative dermal scar (n=1). The mean follow-up was 24 months and authors concluded iliac vein approach was satisfactory and less invasive alternative to epicardial lead implantation. However, the authors reported that incidence of atrial lead dislodgement using this approach in the literature ranged from 7 to 21%. Experts who provided clinical input reported that trans-iliac or surgical epicardial approach require special expertise and long term performance is suboptimal.<sup>[7]</sup>

**Table 1. Reported Complication Rates with Conventional Pacemakers**

<b>Complications</b>	<b>Rates, %<sup>[8-10]a</sup></b>
<b>Traumatic complications</b>	
RV perforation	0.2-0.8
RV perforation with tamponade	0.07-0.4
Pneumo(hemo)thorax	0.7-2.2
<b>Pocket complications</b>	
Including all hematomas, difficult to control bleeding, infection, discomfort, skin erosion	4.75
Including only those requiring invasive correction or reoperation	0.66-1.0
<b>Lead-related complications</b>	
Including lead fracture, dislodgement, insulation problem, infection, stimulation threshold problem, diaphragm or pocket stimulation, other	1.6-3.8
All system related infections requiring reoperation or extraction	0.5-0.7

Adapted from Food and Drug Administration executive summary memorandum (2016).<sup>[11]</sup>

<sup>a</sup> Rates are for new implants only and ventricular single-chamber devices when data were available. Some rates listed in this column are for single- and dual-chamber devices when data were not separated in the publication. Note that Micra transcatheter pacing system is a single-chamber device.

## **POTENTIAL ADVANTAGES OF LEADLESS CARDIAC PACEMAKERS OVER CONVENTIONAL PACEMAKERS**

The potential advantages of leadless pacemakers fall into three categories: avoidance of risks associated with intravascular leads in conventional pacemakers, avoidance of risks associated with pocket creation for placement of conventional pacemakers, and an additional option for patients who require a single-chamber pacer.<sup>[12]</sup>

Lead complications include lead failure, lead fracture, insulation defect, pneumothorax, infections requiring lead extractions and replacements that can result in a torn subclavian vein or tricuspid valve. In addition, there are risks of venous thrombosis and occlusion of the subclavian system from the leads. Use of a leadless system eliminates such risks with the added advantage that a patient has vascular access preserved for other medical conditions (e.g., dialysis, chemotherapy).

Pocket complications include infections, erosions, and pain that can be eliminated with leadless pacemakers. Further, a leadless cardiac pacemaker may be more comfortable and appealing because, unlike conventional pacemakers, patients are unable to see or feel the device or have an implant scar on the chest wall.

Leadless pacemakers may also be a better option than surgical endocardial pacemakers for patients with no vascular access due to renal failure or congenital heart disease.

## **LEADLESS CARDIAC PACEMAKERS IN CLINICAL DEVELOPMENT**

Leadless pacemakers are self-contained in a hermetically sealed capsule. The capsule houses a battery and electronics to operate the system. Similar to most pacing leads, the tip of the capsule includes a fixation mechanism and a monolithic controlled-release device. The controlled-release device elutes glucocorticosteroid to reduce acute inflammation at the implantation site. Leadless pacemakers have rate-responsive functionality, and current device longevity estimates are based on bench data. Estimates have suggested that these devices may last over 10 years, depending on the programmed parameters.<sup>[11]</sup>

Three systems are currently being evaluated in clinical trials: (1) the Micra Transcatheter Pacing System (Medtronic), (2) the Nanostim leadless pacemaker (St. Jude Medical); and (3) the WiCS Wireless Cardiac Stimulation System (EBR Systems). The first two devices are free-standing capsule-sized devices that are delivered via femoral venous access using a steerable delivery sheath. However, the fixing mechanism differs between the two devices. In the Micra Transcatheter Pacing System, the fixation system consists of four self-expanding nitinol tines, which anchor into the myocardium; for the Nanostim device, there is a screw-in helix that penetrates about 1 mm into the myocardium, with nylon tines that provide secondary fixation. In both devices, the cathode is steroid eluting and delivers pacing current; the anode is located in a titanium case. The third device, WiCS system differs from the other devices; this system requires implanting a pulse generator subcutaneously near the heart, which then wirelessly transmits ultrasound energy to a receiver electrode implanted in the left ventricle. The receiver electrode converts the ultrasound energy and delivers electrical stimulation to the heart sufficient to pace the left ventricle synchronously with the right.<sup>[11]</sup>

Of these three, only the Micra transcatheter pacing system is approved by FDA and commercially available in the United States. Multiple clinical studies of Nanostim have been published<sup>[1,13-18]</sup> but trials have been halted due to the migration of the docking button in the device. Evidence on Nanostim is not reviewed further because the device is not yet FDA approved.

The Micra is about 26 mm in length and introduced using a 23 French catheter via the femoral vein to the right ventricle. It weighs about two grams and has an accelerometer-based rate response.

Nanostim is about 40 mm in length and introduced using an 18 French catheter to the right ventricle. It also weighs about two grams and uses a temperature-based rate response sensor.<sup>[19]</sup>

## REGULATORY STATUS

In April 2016, the Micra™ transcatheter pacing system (Medtronic) was approved by FDA through the premarket approval process for use in patients who have experienced one or more of the following conditions:

- symptomatic paroxysmal or permanent high-grade arteriovenous block in the presence of atrial fibrillation
- paroxysmal or permanent high-grade arteriovenous block in the absence of atrial fibrillation, as an alternative to dual-chamber pacing, when atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy
- symptomatic bradycardia-tachycardia syndrome or sinus node dysfunction (sinus bradycardia or sinus pauses), as an alternative to atrial or dual-chamber pacing, when

atrial lead placement is considered difficult, high risk, or not deemed necessary for effective therapy.

## EVIDENCE SUMMARY

Conventional pacemaker systems have been in use for over 50 years and current technology has matured with significant similarities in designs across models. Extensive bench testing data with conventional pacemakers and a good understanding of operative and early postimplant safety and effectiveness are available, which limits the need for clinical data collection to understand their safety and effectiveness with regard to implantation, tip fixation, electrical measures, and rate response. As such, a randomized controlled trial comparing the leadless pacemakers with conventional pacemakers was not required by the Food and Drug Administration (FDA).

### **VENTRICULAR PACING FOR INDIVIDUALS WHO ARE MEDICALLY ELIGIBLE FOR A CONVENTIONAL PACING SYSTEM**

#### **Nonrandomized Controlled Trials**

##### Pivotal Trial

The pivotal investigational device exemption (IDE) trial was a prospective single cohort study enrolled 744 patients with a class I or II indications for implantation of a single-chamber ventricular pacemaker based on national guidelines. Details on the design<sup>[20]</sup>, and results of the IDE trial have been published.<sup>[21-23]</sup> Trial characteristics and results at six months are summarized in Tables 2 and 3, respectively. System performance from the pivotal trial has been published,<sup>[24]</sup> but results are not discussed further.

Of the 744 patients enrolled, implantation of the Micra transcatheter pacing system was successful in 719 (99.2%) of the 725 patients who underwent the procedure. The demographics of the trial population were typical for a single-chamber pacemaker study performed in the U. S., with 42% being female and the average age was 76 years. Sixty-four percent had a pacing indication associated with persistent or permanent atrial arrhythmias, 72.6% had any atrial fibrillation at baseline, and 27.4% did not have a history of atrial fibrillation. Among those 27.4% (n=199) without atrial fibrillation, 16.1% (n=32) had a primary indication of sinus bradycardia and 3.5% (n=7) had a primary indication of tachycardia-bradycardia.<sup>[23]</sup>

The IDE trial had two primary endpoints related to safety and efficacy. The trial would meet its safety endpoint if the lower bound of the 95% confidence interval (CI) for the rate of freedom from major complications related to the Micra transcatheter pacing system or implantation procedure exceeded 83% at six months. Major complications were defined as those resulting in any of the following; death, permanent loss of device function due to mechanical or electrical dysfunction of the device (e.g., pacing function disabled, leaving device abandoned electrically), hospitalization, prolonged hospitalization by at least 48 hours, or system revision (reposition, replacement, explant).<sup>[25]</sup> The trial would meet its efficacy endpoint if the lower bound of the 95% CI for the proportion of patients with adequate pacing capture thresholds (PCT) exceeded 80% at six months. PCT as an effectiveness objective is a common electrical measure of pacing efficacy and is consistent with recent studies. Pacing capture threshold measured in volts is defined as the minimum amount of energy needed to capture the myocardial tissue electrically. Unnecessary high pacing output adversely shortens the battery

life of the pacemaker and is influenced by physiologic and pharmacologic factors.<sup>[25]</sup> As per the FDA, demonstrating that “PCT is less than 2 Volts for the vast majority of subjects will imply that the Micra system will have longevity similar to current pacing systems since Micra’s capture management feature will nominally set the safety margin to 0.5 Volts above the PCT with hourly confirmation of the PCT.”<sup>[25]</sup>

