Overview

This Coverage Policy addresses multiple services and procedures.

Coverage Policy

Currently, the evidence does not support any definitive benefit for one type of oxygen delivery system over another. As the operational costs of liquid oxygen systems may be significantly higher than other oxygen systems (e.g., portable or stationary oxygen concentrators), coverage of liquid oxygen systems may depend on the applicable health benefit plan definition of medical necessity. Where that definition
limits coverage to the most cost-effective equivalent treatment, the use of liquid oxygen system is not considered medically necessary. In addition when another type of oxygen system (e.g., concentrators) is available in network, a network adequacy exception for liquid oxygen will not be made.

**High Resolution Anoscopy (CPT Codes 46601, 46607)**

High resolution anoscopy (HRA) is considered medically necessary for diagnosis of EITHER of the following:

- suspicious anal lesion, including high-grade suspicious intraepithelial lesion (HSIL)
- anal dysplasia found in prior cytology/biopsy

HRA for any other indication is considered experimental, investigational and unproven.

**Tumor Treatment Fields (TTF) Therapy (HCPCS Codes A4555, E0766, 64999)**

TTF therapy (i.e., Optune™) is considered medically necessary for individual 22 years of age or older with presence of histologically-confirmed glioblastoma multiforme (GBM) when EITHER of the following criteria are met:

- with confirmed recurrence after receiving chemotherapy and the device is being used as a monotherapy for adjuvant therapy with temozolomide

TTF (i.e., Optune™) for any other indication is considered experimental, investigational or unproven.

The use of treatment planning software (i.e., NovoTAL) (CPT code 64999) for use with tumor treatment fields for any indication, is considered experimental, investigational or unproven.

**Insertion of Ocular Telescope Prosthesis Including Crystalline Lens (CPT Code 0308T, HCPCS Code C1840)**

Intraocular telescope (Implantable Miniature Telescope [IMT]) is considered medically necessary for an individual 65 years of age or older when ALL of the following criteria are met:

- with stable severe to profound vision impairment (best corrected distance visual acuity 20/160 to 20/800) caused by bilateral central scotomas associated with end-stage age-related macular degeneration (AMD)
- has retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography
- has evidence of visually significant cataract (≥ grade 2)
- agrees to undergo pre-surgery training and assessment (two to four visits) with low vision specialists (e.g., optometrist or occupational therapist) in the use of an external telescope
- achieve at least a 5-letter improvement on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart with an external telescope on the eye scheduled for surgery
- have adequate peripheral vision in the eye not scheduled for surgery
- agree to participate in postoperative visual training with a low vision specialist

**Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed (CPT Code 55874)**

Transperineal placement of biodegradable material, peri-prostatic, (i.e. SpaceOAR) is considered medically necessary for men undergoing external beam radiation therapy (EBRT) for prostate cancer.

Transperineal placement of biodegradable material, peri-prostatic for any other indication is considered experimental, investigational or unproven.
**Calprotectin, fecal (CPT Code 83993)**

Fecal calprotectin is considered medically necessary when ALL of the following criteria are met:
- for the evaluation of chronic diarrhea (>4 weeks)
- for purpose of distinguishing irritable bowel syndrome (IBS) from inflammatory bowel disease (IBD)

Fecal calprotectin for any other indication, including but not limited to management of IBD, is considered experimental, investigational or unproven.