Safety and efficacy results of the IDE trial are summarized in Table 3. At six months, the trial met both of its efficacy and safety primary endpoints including freedom from major complications related to the system or procedure in 96.0% of the patients (95% CI 93.9% to 97.3%), compared with a performance goal of 83%, and an adequate pacing capture threshold in 98.3% of the patients (95% CI 96.1% to 99.5%), compared with a performance goal of 80%.<sup>[23]</sup>

Quality of life results of the IDE trial were published in 2018. At baseline and 12 months, 702 (98%) and 635 (88%) participants completed the 36-Item Short Form questionnaire, respectively.<sup>[22]</sup> The mean 36-Item Short Form Physical Component Scale at baseline was 36.3 (standard deviation [SD] 9.0) and the mean 36-Item Short Form Mental Component Scale was 47.3 (SD 12.5); the general population mean for both scores is 50. Both the Physical Component Scale and Mental Component Scale improved at 12 months post-implant to a mean Physical Component Scale score of 38.6 (SD 9.4,  $p < 0.001$ ) and a mean Mental Component Scale score of 50.7 (SD 12.2,  $p < 0.001$ ) compared with baseline.

IDE trial results were compared post hoc with a historical cohort of 2,667 patients generated from six previous pacemaker studies, conducted between 2005 and 2012 by Medtronic, that evaluated the performance requirement at six months postimplant of right ventricle pacing leads (single-chamber rates obtained by excluding any adverse events only related to the right atrial lead from the analysis). The Micra device was associated with fewer complications than the historical control (4.0% vs 7.4%, hazard ratio [HR], 0.49, 95% CI 0.33 to 0.75,  $p = 0.001$ ).<sup>[23]</sup> Because there were differences in baseline patient characteristics between the two cohorts (patients in the historical cohort were younger and had a lower prevalence of coexisting conditions vs the IDE trial), an additional propensity-matched analysis was conducted. It showed similar results (HR 0.46, 95% CI 0.28 to 0.74). As per the FDA, the lower rate of major complications with the Micra device was driven by reductions in access site events (primarily implant site hematoma and implant site infections), pacing issues (primarily device capture and device pacing issues), and fixation events (there was no device or lead dislodgements in the Micra IDE trial).<sup>[11]</sup>

While the overall rate of complications was low, the rate of major complications related to cardiac injury (i.e., pericardial effusion or perforation) was higher in the Micra IDE trial than in the six reference Medtronic pacemaker studies (1.6% vs 1.1%,  $p = 0.288$ ).<sup>[11]</sup> Thus, there appears to be a trade-off between types of adverse events with the Micra transcatheter pacing system and conventional pacemakers. While adverse events related to leads and pocket are eliminated or minimized with the Micra device, certain adverse events (e.g., groin vascular complications, vascular or cardiac bleeding) occur at a higher frequency or are additive (new events) compared with conventional pacemakers. Of these, procedural complications (e.g., acute cardiac perforations) that were severe enough to result in tamponade and emergency surgery were most concerning.<sup>[11]</sup>

In addition to lack of adequate data on long-term safety, effectiveness, reliability, and incidence of late device failures and battery longevity, there is also inadequate clinical experience with

issues related to devices that have reached end-of-life, including whether to extract or leave the device in situ and possible device-device interactions.<sup>[26]</sup> There are limited data on device-device interactions (both electrical and mechanical) that may occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. Even though there have only been few device retrievals and very limited experience with the time course of encapsulation of these devices in humans, it is highly likely that these devices will be fully encapsulated by the end of its typical battery life, and therefore device retrieval is unlikely.<sup>[26]</sup> Current recommendations for end-of-device-life care for a Micra device may include the addition of a replacement device with or without explantation of the Micra device, which should be turned off.<sup>[27]</sup>

Grubman (2017) reported on system revisions including patients from the IDE study (n=720) and the Micra Transcatheter Pacing System Continued Access Study (n=269).<sup>[28]</sup> The Continued Access study was conducted to allow for continued access of the Micra in the same centers as the IDE study while the device was pending the FDA approval. The mean follow-up duration was 13 months (16 months in the IDE patients and two months in the continued access patients). There were 11 system revisions in 10 patients, corresponding to a 1.4% (95% CI 0.7% to 2.6%) actuarial rate of revisions through 24 months. Micra was disabled and left in situ in 7 of 11 revisions including five patients in which there was no retrieval attempt, one patient in which retrieval was aborted because of fluoroscopy failure, and one patient in which retrieval was unsuccessful because of inability to dislodge the device. There were three percutaneous retrievals and one retrieval during surgical valve replacement. There were no complications associated with retrievals. The report indicates that there when a transvenous system was implanted with a deactivated Micra, there were no reported interactions between the two systems, although it is not clear how often this occurred. In the historical controls from the IDE study, there were 123 revisions in 117 patients through 24 months (actuarial rate 5.3%, 95% CI 4.4% to 6.4%). Using propensity score matching, the reduction in system revisions for Micra compared to historical controls was significant (HR 0.27, 95% CI 0.14 to 0.54, p<0.001).

## Postapproval Study

The FDA approval of the Micra transcatheter pacing system was contingent on multiple postapproval studies to provide reasonable assurance of continued safety and effectiveness of the device. Among these, the Micra Transcatheter Pacing System Post-Approval Study, a global, prospective, observational, multicenter study, enrolled 1,830 patients to collect data on 1,741 patients to estimate the acute complication rate within 30 days of the implant, 500 patients to estimate the nine-year complication-free survival rate, and a minimum of 200 patients with a Micra device revision for characterizing device end of service.<sup>[25]</sup> As per the protocol, if a subsequent device is placed and the Micra is deactivated or explanted, Medtronic would contact the implanting center and request the patient's clinical data concerning the revision. All such data would be summarized, including the type of system revision, how the extraction was attempted, success rate, and any associated complications.<sup>[26]</sup>

Study characteristics and results at one year (reported in the FDA documents and published) are summarized in Table 2 and 3, respectively. The postapproval study completed enrollment in early March 2018. The definition of a major complication in the postapproval study was the same as the Micra IDE trial. Although some patients who participated in the IDE study consented to also participate in the PAR study, the publication excludes those patients from analysis and therefore includes an independent population. Results summarized in Table 3

summarize the data at 30 days published by Roberts (2017)<sup>[29]</sup> and El-Chami (2018),<sup>[30,31]</sup> with a mean follow-up of 6.8 months for 1817 patients, of whom 465 patients had a follow-up for more than one year.

At 30 days, the major complication rate was 1.51% (95% CI 0.78 to 2.62%). The major complication rate was lower in the postapproval study than in the IDE trial (odds ratio, 0.58, 95% CI 0.27 to 1.25) although this did not reach statistical difference. The lower rate of major complications was associated with a decrease in events that led to hospitalization, prolonged hospitalization, or loss of device function in the postapproval study compared with the IDE trial.<sup>[29]</sup>

After a mean follow-up of 6.8 months, the estimated major complication rate at 12 months was 2.7% (95% CI 2.0% to 3.7%), corresponding to 46 major complications in 41 patients, the majority of which (89%) occurred within 30 days of implantation. The major complications included 14 device pacing issue events, 11 events at the groin puncture site, eight cardiac effusion/perforation events, three infections, one cardiac failure event, one cardiomyopathy event, and one pacemaker syndrome event. Authors compared these results with the same historical cohort of 2,667 patients used in the IDE trial and reported a 63% reduction in the risk for major complications through 12 months with the Micra transcatheter pacing system relative to conventional pacemakers (HR 0.37, 95% CI 0.27 to 0.52). Additionally, the risk for major complications was lower in the Micra postapproval study than in the IDE trial but it was a statistically significant difference (HR 0.71, 95% CI 0.44 to 1.1).<sup>[30]</sup> The reduction in major complications compared to historical controls was primarily driven by a significant 74% (95% CI 54 to 85, p=0.0001) relative risk reduction in system revisions and 71% (95% CI 51 to 83, p=0.0001) relative risk reduction in hospitalizations. The reduction in risk compared to the IDE trial was driven by significantly lower pericardial effusion rates in the post-approval study.