**EXPERIMENTAL, INVESTIGATIONAL OR UNPROVEN SERVICES**

Each of the following services for any indication is considered experimental, investigational or unproven:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>32994</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>33289</td>
<td>Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision and interpretation, and pulmonary artery angiography, when performed</td>
<td></td>
</tr>
<tr>
<td>34717</td>
<td>Endovascular repair of iliac artery at the time of aorto-iliac artery endograft placement by deployment of an iliac branched endograft including pre-procedure sizing and device selection, all ipsilateral selective iliac artery catheterization(s), all associated radiological supervision and interpretation, and all endograft extension(s) proximally to the aortic bifurcation and distally in the internal iliac, external iliac, and common femoral artery(ies), and treatment zone angioplasty/stenting, when performed, for rupture or other than rupture (eg, for aneurysm, pseudoaneurysm, dissection, arteriovenous malformation, penetrating ulcer, traumatic disruption), unilateral (List separately in addition to code for primary procedure)</td>
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</tr>
<tr>
<td>34718</td>
<td>Endovascular repair of iliac artery, not associated with placement of an aorto-iliac artery endograft at the same session, by deployment of an iliac branched endograft, including pre-procedure sizing and device selection, all ipsilateral selective iliac artery</td>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>34839</td>
<td>Physician planning of a patient-specific fenestrated visceral aortic endograft requiring a minimum of 90 minutes of physician time</td>
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<tr>
<td>34841</td>
<td>Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)</td>
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<tr>
<td>34842</td>
<td>Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])</td>
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<tr>
<td>34843</td>
<td>Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])</td>
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<tr>
<td>34844</td>
<td>Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])</td>
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<tr>
<td>34845</td>
<td>Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, ...</td>
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<td>Code</td>
<td>Description</td>
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<tr>
<td>34846</td>
<td>Endovascular repair of visceral aorta and infrarenal abdominal aorta (e.g., aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)</td>
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<tr>
<td>34847</td>
<td>Endovascular repair of visceral aorta and infrarenal abdominal aorta (e.g., aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])</td>
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<tr>
<td>34848</td>
<td>Endovascular repair of visceral aorta and infrarenal abdominal aorta (e.g., aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])</td>
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<tr>
<td>46999</td>
<td>Unlisted procedure, anus</td>
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<tr>
<td></td>
<td>Considered Experimental/Investigational/Unproven when used to report transanal radiofrequency therapy for fecal Incontinence (e.g., SECCA procedure)</td>
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<tr>
<td>53860</td>
<td>Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence</td>
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<tr>
<td>Code</td>
<td>Description</td>
<td>Considered Status</td>
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<tr>
<td>-------</td>
<td>-----------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>58674</td>
<td>Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency</td>
<td>Considered Experimental/Investigational/Unproven when used to report placement of intraocular radiation source applicator</td>
</tr>
<tr>
<td>67299</td>
<td>Unlisted procedure, posterior segment</td>
<td>Considered Experimental/Investigational/Unproven when used to report conjunctival incision with posterior extrascleral placement of a pharmacologic agent</td>
</tr>
<tr>
<td>68399</td>
<td>Unlisted procedure, conjunctiva</td>
<td>Considered Experimental/Investigational/Unproven when used to report conjunctival incision with posterior extrascleral placement of a pharmacologic agent</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
<td>Considered Experimental/Investigational/Unproven when used to report Donor-Derived Cell-Free DNA (AlloSure®)</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
<td>Considered Experimental/Investigational/Unproven when used to report Holotranscobalamin, quantitative (Holotranscobalamin Testing)</td>
</tr>
<tr>
<td>88749</td>
<td>Unlisted in vivo (eg, transcutaneous) laboratory service</td>
<td>Considered Experimental/Investigational/Unproven when used to report skin advanced glycation endproducts measurement by multi-wavelength fluorescent spectroscopy</td>
</tr>
<tr>
<td>91112</td>
<td>Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report</td>
<td>Considered Experimental/Investigational/Unproven when used to report 13C-Spirulina Gastric Emptying Breath Test (GEBT)</td>
</tr>
<tr>
<td>91299</td>
<td>Unlisted diagnostic gastroenterology procedure</td>
<td>Considered Experimental/Investigational/Unproven when used to report 13C-Spirulina Gastric Emptying Breath Test (GEBT)</td>
</tr>
<tr>
<td>92499</td>
<td>Unlisted ophthalmological service or procedure</td>
<td>Considered Experimental/Investigational/Unproven when used to report computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report</td>
</tr>
<tr>
<td>92499</td>
<td>Unlisted ophthalmological service or procedure</td>
<td>Considered Experimental/Investigational/Unproven when used to report quantitative pupillometry with interpretation and report, unilateral or bilateral</td>
</tr>
<tr>
<td>93264</td>
<td>Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional</td>
<td>Considered Experimental/Investigational/Unproven when used to report quantitative pupillometry with interpretation and report, unilateral or bilateral</td>
</tr>
<tr>
<td>93701</td>
<td>Bioimpedance-derived physiologic cardiovascular analysis</td>
<td>Considered Experimental/Investigational/Unproven when used to report quantitative pupillometry with interpretation and report, unilateral or bilateral</td>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>93702</td>
<td>Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)</td>
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<tr>
<td>93799</td>
<td>Unlisted cardiovascular service or procedure</td>
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<tr>
<td>93998</td>
<td>Unlisted noninvasive vascular diagnostic study</td>
<td></td>
</tr>
<tr>
<td>95999</td>
<td>Unlisted neurological or neuromuscular diagnostic procedure</td>
<td></td>
</tr>
<tr>
<td>99199</td>
<td>Unlisted special service, procedure or report</td>
<td></td>
</tr>
<tr>
<td>0100T</td>
<td>Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy</td>
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<tr>
<td>0106T</td>
<td>Quantitative sensory testing (QST), testing and interpretation per extremity; using touch pressure stimuli to assess large diameter sensation</td>
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<tr>
<td>0106U</td>
<td>Gastric emptying, serial collection of 7 timed breath specimens, non-radioisotope carbon-13 (13C) spirulina substrate, analysis of each specimen by gas isotope ratio mass spectrometry, reported as rate of 13CO2 excretion</td>
<td></td>
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<tr>
<td>0107T</td>
<td>Quantitative sensory testing (QST), testing and interpretation per extremity; using vibration stimuli to assess large diameter fiber sensation</td>
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<tr>
<td>0108T</td>
<td>Quantitative sensory testing (QST), testing and interpretation per extremity; using cooling stimuli to assess small nerve fiber sensation and hyperalgesia</td>
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<tr>
<td>0109T</td>
<td>Quantitative sensory testing (QST), testing and interpretation per extremity; using heat-pain stimuli to assess small nerve fiber sensation and hyperalgesia</td>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>0110T</td>
<td>Quantitative sensory testing (QST), testing and interpretation per extremity; using other stimuli to assess sensation</td>
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<tr>
<td>0174T</td>
<td>Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)</td>
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<tr>
<td>0175T</td>
<td>Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation</td>
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<tr>
<td>0207T</td>
<td>Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral</td>
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<tr>
<td>0208T</td>
<td>Pure tone audiometry (threshold), automated; air only</td>
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<tr>
<td>0209T</td>
<td>Pure tone audiometry (threshold), automated; air and bone</td>
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<tr>
<td>0210T</td>
<td>Speech audiometry threshold, automated;</td>
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<tr>
<td>0211T</td>
<td>Speech audiometry threshold, automated; with speech recognition</td>
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<tr>
<td>0212T</td>
<td>Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated</td>
<td></td>
</tr>
<tr>
<td>0254T</td>
<td>Endovascular repair of iliac artery bifurcation (eg, aneurysm, pseudoaneurysm, arteriovenous malformation, trauma, dissection) using bifurcated endograft from the common iliac artery into both the external and internal iliac artery, including all selective and/or nonselective catheterization(s) required for device placement and all associated radiological supervision and interpretation, unilateral (Code deleted 12/31/2019)</td>
<td></td>
</tr>
<tr>
<td>0266T</td>
<td>Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intraoperative interrogation, programming, and repositioning, when performed)</td>
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<tr>
<td>0267T</td>
<td>Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming and repositioning, when performed)</td>
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<td>Code</td>
<td>Description</td>
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<tr>
<td>0268T</td>
<td>Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)</td>
<td></td>
</tr>
<tr>
<td>0269T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)</td>
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</tr>
<tr>
<td>0270T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)</td>
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</tr>
<tr>
<td>0271T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)</td>
<td></td>
</tr>
<tr>
<td>0272T</td>
<td>Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day);</td>
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<tr>
<td>0273T</td>
<td>Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (eg, battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming</td>
<td></td>
</tr>
<tr>
<td>0338T</td>
<td>Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral</td>
<td></td>
</tr>
<tr>
<td>0339T</td>
<td>Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast</td>
<td></td>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>0314</td>
<td>Injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral</td>
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<tr>
<td>0341T</td>
<td>Quantitative pupillometry with interpretation and report, unilateral or bilateral (Code deleted 12/31/2019)</td>
<td></td>
</tr>
<tr>
<td>0342T</td>
<td>Therapeutic apheresis with selective HDL delipidation and plasma reinfusion</td>
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</tr>
<tr>
<td>0351T</td>
<td>Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative</td>
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<tr>
<td>0352T</td>
<td>Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred</td>
<td></td>
</tr>
<tr>
<td>0353T</td>
<td>Optical coherence tomography of breast, surgical cavity; real-time intraoperative</td>
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</tr>
<tr>
<td>0354T</td>
<td>Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred</td>
<td></td>
</tr>
<tr>
<td>0378T</td>
<td>Visual field assessment, with concurrent real-time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional</td>
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</tr>
<tr>
<td>0379T</td>
<td>Visual field assessment, with concurrent real-time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; technical support and patient instructions, surveillance, analysis, and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional</td>
<td></td>
</tr>
<tr>
<td>0380T</td>
<td>Computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report (Code deleted 12/31/2019)</td>
<td></td>
</tr>
<tr>
<td>0381T</td>
<td>External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
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<tr>
<td>0382T</td>
<td>External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion</td>
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<td>Code</td>
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<tr>
<td>0383T</td>
<td>External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
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<tr>
<td>0384T</td>
<td>External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only</td>
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</tr>
<tr>
<td>0385T</td>
<td>External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
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</tr>
<tr>
<td>0386T</td>
<td>External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only</td>
<td></td>
</tr>
<tr>
<td>0397T</td>
<td>Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)</td>
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<tr>
<td>0404T</td>
<td>Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency</td>
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<tr>
<td>0408T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes</td>
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<tr>
<td>0409T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only</td>
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</tr>
<tr>
<td>0410T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only</td>
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<tr>
<td>0411T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system,</td>
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including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>0412T</td>
<td>Removal of permanent cardiac contractility modulation system; pulse generator only</td>
</tr>
<tr>
<td>0413T</td>
<td>Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)</td>
</tr>
<tr>
<td>0414T</td>
<td>Removal and replacement of permanent cardiac contractility modulation system pulse generator only</td>
</tr>
<tr>
<td>0415T</td>
<td>Repositioning of previously implanted cardiac contractility modulation system transvenous electrode, (atrial or ventricular lead)</td>
</tr>
<tr>
<td>0416T</td>
<td>Relocation of skin pocket for implanted cardiac contractility modulation pulse generator</td>
</tr>
<tr>
<td>0417T</td>
<td>Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system</td>
</tr>
<tr>
<td>0418T</td>
<td>Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter; implantable cardiac contractility modulation system</td>
</tr>
<tr>
<td>0465T</td>
<td>Suprachoroidal injection of a pharmacologic agent (does not include supply of medication)</td>
</tr>
<tr>
<td>0472T</td>
<td>Device evaluation, interrogation, and initial programming of intraocular retinal electrode array (eg, retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed values with analysis, including visual training, with review and report by a qualified health care professional</td>
</tr>
<tr>
<td>0473T</td>
<td>Device evaluation and interrogation of intraocular retinal electrode array (eg, retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional</td>
</tr>
<tr>
<td>0493T</td>
<td>Near-infrared spectroscopy studies of lower extremity wounds (eg, for oxyhemoglobin measurement)</td>
</tr>
<tr>
<td>0506T</td>
<td>Macular pigment optical density measurement by heterochromatic flicker photometry, unilateral or bilateral, with interpretation and report</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
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</tr>
<tr>
<td>0507T</td>
<td>Near-infrared dual imaging (ie, simultaneous reflective and transilluminated light) of meibomian glands, unilateral or bilateral, with interpretation and report</td>
</tr>
<tr>
<td>0525T</td>
<td>Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; complete system (electrode and implantable monitor)</td>
</tr>
<tr>
<td>0526T</td>
<td>Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; electrode only</td>
</tr>
<tr>
<td>0527T</td>
<td>Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; implantable monitor only</td>
</tr>
<tr>
<td>0528T</td>
<td>Programming device evaluation (in person) of intracardiac ischemia monitoring system with iterative adjustment of programmed values, with analysis, review, and report</td>
</tr>
<tr>
<td>0529T</td>
<td>Interrogation device evaluation (in person) of intracardiac ischemia monitoring system with analysis, review, and report</td>
</tr>
<tr>
<td>0530T</td>
<td>Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; complete system (electrode and implantable monitor)</td>
</tr>
<tr>
<td>0531T</td>
<td>Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; electrode only</td>
</tr>
<tr>
<td>0532T</td>
<td>Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; implantable monitor only</td>
</tr>
<tr>
<td>0546T</td>
<td>Radiofrequency spectroscopy, real time, intraoperative margin assessment, at the time of partial mastectomy, with report</td>
</tr>
<tr>
<td>0548T</td>
<td>Transperineal periurethral balloon continence device; bilateral placement, including cystoscopy and fluoroscopy</td>
</tr>
<tr>
<td>0549T</td>
<td>Transperineal periurethral balloon continence device; unilateral placement, including cystoscopy and fluoroscopy</td>
</tr>
<tr>
<td>0550T</td>
<td>Transperineal periurethral balloon continence device; removal, each balloon</td>
</tr>
<tr>
<td>0551T</td>
<td>Transperineal periurethral balloon continence device; adjustment of balloon(s) fluid volume</td>
</tr>
<tr>
<td>0563T</td>
<td>Evacuation of meibomian glands, using heat delivered through wearable, open-eye eyelid treatment devices and manual gland expression, bilateral</td>
</tr>
<tr>
<td>HCPCS Codes</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>A4563</td>
<td>Rectal control system for vaginal insertion, for long term use, includes pump and all supplies and accessories, any type each</td>
</tr>
<tr>
<td>C1824</td>
<td>Generator, cardiac contractility modulation (implantable)</td>
</tr>
<tr>
<td>C1841</td>
<td>Retinal prosthesis, includes all internal and external components</td>
</tr>
<tr>
<td>C1842</td>
<td>Retinal prosthesis, includes all internal and external components; add-on to C1841</td>
</tr>
<tr>
<td>C2624</td>
<td>Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components</td>
</tr>
<tr>
<td>E2120</td>
<td>Pulse generator system for tympanic treatment of inner ear endolympathic fluid</td>
</tr>
<tr>
<td>G0255</td>
<td>Current perception threshold/sensory nerve conduction test, (sNCT) per limb, any nerve</td>
</tr>
<tr>
<td>L8608</td>
<td>Miscellaneous external component, supply or accessory for use with the argus ii retinal prosthesis system</td>
</tr>
<tr>
<td>S2103</td>
<td>Adrenal tissue transplant to brain</td>
</tr>
</tbody>
</table>