**Table 2. Summary of Key Nonrandomized Trial Characteristics**

Study; Trial	Study; Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Reynolds (2016) <sup>[23]</sup> NCT02004873	Prospective single cohort	19 countries in North America, Europe, Asia, Australia, and Africa	2013-2015	Patients who met a class I or II guidelines-based indication for pacing and suitable candidates for single-chamber ventricular demand pacing	Micra pacemaker (n=744)	6
Roberts (2017) <sup>[29]</sup> El-Chami (2018) <sup>[30,31]</sup> NCT02536118	Prospective single cohort (Micra Post-Approval Study)	23 countries in North America, Europe, Asia, Australia, and Africa	2016-2018	Any patient to be implanted with a Micra device	Micra pacemaker (n=795 <sup>a</sup> and 1830 <sup>b</sup> )	1.8 <sup>a</sup> 6.8 <sup>b</sup>

<sup>a</sup> 30-day results reported by Roberts (2017).<sup>[29]</sup>

<sup>b</sup> Results after a mean follow-up of 6.8 months reported by El-Chami (2018)<sup>[30,31]</sup>

**Table 3. Summary of Key Nonrandomized Trial Results**

<b>Study</b>	<b>Freedom from System- or Procedure-Related Major Complications</b>	<b>Percentage of Patients with Adequate Pacing Capture Thresholds</b>	<b>Major Complications Criteria, n (%)</b>	<b>Major Complications, n (%)</b>
<b>IDE Trial</b>				
	<b>6 Months</b>	<b>6 Months</b>	<b>6 Months</b>	<b>6 Months</b>
Reynolds (2016) <sup>[23]</sup>				
N	719 <sup>a</sup> ;300 <sup>b</sup>	719	725	725
Micra	96.0%	98.3% ( $\leq 2.0$ V)	Death: 1 (0.1)  Loss of device function: 1 (0.1)  Hospitalization: 13 (2.3)  Prolonged hospitalization ( $\geq 48$ h): 16 (2.6)  System revision: 3 (0.4)	TMCs: 28 in 25 patients (3.5%)  <ul style="list-style-type: none"> <li>• DVT: 1 (0.1)</li> <li>• Pulmonary TE: 1 (0.1)</li> <li>• Events at groin puncture site: 5 (0.7)</li> <li>• Cardiac perforation: 11 (1.6)</li> <li>• Pacing issues: 2 (0.3)</li> <li>• Others: 8 (1.7)</li> </ul>
95% CI	93.9% to 97.3%	95.4% to 99.6%	NA	NA
	<b>12 Months</b>	<b>12 Months</b>	<b>12 Months</b>	<b>12 Months</b>
Duray (2017) <sup>[32]</sup>				
N	726	NA	726	726
Micra	96.0%	NR (93%)	Death: NR (0.1)  Loss of device function: NR (0.1)  Hospitalization: NR (2.3)  Prolonged hospitalization ( $\geq 48$ h): NR (2.2)  System revision <sup>c</sup> : NR (0.7)  Loss of device function: NR (0.3)	TMCs: 32 in 29 patients (4.0)  <ul style="list-style-type: none"> <li>• DVT: 1 (0.1)</li> <li>• Pulmonary TE: 1 (0.1)</li> <li>• Events at groin puncture site: 5 (0.7)</li> <li>• Cardiac perforation: 11 (1.6)</li> <li>• Pacing issues: 2 (0.3)</li> <li>• Others: 11 (1.7)</li> </ul>
95% CI	94.2% to 97.2%	NA		
<b>Micra Post-Approval Study</b>				

<b>Study</b>	<b>Freedom from System- or Procedure-Related Major Complications</b>	<b>Percentage of Patients with Adequate Pacing Capture Thresholds</b>	<b>Major Complications Criteria, n (%)</b>	<b>Major Complications, n (%)</b>
	<b>30 Days</b>	<b>30 Days</b>	<b>30 Days</b>	<b>30 Days</b>
Roberts (2017) <sup>[29]</sup>				
N	795	NA	795	795
Micra	97.3% <sup>d</sup>	87.2% ( $\leq 1.0$ V) 97.0% ( $\leq 2.0$ V)	Death: 1 (0.13%) Hospitalization: 4 (0.50) Prolonged hospitalization ( $\geq 48$ h): 9 (1.01) System revision <sup>c</sup> : 2 (0.25)	TMCs: 13 in 12 patients (1.51% [95% CI 0.78% to 2.62%]) <ul style="list-style-type: none"><li>• DVT: 1 (0.13)</li><li>• Events at groin puncture site: 6 (0.75)</li><li>• Cardiac effusion/perforation: 1 (0.13)</li><li>• Device dislodgement: 1 (0.13)</li><li>• Pacing issues: 1 (0.13)</li><li>• Others: 3 (0.38)</li></ul>
OR (95% CI)	0.58 (0.27 to 1.25) <sup>e</sup>	NA	NA	NA
	<b>1 Year</b>	<b>1 Year</b>	<b>1 Year</b>	<b>1 Year</b>
El-Chami (2018) <sup>[30,31]</sup>				
N	1817	NA	NA	1,817
Micra	97.3% <sup>d</sup>	NA	NA	TMCs: 46 in 41 patients (2.7% [95% CI 2.0% to 3.6%]) <ul style="list-style-type: none"><li>• Pericardial effusions: 8 (0.44)</li><li>• Dislodgement: 1 (0.06)</li><li>• Procedure-related infections: 3 (0.17)</li><li>• Procedure-related deaths: 5 (0.28)</li></ul> As per FDA: Complications <sup>f</sup> : 61 in 53

Study	Freedom from System- or Procedure-Related Major Complications	Percentage of Patients with Adequate Pacing Capture Thresholds	Major Complications Criteria, n (%)	Major Complications, n (%)
				(deaths: 4 procedure-related; 3 unknown relatedness; 3 pending adjudication)
HR (95% CI)	0.71 (0.44 to 1.1) <sup>e</sup>  0.37 (0.27 to 0.52) <sup>g</sup>	NA	NA	NA

CI: confidence interval; DVT: deep vein thrombosis; FDA: Food and Drug Administration; HR: hazard ratio; IDE: investigational device exemption; OR: odds ratio; NA: not available; NR: not reported; TE: thromboembolism; TMC: Total major complication.

<sup>a</sup> Total number of patients who received the implant successfully.

<sup>b</sup> Number of patients for whom data were available for six-month evaluation.

<sup>c</sup> Device explant, reposition, or replacement.

<sup>d</sup> Calculations based on the major complication rate (2.7%, 95% CI 2.0 to 3.6%) reported by El-Chami (2018).

<sup>e</sup> Major complication vs IDE trial.

<sup>f</sup> Unclear if the complications met the definition of a major complication as events leading to death, hospitalization, prolonged hospitalization by 48 hours, system revision, or loss of device therapy.

<sup>g</sup> Major complication vs historical controls.

## Section Summary: Ventricular Pacing for Individuals Who Are Medically Eligible for a Conventional Pacing System

The evidence for use of the Micra transcatheter pacing system consists of a pivotal prospective cohort study and a postapproval prospective cohort study. Results at six months and one year for the pivotal study reported high procedural success (>99%) and device effectiveness (pacing capture threshold met in 98% patients). Most of the system- or procedural-related complications occurred within 30 days. At one year, the incidence of major complications did not increase substantially from six months (3.5% at six months vs 4% at one year). Results of the postapproval study were consistent with a pivotal study and showed a lower incidence of major complications up to 30 days postimplantation and one year (1.5% and 2.7%, respectively). In both studies, the point estimates of major complication were lower than the pooled estimates from six studies of conventional pacemakers used as a historical comparator. While the Micra transcatheter pacing system eliminates adverse events associated with lead and pocket issue, its use results in additional complications related to the femoral access site (groin hematomas, access site bleeding) and implantation and release of the device (traumatic cardiac injury). Considerable uncertainties and unknowns remain in terms of the durability of device and end-of-life device issues. Early and limited experience has suggested that retrieval of these devices is unlikely because in due course of time, the devices will be encapsulated. There are limited data on device-device interactions (both electrical and mechanical), which might occur when there is a deactivated Micra device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present.

## VENTRICULAR PACING FOR INDIVIDUALS WHO ARE MEDICALLY INELIGIBLE FOR A CONVENTIONAL PACING SYSTEM

### Nonrandomized Controlled Trials

No studies that exclusively enrolled patients who were medically ineligible to receive a conventional pacing system were identified.

In the IDE trial, 6.2% or 45 patients received the Micra Transcatheter Pacing System because they were medically ineligible for a conventional pacing system due to compromised venous access, the need to preserve veins for hemodialysis, thrombosis, a history of infection, or the need for an indwelling venous catheter. A stratified analysis of these 45 patients was not presented in the published paper<sup>[23]</sup> or the FDA documents.<sup>[11,19,25,26]</sup>

In the postapproval registry as an abstract, the authors reported stratified results for 105 of 1,820 patients who had previous cardiac implantable electronic device (CIED) infection.<sup>[30,33]</sup> Of these 105, 83 patients (79%) were classified as medically ineligible to receive a conventional pacemaker in the opinion of the physician. A stratified analysis of these 83 patients was not presented in the publication. Trial characteristics and results are summarized in Tables 4 and 5, respectively. In this cohort of patients with CIED infection, the Micra device was implanted successfully in 104 patients and the previous CIED was explanted the same day as the Micra device was implanted in 37% of patients. Major complications were reported in 3.8% of patients with an average follow-up of 8.5 months. Ten deaths were reported (14% at 12 months) but none were related to the Micra transcatheter pacing system or the implantation procedure.

**Table 4. Summary of Key Nonrandomized Trial Characteristics in Patients Ineligible for a Conventional Pacing System and/or Previous CIED Infection**

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
El-Chami (2018) <sup>[30,33]</sup>	Prospective single cohort (Micra Post-Approval Registry)	23 countries in North America, Europe, Asia, Australia, and Africa	2016-2018	Any patient to be implanted with a Micra with a CIED infection	Micra pacemaker (n=105)	8.5 (range 0 to 28.5)

CIED: cardiac implantable electronic device.

**Table 5. Summary of Key Nonrandomized Trial Results in Patients Ineligible for a Conventional Pacing System and/or Previous Cardiac Implantable Electronic Device Infection**

Study	No. of Patients With System- or Procedure-Related Major Complications at One Year	Average Pacing Threshold at One Year	Major Complications at 1 Year
El-Chami (2018) <sup>[30,33]</sup>			
N	105	82	105
Micra	4 (4/105)	0.6 V	Total major complications: 6 in 4 patients  (patient 1: effusion requiring pericardiocentesis; patient 2: elevated thresholds, complication of device removal [IVC filter entanglement], and

Study	No. of Patients With System- or Procedure-Related Major Complications at One Year	Average Pacing Threshold at One Year	Major Complications at 1 Year
			subsequent abdominal wall infection, patients 3 and 4: pacemaker syndrome)

IVC: in cava filter.

### Section Summary: Ventricular Pacing for Individuals Who Are Medically Ineligible for a Conventional Pacing System

No studies that exclusively enrolled patients who were medically ineligible for a conventional pacing system were identified. However, a subgroup of patients in whom the use of conventional pacemakers was precluded was enrolled in the pivotal and the postapproval trials. Information on the outcomes in these subgroups of patients from the postapproval study showed that Micra was successfully implanted in 98% of cases and safety outcomes were similar to the original cohort. Even though the evidence is limited, and long-term effectiveness and safety are unknown, the short-term benefits may outweigh the risks in the context of the life-saving potential of pacing systems in patients that are ineligible for conventional pacing systems.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION, AMERICAN HEART ASSOCIATION, AND HEART RHYTHM SOCIETY

The American College of Cardiology Foundation, American Heart Association, and Heart Rhythm Society’s (2012) focused update on device-based therapy of cardiac rhythm abnormalities incorporated into their joint 2008 guidelines for device-based therapy of cardiac rhythm abnormalities does not include recommendations on leadless cardiac pacemakers.<sup>[34]</sup>

The Heart Rhythm Society and American College of Cardiology Foundation (2012) expert consensus statement on pacemaker device and mode selection did not include recommendations on leadless cardiac pacemakers.<sup>[35]</sup>

## SUMMARY

There is enough research to show that an FDA-approved leadless pacing system may improve health outcomes for patients with a guidelines-based indication for a ventricular pacing system who are medically ineligible for a conventional pacing system. Although evidence is limited and long-term effectiveness and safety are unknown, the short-term benefits may outweigh the risks, in the context of the life-saving potential of pacing systems for patients who are ineligible for conventional pacing systems. Therefore, a leadless pacemaker system may be considered medically necessary in patients who meet the policy criteria.

There is not enough research to show that a leadless pacing system can improve health outcomes for patients who do not meet medical necessity criteria, including the use of a non-FDA-approved system, or in patients who are eligible for a conventional pacing system. There is little evidence regarding the durability of devices, device end-of-life issues, and

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device-device interactions (both electrical and mechanical), which may occur when there is a deactivated leadless device alongside another leadless pacemaker or when a leadless pacemaker and transvenous device are both present. Therefore, a leadless pacemaker is considered investigational when criteria are not met.

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## CODES

Codes	Number	Description
CPT	33274	Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed (new eff 1/1/19)
	33275	Transcatheter removal of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography), when performed
HCPCS	None	

**Date of Origin:** December 2018

## Hysterectomy

**Effective:** June 1, 2020

**Next Review:** April 2021

**Last Review:** April 2020

### IMPORTANT REMINDER

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

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

### DESCRIPTION

Hysterectomy (surgical removal of the uterus) may be performed for a variety of indications, including abnormal uterine bleeding, fibroids, and pelvic pain.

### MEDICAL POLICY CRITERIA

**Notes:** This policy only addresses abnormal uterine bleeding, pelvic pain, chronic pelvic inflammatory disease, pelvic adhesive disease, pelvic venous congestion, adenomyosis, cervical intraepithelial neoplasia, and leiomyoma.

- I. Hysterectomy surgery may be considered **medically necessary** when any of the following criteria are met:
  - A. Abnormal uterine bleeding when the clinical records document all of the following criteria are met (1. – 4.):
    1. Hysteroscopy, sonohysterography (SIS), or pelvic ultrasound has been performed; and
    2. No specific etiology of abnormal uterine bleeding (e.g. endometrial hyperplasia, leiomyoma, polyps) has been identified; and

3. Hormonal treatment options (intrauterine delivery system or systemic hormonal therapy, e.g., oral contraceptive pills or progestins) cannot be used because of one or more of the following:
  - a. They are contraindicated; or
  - b. They are not tolerated; or
  - c. Symptoms are ongoing despite an adequate trial; or
  - d. They are not appropriate for severity of patient's condition (e.g., severe persistent bleeding, acute anemia, postmenopausal age) or clinical scenario.
4. Conservative surgery (e.g., endometrial ablation, endometrial polypectomy, D&C) cannot be used because of one or more of the following:
  - a. Procedure is contraindicated (extreme uterine flexion or version, extremely thin myometrium); or
  - b. Procedure was tried but did not adequately treat patient's condition; or
  - c. Procedure is not appropriate for severity of patient's condition or clinical scenario; or
  - d. Hysterectomy is preferred (e.g., patient concern about recurrence after conservative surgery).
- B. Adenomyosis when the clinical records document all of the following criteria are met (1. – 2.):
  1. Adenomyosis is suspected on ultrasound or MRI; and
  2. Patients have been counseled with their alternative options (e.g. conservative surgery or medical therapy).
- C. Cervical intraepithelial neoplasia (CIN) and one or more of the following:
  1. Both of the following (a. – b.):
    - a. Recurrent biopsy-confirmed CIN-2,3 after ablative or excisional procedure; and
    - b. Repeat excisional procedure or ablative procedures is not feasible.
  2. CIN III with negative margins on a cone, but with glandular involvement; or
  3. Spontaneous CIN III or carcinoma in situ (CIS) with rapid development (no other recent history); or
  4. Any CIN II or III (after cone or LEEP rules out invasion) on an immunocompromised (e.g.; HIV) patient; or
  5. Persistent high-risk HPV (especially 16/18) in a patient over the age of 40; or
  6. Glandular dysplasias (as opposed to squamous) due to the skip nature of the lesions.
- D. Chronic pelvic inflammatory disease (PID) persisting after at least 6 months of treatment and diagnosed by one of more of the following:
  1. Endometrial biopsy with histopathologic evidence of endometritis; or