**General Background**

**Subsections:**
- Services without Food and Drug Administration (FDA) Approval
- Cardiovascular
- Pulmonary
- Gastroenterology
- Neurology
- Obstetrics/Gynecology
- Urology
- Ophthalmology
- Oncology
- Otolaryngology
- Other

**Services without Food and Drug Administration (FDA) Approval**

This policy discusses the safety and effectiveness of certain technologies, services, and procedures, including those represented by some Category III CPT® codes. Category III codes are temporary codes that allow for data collection for these services/procedures.

Additionally, there are certain codes, including mainly Category III codes that represent services which have not yet received Food and Drug Administration (FDA) approval:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>67299</td>
<td>Unlisted procedure, posterior segment</td>
<td>Considered Experimental/Investigational/Unproven when used to report placement of intraocular radiation source applicator</td>
</tr>
<tr>
<td>88749</td>
<td>Unlisted in vivo (eg, transcutaneous) laboratory service</td>
<td>Considered Experimental/Investigational/Unproven</td>
</tr>
</tbody>
</table>
Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral

Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral

Therapeutic apheresis with selective HDL delipidation and plasma reinfusion


**Cardiovascular**

**Chronic baroreceptor stimulation of the carotid sinus (CPT codes 0266T, 0267T, 0268T, 0269T, 0270T, 0271T, 0272T, 0273T)**

The Barostim® neo implantable device (CVRx, Minneapolis, MN) has been proposed for treatment of heart failure and high blood pressure. According to the product website, it a patented technology designed to trigger the body's own natural blood flow regulation system to treat these conditions. The Barostim neo implantable device replaced the Rheos Baroreflex Hypertension device. The device consists of an implantable pulse generator (IPG), one connecting lead wire, and an external wireless programmer system that allows physicians to modify device therapy. It is implanted under the skin beneath the collar bone with the lead positioned outside the carotid artery to conduct energy from the IPG to carotid baroreceptors.