2. Ultrasound, computed tomography (CT), or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex; or
  3. Laparoscopic abnormalities consistent with PID.
- E. Endometriosis when the clinical records document all of the following criteria are met (1. – 3.):
1. One or more of the following has been used to confirm a diagnosis of endometriosis:
    - a. Histology on biopsy
    - b. Laparoscopic visualization
    - c. Identification of endometrioma on ultrasound or MRI
  2. Pelvic pain is associated with endometriosis; and
  3. Symptoms are ongoing or recurrent despite treatment with conservative surgery (e.g., destruction of implants, removal of endometrioma, lysis of adhesions).
- F. Leiomyoma ("fibroid") when the clinical records document all of the following criteria are met (1. – 3.):
1. Significant clinical manifestations or findings attributable to leiomyoma, including one or more of the following:
    - a. Abnormal uterine bleeding
    - b. Iron-deficiency anemia
    - c. Dyspareunia
    - d. Malignancy suspected
    - e. Pelvic pain or pressure
    - f. Urinary or bowel dysfunction
  2. Imaging (e.g. ultrasound, CT, MRI) has ruled out other significant abnormalities and is consistent with a diagnosis of leiomyoma; and
  3. Conservative surgery or medical therapy has been unsuccessful or is not desired.
- G. Pelvic pain associated with any of the following:
1. Unknown etiology when the clinical records document all of the following criteria are met (a. – d.):
    - a. Comprehensive evaluation (e.g., pain specialist, mental health evaluation) has been performed or clinical documentation for why it is not indicated is provided; and
    - b. No specific etiology of symptoms (e.g., interstitial cystitis, inflammatory bowel disease) has been identified via appropriate investigations (e.g., laparoscopy, endoscopy, imaging); and
    - c. Pain is ongoing for at least 6 months; and

- d. Conservative treatments (e.g., oral contraceptives, progestins, gonadotropin-releasing hormone analogues, analgesics, antidepressants, physical therapy) have been unsuccessful.
  - 2. Essure placement when pelvic pain did not exist prior to Essure placement; or
  - 3. Refractory cervical stenosis; or
  - 4. Prior endometrial ablation (EA), with or without abnormal uterine bleeding; or
  - 5. Vaginal agenesis (also known as Mullerian agnesis, Mayer-Rokitansky Kuster Hauser syndrome, or obstructed uterine rudimentary horn).
- H. Pelvic adhesive disease resulting from prior multiple gynecological/abdominal surgeries and one or more of the following:
- 1. Adhesiolysis failure; or
  - 2. Adhesiolysis contraindicated or relatively contraindicated because of the presence of one or more other conditions; or
  - 3. Frozen pelvis (scarred down pelvis) documented by laparoscopy or laparotomy.
- I. Pelvic Venous Congestion (PVC) syndrome when diagnosis of PVC is documented, including all of the following (1. – 3.):
- 1. Documentation of characteristic symptoms is submitted, including but not limited to one or more of the following:
    - a. Chronic pelvic discomfort, exacerbated by increased abdominal pressure
    - b. Sharp pelvic pains
    - c. Dysmenorrhea
    - d. Deep dyspareunia
    - e. Urinary urgency
    - f. Dilated pelvic veins
    - g. Gluteal, vulvar and/or thigh varices
  - 2. Tenderness on physical exam (ovarian, cervical motion, and uterine tenderness with direct palpation); and
  - 3. Imaging or laparoscopy/laparotomy identifies pelvic venous changes.
- II. Hysterectomy surgery for the treatment of abnormal uterine bleeding, pelvic pain, chronic pelvic inflammatory disease, pelvic adhesive disease, pelvic venous congestion, adenomyosis, cervical intraepithelial neoplasia, or leiomyoma is considered **not medically necessary** 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

### RECURRENT ENDOMETRIOSIS

- Recurrent endometriosis symptoms (pelvic pain) do not require another diagnostic workup, medical management, or other uterine sparing procedure if tried in the past.
- For recurrent endometriosis, diagnosis and/or treatment during previous exacerbations of endometriosis may be considered in determining whether criteria are met.

## MULTIPLE CONDITIONS

- It should be reasonable to expect that hysterectomy would resolve the dominant condition or related symptoms.
- If there is more than one dominant condition for which the clinical information submitted may meet guideline criteria, also apply criteria for those other conditions, if appropriate.
- Patient only needs to meet criteria for the dominant condition to qualify for a hysterectomy.

## HORMONE THERAPY

Possible relative contraindications for hormonal therapy include a 3 or greater per the [CDC Medical Eligibility Criteria for Contraceptive Use](#).

## LIST OF INFORMATION NEEDED FOR REVIEW

### REQUIRED DOCUMENTATION:

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

- History and physical/chart notes
- Conservative treatment provided, if any
  - If options for more conservative management are relatively or absolutely contraindicated, those contraindications should be specified.
  - If options for more conservative management previously have been tried and have been ineffective or not tolerated, clinical information regarding those previous treatments should be provided.
  - If an option or options for conservative management is/are felt to be unlikely to be successful, reasons should be specified.
  - If options for more conservative management are declined based on choice in the absence of clinical reasons such as contraindication(s) or a history of ineffectiveness or intolerance, those reasons for choosing to decline more conservative management should be specified.
- Relevant imaging (ultrasound, CT, hysteroscopy etc) reports
- Lab/pathology reports

## CROSS REFERENCES

1. [Gender Affirming Interventions for Gender Dysphoria](#), Medicine, Policy No. 153
2. [Endometrial Ablation](#), Surgery, Policy No. 01

## BACKGROUND

### HYSTERECTOMY

An assessment of hysterectomies performed in the United States found that in 2013, 35 out of every 10,000 women underwent a hysterectomy (surgical removal of the uterus).<sup>[1]</sup> According to the same study, also in 2013, just over 43% of hysterectomies were performed laparoscopically. Other surgical approaches for hysterectomy are abdominal, laparoscopic assisted vaginal, and vaginal. According to the American College of Obstetricians and Gynecologists, when hysterectomy is used for the treatment of benign indications, the choice of approach depends on anatomical features as well as, “extent of extrauterine disease; the need for concurrent procedures; surgeon training and experience; average case volume; available hospital technology, devices, and support; whether the case is emergent or scheduled; and preference of the informed patient.”

Laparoscopic and vaginal hysterectomies generally require shorter hospital stays and shorter postoperative recovery times than open abdominal hysterectomies. Vaginal hysterectomies are associated with better outcomes than laparoscopic and abdominal hysterectomies. In cases where extrauterine disease prevents the use of a vaginal approach, another minimally invasive approach is preferred.

## INDICATIONS FOR HYSTERECTOMY

Hysterectomies are commonly performed for abnormal uterine bleeding, fibroids, endometriosis, and pelvic pain. Other indications not reviewed here include cancer, uterine prolapse, and high risk of cancer based on genetic testing or family or personal history. For some conditions, hysterectomy is the definitive treatment. For others, due to the nature of the condition, the safety and efficacy of alternative options must be weighed against hysterectomy.

Alternative treatments vary by condition. For the treatment of fibroids, treatment options include myomectomy, uterine artery embolization or occlusion (UAE or UAO), myolysis, and endometrial ablation. Alternatives for abnormal uterine bleeding include endometrial ablation, levonorgestrel intrauterine system (LNG-IUS), and medications. Utero-sacral nerve ablation, presacral neurectomy, lysis of adhesions, utero-sacral ligament resection, and a variety of medications have been used for the treatment of pelvic pain. Hysterectomy is considered the most invasive of these options.

## EVIDENCE SUMMARY

### Systematic Reviews

Systematic reviews (SRs) have evaluated the accumulated evidence for hysterectomy for a number of indications. Key outcomes following therapy depend on the indication for the intervention, but include bleeding, pain, quality of life, sexual health, and re-intervention.

A 2019 Cochrane SR by Fergusson compared the safety and effectiveness of hysterectomy versus endometrial ablation or resection for heavy menstrual bleeding.<sup>[2]</sup> A total of nine RCTs met inclusion criteria. Bleeding outcomes were assessed differently in the different trials, but generally hysterectomy was associated with better bleeding outcomes. Adverse events were more common in patients who underwent hysterectomy. During the hospital stay, those in the endometrial ablation group were less likely to experience sepsis (RR 0.19, 95% CI 0.12 to 0.31; participants = 621; studies = 4;  $I^2 = 62\%$ ), blood transfusion (RR 0.20, 95% CI 0.07 to 0.59; 791 women; 5 studies;  $I^2 = 0\%$ ), pyrexia (RR 0.17, 95% CI 0.09 to 0.35; 605 women; three studies;  $I^2 = 66\%$ ), vault hematoma (RR 0.11, 95% CI 0.04 to 0.34; 858 women; five studies;  $I^2 = 0\%$ ) and wound hematoma (RR 0.03, 95% CI 0.00 to 0.53; 202 women; one

study). The SR authors concluded that the benefits of hysterectomy are permanent and immediate relief from heavy menstrual bleeding and the benefits of endometrial resection/ablation are shorter operating and recovery time and lower postoperative complications.

In 2017, Hartmann published a Comparative Effectiveness review for the Agency for Healthcare Research and Quality (AHRQ) on the management of uterine fibroids.<sup>[3]</sup> For hysterectomy, the authors identified 14 studies reported in 23 publications. Comparators were most often different approaches to hysterectomy; however, some studies did report alternative treatments as comparators. One randomized controlled trial (RCT) compared GnRH agonist (n=59) to hysterectomy (n=13). Individuals in the GnRH group could opt for hysterectomy at any time. In the GnRH group, 23 patients assigned to medication continued to hysterectomy by the end of the third year of follow-up. Three randomized studies compared UAE with hysterectomy, with a total of 291 women ages 33 to 57 years who had symptomatic uterine fibroids and were eligible for hysterectomy. Follow-up was six months to five years. Length of hospital stay and time to usual activities was significantly shorter in the UAE group (p<0.001 for both). Re-admission rates were the same in one study (5%) and higher after UAE (11% vs. 0%, p<0.003) in another. Relief from pain was not significantly different between groups, but improvement in pressure symptoms was significantly greater in the UAE group (p=0.03) and urinary bladder symptoms were greater in the hysterectomy group (p=0.03). There was no difference in one study in overall health-related quality of life or sexual function at 24 months or later. In all three studies, subsequent treatment was higher in those treated with UAE at each time point in follow-up. The review concluded that although subsequent intervention is more common after UAE than hysterectomy, the majority of women in the UAE group avoided hysterectomy for the duration of follow-up. They additionally concluded that the evidence is currently insufficiently to shape clinical decisions.

Marjoribanks published a 2016 Cochrane SR that evaluated surgery versus medical therapy for heavy menstrual bleeding in patients with no abnormal endometrial pathology or other uterine abnormalities such as polyps or fibroids.<sup>[4]</sup> Medical therapy included use of a hormone-releasing intrauterine device (LNG-IUS) and oral medication. A total of 15 parallel-group RCTs including 1,289 women met inclusion criteria. Of these, one RCT compared hysterectomy with oral medication and two with LNG-IUS. Results from the one RCT that reported objective assessment of bleeding indicated that hysterectomy was more likely to have objective control of bleeding at one year than medical therapy. In one RCT, women in the hysterectomy group reported statistically significantly higher levels of satisfaction with symptom resolution and overall health than women in the medical group at the six-month follow-up, but not at the two-year follow-up. With respect to complications, one RCT reported 35 operative and postoperative complications in the 107 hysterectomy patients and failure of the insertion in three LNG-IUS patients (unable to insert in two and removal in one). The other RCT comparing the same interventions reported that there were no postoperative complications in either group that necessitated readmission, blood transfusion or repeat surgery. The SR authors concluded that surgery, particularly hysterectomy, reduces menstrual bleeding more than medical treatment at one year but that there is no conclusive evidence of a difference in satisfaction rates between surgery and LNG-IUS. They stated that overall, oral medication suits a minority of women in the long term, and that for most women, the LNG-IUS device provides a better alternative to surgery.

A Cochrane SR published by Lethaby in 2015 compared the safety and effectiveness of progesterone or progestogen-releasing intrauterine devices versus other treatments for heavy

menstrual bleeding, with hysterectomy as a comparator.<sup>[5]</sup> Only RCTs of women of reproductive age were included. A total of 21 RCTs met inclusion criteria, three of which compared progestogen-releasing intrauterine devices with hysterectomy. Evidence from these studies was rated as high quality. One study reported that progestogen-releasing intrauterine devices were not as successful as hysterectomy at reducing heavy menstrual bleeding long-term (24 months), though the 12-month outcomes were similar. Two of the three RCTs reported equivalent improvements in quality of life between the groups while the third reported different outcomes for different quality of life measures.

Chen published a 2016 Canadian Agency for Drugs and Technology in Health (CADTH) SR that compared uterine-preserving interventions for symptomatic uterine fibroids to each other and to hysterectomy.<sup>[6]</sup> A total of 26 studies were included on the safety and efficacy of uterine-preserving interventions. One nonrandomized study reported that compared with myomectomy, patients treated with hysterectomy reported statistically significant improvements in symptom severity/quality of life measures. In the four studies that evaluated complications from myomectomy versus hysterectomy (one three-arm prospective cohort study and three retrospective cohort studies), overall, open abdominal hysterectomy was related to more peri-procedural complications (blood loss and organ injury) than abdominal myomectomy whereas laparoscopic myomectomy was related to fewer organ injuries but higher risk of converting to the open surgery, compared to laparoscopic hysterectomy. Hysterectomy and uterine artery ablation were both reported to ease pelvic pressure and increase health-related quality of life, though whether one procedure did to a greater degree was inconsistent between two RCTs. On the other hand, uterine artery ablation was reported to result in statistically significantly less blood loss and severe pain compared to hysterectomy, according to the six studies that reported on complications, and shorter hospital stays according to the five studies that reported on this outcome. One multi-center prospective study compared magnetic resonance-guided focused ultrasound with hysterectomy. The difference in the number of adverse events experienced was significantly significant, with fewer patients in the MRgFUS group reporting adverse events. Overall, the authors concluded that the quality of the available studies was low due to small sample sizes and study design and inconsistent results were reported across the included studies.

In 2012, the AHRQ published a Comparative Effectiveness review of therapies for noncyclic chronic pelvic pain.<sup>[7]</sup> A total of 18 randomized controlled trials (RCTs) (2 good, 3 fair, and 13 poor quality); three cohort studies (three poor quality); and 15 cross-sectional studies addressing the prevalence of comorbidities (quality varied by comorbidity) met inclusion criteria and were included in the review. Only one study compared hysterectomy with nonsurgical therapy, and it was determined to be of poor quality. This study reported 12-month outcomes for 380 patients in the nonsurgical group and 311 in the hysterectomy group. All patients were being treated for chronic pelvic pain. Significant improvements in mean number of days with pain per month (determined via interview) were reported for both groups. The mean reduction in days with pain per month was 7 ( $p < 0.001$ ) and 18 ( $p < 0.001$ ) for the nonsurgical and hysterectomy groups, respectively. Statistically significant improvements in all quality of life measures were reported for the hysterectomy group ( $p < 0.001$ ) while statistically significant improvements in only two quality of life measures were reported for the nonsurgical management group ( $p < 0.001$  for both). Overall, the authors of the SR concluded that the strength of the evidence for the surgical approaches, including hysterectomy, was low, and that the evidence was insufficient to comment on relief of pain after hysterectomy.