The Barostim neo implantable device is proposed to address cases of unmet treatment needs in patients with drug resistant hypertension and heart failure. Activated baroreceptors signal the brain to respond to a rise in blood pressure. The brain responds by stimulating pathways of the autonomic nervous system responsible for arterial vessel dilation, heart rate, and fluid excretion.

**U.S. Food and Drug Administration (FDA)**

December 2014 the Barostim neo® Legacy System received humanitarian device exemption (HDE). The device is indicated for use in patients with resistant hypertension who have had bilateral implantation of the Rheos® Carotid Sinus Leads Models 1010R, 1010L, 1014L, and 1014R (which have been discontinued and are obsolete) and were determined responders in the Rheos® pivotal clinical study.

August 16, 2019, the FDA granted premarket approval (PMA) for the Barostim neo System. The device is indicated for the improvement of symptoms of heart failure (HF) (quality of life, 6-minute hall walk, and functional status) for patients who remain symptomatic despite treatment with GDMT, are NYHA Class III or Class II (who had a recent history of Class III), have an LVEF ≤ 35%, an NT-proBNP < 16000 pg/mL, and excluding patients indicated for CRT according to the AHA/ACC/ESC guidelines. The PMA for the device was supported by the
pivotal BeAT-HF trial. The results of this trial have been presented at conference proceedings, but are not published to date. The FDA is requiring the manufacturer to conduct a post-approval study to evaluate the device’s effect on long-term survival and reducing hospitalizations.

**Literature Review—Barostim neo for Drug Resistant Hypertension**

Wallbach et al. (2016) reported on a prospective study that evaluated ambulatory BP measurement (ABPM) data in patients with therapy–refractory hypertension (HTN) treated with the Baroreflex activation therapy (BAT) neo device. ABPM was performed before BAT implantation and six months after initiation of BAT. A total of 51 patients were included into this study, with seven dropping out from analysis. After six months, 24-hour ambulatory systolic (from 148 ± 17 mm Hg to 140 ± 23 mm Hg, P<0.01), diastolic (from 82 ± 13 mm Hg to 77 ± 15 mm Hg, P<0.01), day- and night-time systolic and diastolic BP (all P ≤ 0.01) decreased while the number of prescribed antihypertensive classes could be reduced from 6.5 ± 1.5 to 6.0 ± 1.8 (P=0.03). Heart rate and pulse pressure remained unchanged. BAT was equally effective in reducing ambulatory BP in all subgroups of patients. The authors note that randomized controlled trials are needed to evaluate BAT effects on ABPM in patients with resistant hypertension accurately. This study is limited by the small number of subjects and lack of randomization.

Biognano et al. (2011) published the pivotal study regarding Baroreflex activation therapy (BAT) of the Rheos device. Patients were randomized to receive either active BAT (group A, n=181) or deferred BAT (group B, n=84) with the Rheos system. Active BAT was initiated one month after implantation, while deferred BAT was started seven months after implantation. This design allowed short term comparison between BAT and medical management. The coprimary endpoints: 1) acute systolic blood pressure (SBP) responder rate at 6 months; 2) sustained responder rate at 12 months; 3) procedure safety; 4) BAT safety; and 5) device safety. At 6-month follow-up, 54% of active group patients and 45% of those not receiving active therapy achieved the preset acute efficacy goal of at least 10 mm Hg reduction in (SBP); between-group comparison was not statistically significant. The 30-day rate of procedure- or device-related serious adverse events was 25.5%, which did not meet the preset objective performance criterion (OPC) for procedural safety. Although the 12-month sustained efficacy endpoint was met, this endpoint was assessed by comparing Group A patient outcomes with OPC rather than with Group B outcomes, leading to difficulty in interpretation of the clinical relevance of this result. The long-term device safety and short-term BAT safety primary outcomes were met.

Following completion of the randomized Rheos Pivotal Trial, Bakris et al. (2012) conducted an open-label, nonrandomized single-arm follow-up to assess safety and efficacy of BAT. Blood pressure reductions were measured relative to a pre-implant baseline as well as the results achieved at the completion of 1 year of follow-up in the randomized phase. Clinically significant responder status was assessed according to FDA-mandated criteria. Of the 322 patients implanted, 76% (n=245) qualified as clinically significant responders, an additional 10% were indeterminate. Among long-term responders receiving BAT, the mean blood pressure drop was 35/16 mm Hg. Among responders, 55% achieved goal blood pressures (<140 mm Hg or <130 mm Hg in diabetes or kidney disease). Blood pressures of all active patients remained stable from completion of the randomized phase through long-term follow-up. BAT substantially reduced arterial pressure for most patients participating in the Rheos Pivotal Trial. This blood pressure reduction or goal achievement was maintained over long-term follow-up of 22 to 53 months.