A 2012 SR by Matteson compared hysterectomy with less-invasive alternatives for the treatment of abnormal uterine bleeding.<sup>[8]</sup> Only RCTs were included in the SR, and nine RCTs described in 18 articles met inclusion criteria. Of the nine RCTs, seven (one rated as “A” quality and the rest as “B”) compared hysterectomy to endometrial ablation, one (“A” quality) compared hysterectomy to LNG-IUS, and one (“A” or “B” quality for different outcomes) compared hysterectomy to medication. In the comparisons with endometrial ablation, follow-up was between 4 and 48 months. All seven RCTs reported bleeding control. Bleeding control was implied to be 100% in most studies (although one did report a woman with post-hysterectomy bleeding). In comparison, there was a 13 to 64% rate of amenorrhea following endometrial ablation. Generally, quality of life measures were not different between groups. Although a few studies did report statistically significant differences in some measures, the SR concluded that moderate strength of evidence indicated no difference between hysterectomy and ablation in quality of life. Of the five trials that assessed pain beyond the immediate post-operative period, all but one reported some measure of pain as superior in the hysterectomy group, although statistical testing was not always done. The SR concluded that based on low strength of evidence, pain beyond the post-operative period favored hysterectomy. Based on quality evidence from five trials, there was no difference in sexual health between groups. Five trials assessed general satisfaction, and overall, based on very low quality of evidence, reported no differences between groups. The need for additional treatment was reported in seven studies. Moderate quality of evidence favored hysterectomy over ablation, with 10 to 29% of endometrial ablation patients undergoing hysterectomy within one to four years post-ablation. The one “A” quality RCT that compared hysterectomy to LNG-IUS included 263 patients with six-month to 10-year follow-up. No differences were reported between groups for quality of life, pain, sexual health, or satisfaction. Hysterectomy was favored over LNG-IUS for bleeding control and need for additional treatments. The one RCT that compared hysterectomy to medical therapy included 63 patients with two-year follow-up. Based on low or very low quality of evidence, no differences were reported between groups for any measure. Overall, the SR authors concluded that hysterectomy had superior long-term bleeding control compared to ablation and LNG-IUS and additionally better long-term pain control than ablation.

## PRACTICE GUIDELINE SUMMARY

### Society of Gynecologic Surgeons

The Society of Gynecologic Surgeons published an evidence-based clinical practice guideline in 2012 regarding the use of hysterectomy versus alternative therapy for abnormal uterine bleeding caused by ovulatory disorders (AUB-O) or by endometrial hemostatic disorders (AUB-E). These guidelines make the following recommendations:

- In women with AUB presumed caused by predominately AUB-O or AUB-E, we suggest that any of the following treatment options may be chosen on the basis of patient values and preferences: hysterectomy, endometrial ablation, systemically administered medical therapies, or LNG IUS. (Weak)
- If the patient’s main preference is for amenorrhea or avoiding additional therapy or experiencing less pain, we suggest hysterectomy rather than endometrial ablation (Weak).
- If the patient’s main preference is for shorter hospitalization and for lower operative and postoperative procedural risk, we suggest endometrial ablation rather than hysterectomy (Weak)

- If the patient’s main preference is for improvement in overall quality of life or sexual health, we suggest that either hysterectomy or endometrial ablation may be chosen and that the selection of treatment be based on additional patient preferences (Weak).
- If the patient’s main preference is for amenorrhea or avoiding additional therapy, we suggest hysterectomy rather than systemically administered medications (Weak).
- If the patient’s main preference is to avoid adverse events, we suggest systemically administered medications rather than hysterectomy (Weak).
- If the patient’s main preference is long-term improvement in QOL, pain or sexual health, we suggest that either hysterectomy or systemically administered medications is appropriate and that the choice of treatment be based on additional patient preferences (Weak).

## **The American College of Obstetricians and Gynecologists**

The American College of Obstetricians and Gynecologists (ACOG) published a Practice Bulletin on “Alternatives to Hysterectomy in the Management of Leiomyomas”.<sup>[9]</sup> This bulletin makes the following recommendations:

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- Abdominal myomectomy is a safe and effective alternative to hysterectomy for treatment of women with symptomatic leiomyomas.
- Based on long- and short-term outcomes, uterine artery embolization is a safe and effective option for appropriately selected women who wish to retain their uteri.
- Gonadotropin-releasing hormone agonists have been shown to improve hematologic parameters, shorten hospital stay, and decrease blood loss, operating time, and postoperative pain when given for 2–3 months preoperatively. Benefits of preoperative use of GnRH agonists should be weighed against their cost and side effects for individual patients. Several studies suggest that the infiltration of vasopressin into the myometrium decreases blood loss at the time of myomectomy.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- The clinical diagnosis of rapidly growing leiomyomas should not be used as an indication for myomectomy or hysterectomy.
- Hysteroscopic myomectomy is an accepted method for the management of abnormal uterine bleeding caused by submucosal leiomyomas.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- There is insufficient evidence to support hysterectomy for asymptomatic leiomyomas solely to improve detection of adnexal masses, to prevent impairment of renal function, or to rule out malignancy.
- Leiomyomas should not be considered the cause of infertility, or significant component of infertility, without completing a basic fertility evaluation to assess the woman and her partner.

- Hormone therapy may cause some modest increase in uterine leiomyoma size but does not appear to have an impact on clinical symptoms. Therefore, this treatment option should not be withheld from women who desire or need such therapy.
- The effect of uterine artery embolization on pregnancy remains understudied.

## SUMMARY

There is enough research to show that when policy criteria are met, hysterectomy for the treatment of abnormal uterine bleeding, pelvic pain, chronic pelvic inflammatory disease, pelvic adhesive disease, pelvic venous congestion, adenomyosis, cervical intraepithelial neoplasia, and leiomyoma improves health outcomes. Clinical guidelines based on research recommend hysterectomy in these clinical scenarios. Therefore, hysterectomy may be considered medically necessary when policy criteria are met.

For abnormal uterine bleeding, pelvic pain, chronic pelvic inflammatory disease, pelvic adhesive disease, pelvic venous congestion, adenomyosis, cervical intraepithelial neoplasia, and leiomyoma, evidence and guidelines do not support the use of endometrial ablation when policy criteria are not met. Therefore, hysterectomy for the treatment of these indications is considered not medically necessary when policy criteria are not met.

## REFERENCES

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## CODES

Codes	Number	Description
CPT	58150	Total abdominal hysterectomy (corpus and cervix), with or without removal of tube(s), with or without removal of ovary(s)
	58152	Total abdominal hysterectomy (corpus and cervix), with or without removal of tube(s), with or without removal of ovary(s); with colpo-urethrocystopexy (eg, Marshall-Marchetti-Krantz, Burch)
	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)
	58263	Vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s), and/or ovary(s), with repair of enterocele
	58267	Vaginal hysterectomy, for uterus 250 g or less; with colpo-urethrocystopexy (Marshall-Marchetti-Krantz type, Pereyra type) with or without endoscopic control
	58270	Vaginal hysterectomy, for uterus 250 g or less; with repair of enterocele
	58275	Vaginal hysterectomy, with total or partial vaginectomy;
	58280	Vaginal hysterectomy, with total or partial vaginectomy; with repair of enterocele
	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)
	58292	Vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s), with repair of enterocele
	58293	Vaginal hysterectomy, for uterus greater than 250 g; with colpo-urethrocystopexy (Marshall-Marchetti-Krantz type, Pereyra type) with or without endoscopic control
	58294	Vaginal hysterectomy, for uterus greater than 250 g; with repair of enterocele
	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; with removal of tube(s) and/or ovary(s)
	58553	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 g

<b>Codes</b>	<b>Number</b>	<b>Description</b>
	58554	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)
	58570	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)
	58572	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)
HCPCS	None	
ICD-10	A18.17	Tuberculous female pelvic inflammatory disease
	A54.24	Gonococcal female pelvic inflammatory disease
	A54.85	Gonococcal peritonitis
	A56.11	Chlamydial female pelvic inflammatory disease
	A74.81	Chlamydial peritonitis
	D06.0	Carcinoma in situ of endocervix
	D06.1	Carcinoma in situ of exocervix
	D06.7	Carcinoma in situ of other parts of cervix
	D06.9	Carcinoma in situ of cervix, unspecified
	D21.9	Benign neoplasm of connective and other soft tissue, unspecified
	D25.0	Submucous leiomyoma of uterus
	D25.1	Intramural leiomyoma of uterus
	D25.2	Subserosal leiomyoma of uterus
	D25.9	Leiomyoma of uterus, unspecified
	F64.0	Transsexualism
	F64.1	Dual role transvestism
	G89.29	Other chronic pain
	K66.0	Peritoneal adhesions (postprocedural) (postinfection)
	N70.01	Acute salpingitis
	N70.02	Acute oophoritis
	N70.03	Acute salpingitis and oophoritis
	N70.11	Chronic salpingitis
	N70.12	Chronic oophoritis
	N70.13	Chronic salpingitis and oophoritis
	N70.91	Salpingitis, unspecified
	N70.92	Oophoritis, unspecified
	N70.93	Salpingitis and oophoritis, unspecified
	N71.0	Acute inflammatory disease of uterus
	N71.1	Chronic inflammatory disease of uterus
	N71.9	Inflammatory disease of uterus, unspecified
	N72	Inflammatory disease of cervix uteri
	N73.0	Acute parametritis and pelvic cellulitis
	N73.1	Chronic parametritis and pelvic cellulitis
	N73.2	Unspecified parametritis and pelvic cellulitis

<b>Codes</b>	<b>Number</b>	<b>Description</b>
	N73.3	Female acute pelvic peritonitis
	N73.4	Female chronic pelvic peritonitis
	N73.5	Female pelvic peritonitis, unspecified
	N73.6	Female pelvic peritoneal adhesions (postinfective)
	N73.8	Other specified female pelvic inflammatory diseases
	N73.9	Female pelvic inflammatory disease, unspecified
	N74	Female pelvic inflammatory disorders in diseases classified elsewhere
	N80.0	Endometriosis of uterus
	N80.1	Endometriosis of ovary
	N80.2	Endometriosis of fallopian tube
	N80.3	Endometriosis of pelvic peritoneum
	N80.4	Endometriosis of rectovaginal septum and vagina
	N80.5	Endometriosis of intestine
	N80.8	Other endometriosis
	N80.9	Endometriosis, unspecified
	N83.6	Hematosalpinx
	N83.7	Hematoma of broad ligament
	N87.0	Mild cervical dysplasia
	N87.1	Moderate cervical dysplasia
	N87.9	Dysplasia of cervix uteri, unspecified
	N92.0	Excessive and frequent menstruation with regular cycle
	N92.1	Excessive and frequent menstruation with irregular cycle
	N92.3	Ovulation bleeding
	N92.4	Excessive bleeding in the premenopausal period
	N92.5	Other specified irregular menstruation
	N92.6	Irregular menstruation, unspecified
	N93.0	Postcoital and contact bleeding
	N93.8	Other specified abnormal uterine and vaginal bleeding
	N93.9	Abnormal uterine and vaginal bleeding, unspecified
	N94.0	Mittelschmerz
	N94.10	Unspecified dyspareunia
	N94.11	Superficial (introital) dyspareunia
	N94.12	Deep dyspareunia
	N94.19	Other specified dyspareunia
	N94.4	Primary dysmenorrhea
	N94.5	Secondary dysmenorrhea
	N94.6	Dysmenorrhea, unspecified
	N94.89	Other specified conditions associated with female genital organs and menstrual cycle
	N94.9	Unspecified condition associated with female genital organs and menstrual cycle
	N95.0	Postmenopausal bleeding

<b>Codes</b>	<b>Number</b>	<b>Description</b>
	N99.4	Postprocedural pelvic peritoneal adhesions
	R10.2	Pelvic and perineal pain
	R87.610	Atypical squamous cells of undetermined significance on cytologic smear of cervix (ASC-US)
	R87.611	Atypical squamous cells cannot exclude high grade squamous intraepithelial lesion on cytologic smear of cervix (ASC-H)
	R87.612	Low grade squamous intraepithelial lesion on cytologic smear of cervix (LGSIL)
	R87.613	High grade squamous intraepithelial lesion on cytologic smear of cervix (HGSIL)
	R87.619	Unspecified abnormal cytological findings in specimens from cervix uteri
	R87.810	Cervical high risk human papillomavirus (HPV) DNA test positive

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## Gender Affirming Interventions for Gender Dysphoria: Clinical Criteria and Policy

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UMP members should refer to Regence medical policy 153 for information about UMP's coverage of transgender services, with the exception of information in the "Medical Policy Criteria" box in policy 153. Instead of the criteria listed in that box, the UMP-specific clinical criteria outlined below must be met to receive transgender surgical services.

### I. Medical Treatments for Gender Dysphoria

- A. Psychotherapy may be considered medically necessary as a treatment of gender dysphoria.
- B. Continuous hormone therapy may be considered medically necessary as a treatment of gender dysphoria when all of the following criteria are met:
  - 1. Clinical records document that the patient has the capacity to make fully informed decisions and consent for treatment; and hormone therapy is part of a comprehensive, patient-centered treatment plan; and
  - 2. A licensed behavioral health practitioner or a licensed physician, advanced registered nurse practitioner (ARNP), physician's assistant (PA) or psychologist is treating the patient for primary care or transgender services and:
    - a) Assesses the patient and makes or confirms the diagnosis of gender dysphoria as defined by the DSM-V criteria, and
    - b) Determines or confirms that the gender dysphoria is not due to another mental or physical health condition.

### II. Surgical Treatments of Gender Dysphoria

- A. Gender reassignment surgery (see UMP clinical criteria policy and Regence medical policy 153 guidelines) may be considered medically necessary in the treatment of gender dysphoria when all of the following criteria are met:
  - 1. Age at least 18 years. For patients younger than 18 years of age, mastectomy may be considered a medically necessary surgical procedures. Other requirements outlined in this section must be met to proceed with mastectomy in those younger than 18 years of age.
  - 2. Clinical records document that the patient has the capacity to make fully informed decisions and consent for treatment as part of a comprehensive, patient-centered treatment plan; and that any other mental health condition, if present, is adequately controlled; and
  - 3. At least 2 licensed mental health professionals have diagnosed gender dysphoria, and recommend surgical treatment (\*Only one mental health professional referral is required for mastectomy); and
    - a) Assesses the patient and makes or confirms the diagnosis of gender dysphoria as defined by the DSM-V criteria, and
    - b) Determines or confirms that the gender dysphoria is not due to another mental or physical health condition; and

4. Documentation of continuous hormonal therapy for at least 12 months, unless there is a documented medical contraindication to hormonal therapy. Hormonal therapy is not required prior to mastectomy; and
  5. Twelve months of living in a gender role that is congruent with the patient's gender identity.
- B. Prior authorization is required for all proposed surgical interventions. Section II.A of this policy lists the requirements and documentation that must be submitted for prior authorization review. Surgeries are not required to be completed at the same time and, instead, may be performed and receive prior authorization in progressive stages. UMP covers the following procedures with prior authorization that meet medical necessity criteria:
1. Blepharoplasty, covered only if restorative function medical criteria are met (not specific to transgender surgery);
  2. Breast augmentation will require preauthorization with following criteria:
    - a) Documentation of continuous hormonal therapy for at least 12 months, unless there is documented medical contraindication to hormonal therapy; and
    - b) Have not reached a Tanner Stage 5.
  3. Bilateral mastectomy with or without chest reconstruction;
  4. Clitoroplasty;
  5. Colovaginoplasty;
  6. Colpectomy;
  7. Genital surgery;
  8. Genital electrolysis and laser hair removal as required as part of the genital surgery is covered with prior authorization and is limited to the genitals and, if applicable, the graft site, as required for genital surgery. Electrolysis and laser hair removal not meeting these guidelines and the guidelines for Surgical Treatments of Gender Dysphoria outlined in the Gender Affirming Interventions for Gender Dysphoria Criteria and Policy is not covered.
  9. Hysterectomy;
  10. Labiaplasty;
  11. Metoidioplasty;
  12. Orchiectomy;
  13. Penectomy;
  14. Phalloplasty;
  15. Placement of testicular prosthesis;
  16. Rhinoplasty, covered only if restorative function medical criteria are met (not specific to transgender surgery);
  17. Salpingo-oophorectomy;
  18. Scrotoplasty;
  19. Urethroplasty;
  20. Vaginectomy; and
  21. Vaginoplasty.
- C. Other than gender reassignment surgeries listed in this policy, surgery and/or additional treatments to change specific appearance characteristics are considered not medically necessary as treatments of gender dysphoria, including, but not limited to the following:
1. Brow lifts;
  2. Calf implants;
  3. Cheek/malar implants;
  4. Chin/nose implants;
  5. Chondrolaryngoplasty;
  6. Collagen injections;

7. Drugs for hair loss or growth;
8. Facial or trunk hair removal via laser or electrolysis;
9. Facial feminization;
10. Face lift;
11. Forehead lift;
12. Hair transplantation;
13. Jaw shortening;
14. Lip reduction;
15. Liposuction;
16. Mastopexy;
17. Neck tightening;
18. Pectoral implants;
19. Reduction thyroid chondroplasty;
20. Removal of redundant skin;
21. Suction-assisted lipoplasty of the waist;
22. Trachea shave;
23. Voice modification surgery; and
24. Voice therapy/lessons.