**Literature Review—Barostim neo for Heart Failure**

Abraham et al. (2015) reported on prospective, randomized, parallel-controlled, clinical trial of baroreflex activation therapy (BAT) in heart failure (HF). Patients with New York Heart Association (NYHA) functional class III HF and ejection fractions ≤35% on chronic stable guideline-directed medical therapy (GDMT) were randomly assigned to receive ongoing GDMT alone (control group) (n=70) or ongoing GDMT plus BAT (treatment group) (n=76) for six months. The primary safety end point was system- and procedure-related major adverse neurological and cardiovascular events. The primary efficacy end points were changes in NYHA functional class, quality-of-life score, and 6-minute hall walk distance. The major adverse neurological and cardiovascular event-free rate was 97.2% (lower 95% confidence bound 91.4%). Patients assigned to BAT, compared with control group patients, experienced improvements in the distance walked in 6 min (59.6 ± 14 m vs. 1.5 ± 13.2 m; p=0.004), quality-of-life score (-17.4 ± 2.8 points vs. 2.1 ± 3.1 points; p< 0.001), and NYHA functional class ranking (p=0.002 for change in distribution). BAT reduced N-terminal pro-brain natriuretic peptide (p=0.02) and was associated with a trend toward fewer days hospitalized for HF (p=0.08). One patient in the control group
died before the activation date, and five patients in the treatment group withdrew consent or were withdrawn by the site before system implantation and their activation dates. Of the 69 patients assigned to the control group who reached their activation dates, 15 did not complete six months of follow-up: four patients died, five withdrew consent, three were lost to follow-up, and three missed the visit. Of the 71 patients who received the BAT system and reached their activation date, seven did not complete six months of follow-up: five died and two withdrew consent. The study was limited by the low number of participants.

Zile et al. (2015) compared outcomes in the GDMT plus BAT group patients with (n=24) and without (n=47) a cardiac resynchronization therapy (CRT) device. Efficacy endpoints were Minnesota Living with Heart Failure Quality of Life (QoL), 6-min hall walk distance (6MHWD), N-terminal pro-brain natriuretic peptide (NT-proBNP), left ventricular ejection fraction (LVEF), and HF hospitalization rate. In the CRT BAT group patients two did not complete 6 months of follow-up (owing to death). In the no-CRT BAT group patients, five did not complete six months of follow-up: three patients died and two withdrew consent. At six months, in patients with CRT, no significant changes in any other efficacy parameter were found in the BAT patients or control patients comparing baseline with six months values or comparing changes in other efficacy parameters between baseline and 6 months in BAT vs. control patients. At 6 months, in patients with no-CRT, statistically significant improvements were observed in NYHA Class, QoL score, 6MHWD, NT-proBNP, LVEF, number of HF hospitalizations and number of days hospitalized with HF in BAT patients compared to control patients. The study was limited by the small number of patients.

Although reports of these trials note improvements in NYHA classification, the relatively small number of patients studied and lack of patient blinding and sham intervention limit interpretation of results. To date, there is insufficient published evidence to draw firm conclusions regarding the safety and efficacy of the Barostim neo System for the treatment of HF. In addition the trials were not designed to examine clinical outcomes. The observations should be confirmed in an adequately powered, prospective, randomized clinical outcome trials.

Professional Societies/Organizations
American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Clinical Practice Guidelines published guidelines for hypertension. The guidelines note regarding resistant hypertension that “Several studies have investigated devices that interrupt sympathetic nerve activity (carotid baroreceptor pacing and catheter ablation of renal sympathetic nerves); however, these studies have not provided sufficient evidence to recommend the use of these device in managing resistant hypertension.” (Whelton, et al., 2018)

American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Clinical Practice Guidelines and the Heart Failure Society of America (HFSA) guideline for the management of heart failure does not include the use of barostimulation for treatment of heart failure (Yancy, et al., 2017; Yancy, et al., 2013).

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L35094) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
National Institute of Health Care and Excellence (NICE): NICE published Interventional procedures guidance regarding implanting a baroreceptor stimulation device for resistant hypertension (2015). The guidance notes that current evidence on the safety and efficacy of implanting a baroreceptor stimulation device for resistant hypertension is inadequate. Therefore, this procedure should only be used in the context of research.

European Society of Cardiology (ESC): ESC published guidelines for the diagnosis and treatment of acute and chronic heart failure (Ponikowski, et al., 2016). The guidelines note that currently, the evidence is considered insufficient to support specific guideline recommendations for other therapeutic technologies, including baroreflex activation therapy and further research is required.

References


**Endovascular repair of visceral aorta for abdominal aortic aneurysm with fenestrated visceral aortic endograft (including planning) (CPT Codes 34839, 34841, 34842, 34843, 34844, 34845, 34846, 34847, 34848)**

The conventional treatment for AAA has been open surgical repair. Open surgical repair involves transabdominal surgery, exposure of the aneurysm, cross-clamping the aorta, resection of the aneurysm, and placement of graft prosthesis. Endovascular AAA repair developed as a minimally invasive alternative to open surgical repair in patients with suitable anatomy. Endovascular repair of infrarenal abdominal or aortoiliac AAA has demonstrated reduced rates of perioperative mortality and morbidity compared to open surgical repair, with equivalent long-term aneurysm-related mortality, although this approach is associated with higher rates of reintervention, and requires long-term radiological monitoring. Endovascular repair may be a reasonable option for selected patients with suitable anatomy for whom the risk/benefit ratio favors endovascular repair.

The use of fenestrated grafts (e.g., Zenith® Fenestrated AAA Endovascular Graft) has been investigated for the treatment of patients with AAA involving the visceral arteries. These grafts include fenestrations, or scallops, in the graft material that allow the proximal edge of the material to be placed above the renal arteries while permitting blood flow to vessels accommodated by the fenestrations. Evidence published in the medical literature consists primarily of registry data, small feasibility studies, and case series with limited outcome data. Additional evidence is needed to determine the safety, efficacy, and long-term outcomes of this procedure and to determine how this approach compares to surgical repair.

**U.S. Food and Drug Administration (FDA)**

The Zenith® Fenestrated AAA Endovascular Graft (with the adjunctive Zenith Alignment Stent) received FDA PMA approval 2012. The Zenith graft is indicated for the endovascular treatment of patients with abdominal aortic or aortoiliac aneurysm having morphology suitable for endovascular repair, including:

- Adequate iliac/femoral access compatible with required introduction systems
- Nonaneurysmal infrarenal aortic segment (neck) proximal to the aneurysms with:
  - Length ≥ 4 mm and unsuitable for a non-fenestrated graft
  - Diameter ≤ 31 mm and ≥ 19 mm
  - Angle < 45 degrees relative to long axis of aneurysm
Angle < 45 degrees relative to axis of suprarenal aorta

- Ipsilateral iliac artery fixation site > 30 mm in length and between 9 - 21 mm in diameter
- Contralateral iliac artery distal fixation site >30 mm in length and between 7 – 21 mm in diameter

The Zenith Alignment Stent is indicated for use as an adjunct to the Zenith Fenestrated AAA Endovascular Graft to secure positive alignment of fenestrations or scallops with the orifice of aortic branch vessels having diameters ranging from 3 to 8 mm. Unlike the standard Zenith AAA Endovascular Graft, the Zenith Fenestrated AAA graft has fenestrations or scallops in the graft material, which allow the proximal edge of graft material to be placed above the renal arteries while still permitting blood flow to vessels accommodated by the fenestrations or scallops. In order to account for anatomical variation, each proximal body graft is made to order for a specific patient. The Zenith fenestrated graft has been available outside the U.S. since 2002.

The CardioMEMS EndoSure™ Wireless AAA Pressure Measurement System was approved for marketing through the 510(k) process on October 12, 2006 for the measurement of intrasac pressure during endovascular AAA repair and for use as an adjunctive tool in the detection of intraoperative leaks. In a subsequent approval on March 15, 2007, measurement of intrasac pressure during thoracic aortic aneurysm repair was added as an intended use.

According to the 510(k) summary, the sensor is implanted in the aneurysm sac during stent graft deployment and is left in place in the excluded portion of the aneurysm as a permanent implant. The main body of the sensor is composed of fused silica coated in silicone. Nitinol loops extend from and surround the sensor body. The sensor is interrogated using the antenna of the EndoSure Electronics System. Once the signal is acquired, a pressure waveform and numerical pressure data are displayed on the touch-screen, and a printout of the data and waveform is generated.

**Literature Review**

**Endovascular Repair Using a Fenestrated Graft:** The British Society for the Endovascular Therapy and the Global Collaborators on Advanced Stent-Graft Repair (GLOBALSTAR) Registry published early results of endovascular repair of juxtarenal aortic aneurysms using the Zenith fenestrated graft in the United Kingdom (2012). Data from 318 patients treated at 14 experienced centers (i.e., > 10 procedures) were retrospectively studied. The primary procedural success rate was 99% (316/318); perioperative mortality was 4.1%; and intraoperative target vessel loss was observed in 5 of 889 target vessels (0.6%). The early reintervention rate (i.e., <30 days) was 7%. There were 11 deaths during the follow-up, but none were aneurysm-related. Freedom from target-vessel loss at one, two, and three years was 93%, 91%, and 85%, respectively, and freedom from late secondary intervention (> 30 days) was 90%, 86%, and 70% at one, two, and three years, respectively. The authors stated that these results support continued use and evaluation of this technique for juxtarenal aneurysms, but illustrate the need for a more robust evidence base.

Amiot et al. (2010) conducted a retrospective analysis to evaluate the medium-term outcomes of aortic aneurysm repair using the Zenith fenestrated graft in 16 French academic centers (n=134). Patients were considered to be at high risk for open surgical repair. The median aneurysm size was 56 mm (range 45-91 mm), and the median patient age was 73 years (range 43-91 years). A total of 403 visceral vessels were treated, including 265 renal arteries. One early conversion to surgery was required. Angiography immediately following the procedure demonstrated patency in 398 of 403 target vessels. The 30-day mortality was 2%. Imaging prior to discharge revealed 16 (12%) endoleaks (3 type I, 12 type II, and 1 type III). Transient or permanent dialysis was required in 4 (3%) and two (1%) patients, respectively. During a median follow-up of 15 months (range 2-53 months), no aneurysms ruptured or required open conversion. Aneurysm sac size decreased by more than 5 mm in 52%, 65.6%, and 75% of patients at one, two and three years, respectively. Three patients had sac enlargement within the first year associated with persistent endoleaks. Four renal artery occlusions were detected during follow-up, and 12 procedures related to reintervention were performed in 12 patients, including six to correct endoleaks and five to correct threatened visceral vessels. Twelve of 131 patients died during follow-up; none of these were aneurysm related.

Greenberg et al. (2009) reported intermediate results of a multicenter prospective case series to assess the safety and efficacy of the Zenith fenestrated devices (n=30) in patients with juxtarenal AAA. Inclusion criteria consisted of aortic or aortoiliac aneurysms with diameter greater than five cm, or with aortic or aortoiliac
aneurysms with a history of growth greater than 0.5 cm per year or clinical indication for AAA repair. Customized devices were designed for each patient based on calculations derived from computed tomography (CT) scan data. A total of 77 visceral vessels were accommodated by fenestrations within the sealing segment of the grafts. The most common design accommodated two renal arteries and the superior mesenteric artery (66.7%). Prostheses were successfully implanted in all patients. Of the 30 patients, 27 were available for follow up at 12 months, and 23 were available at 24 months. There were no aneurysm related deaths, aneurysm ruptures, or conversions during the follow-up period. There were no type I or type III endoleaks reported. Type II endoleaks were reported in six patients (26.1%) at 12 months, and in four (20.0%) at 24 months. None of the patients had aneurysm growth > 5 mm. Aneurysm size at 24 months decreased in 16 of 23 patients (69.6%) and was stable in the remaining patients. A renal event occurred in eight patients. Secondary interventions were performed in five patients. No patients experienced renal failure requiring dialysis. The authors concluded that the intermediate term results of this multicenter study are concordant with previous single-center studies and support the concept the placement of fenestrated endovascular grafts is safe and effective at centers with experience in endovascular repair and renal/mesenteric stent placement.

An Agency for Healthcare Research and Quality (AHRQ) evidence report/technology assessment (Wilt et al., 2006) compared endovascular and open surgical repairs for AAA. Randomized controlled trials of open surgical repair, endovascular repair, or active surveillance; systematic reviews; nonrandomized U.S. trials; and national registries were used to assess clinical outcomes. The assessment concluded that for AAA < 5.5 cm in diameter, active surveillance with delayed open surgical repair results in equivalent mortality, but less morbidity, due to fewer interventions, compared to immediate open surgical repair. Endovascular repair of aneurysms ≥ 5.5 cm has not been shown to improve long-term survival or health status compared to open surgical repair, although perioperative outcomes are improved. The assessment also stated that endovascular repair does not improve survival in patients who are medically unfit for open surgical repair. Endovascular repair is associated with more complications, need for reintervention, and monitoring compared to open surgical repair or no intervention. The AHRQ report recommended U.S. randomized controlled trials be conducted with approved endovascular repair devices to evaluate patient outcomes.

Wang et al. (2018a) reported on a retrospective, single-center, cohort study. A retrospective review of a prospectively maintained fenestrated endovascular aneurysm repair (FEVAR) database was performed for descriptive analysis. Reintervention during the follow-up phase was 20%. Of the 209 visceral arteries stented, six instances of stent thrombosis were noted, along with six of kinking or stenosis, and one of stent fracture in follow-up. Endoleak, most commonly type II, was present or could not be excluded in 15% of all FEVARs at last available computed tomography angiography.

CardioMEMS EndoSure Wireless AAA Pressure Measurement System: Published evidence on the use of the CardioMEMS system consists of several diagnostic cohort studies with short-term preliminary results (Hoppe et al., 2008, n=12; Silveira et al., 2008, n=25; Ohki et al., 2007, n=76). The safety and clinical utility of this technology in the intraoperative or long-term monitoring of patients following endovascular aortic aneurysm repair has not been established.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCDs found.

Use Outside of the US
No relevant information.

References


Endovascular repair of iliac artery bifurcation (CPT codes 34717, 34718, 0254T [Code deleted 12/31/2019]): Involvement of the common iliac arteries occurs in approximately 20% of patients with abdominal aortic aneurysms (AAA) and may present a challenge to endovascular treatment since it may compromises sealing and distal fixation of endoprostheses. Several techniques have been developed to achieve the goal of sealing the aneurysmal sac, with one of the techniques that has been developed is the use of an endoprosthesis in the iliac arteries.

A device that has been developed exclusively for use in the iliac arteries is the GORE® EXCLUDER® Iliac Branch Endoprosthesis (IBE) (W. L. Gore & Associates, Inc., Flagstaff, AZ). It is intended to be used in conjunction with the Gore Excluder abdominal aortic aneurysm (AAA) endoprosthesis to isolate the common iliac artery from the systemic blood flow and is intended to preserve blood flow to the external and internal iliac arteries and preserve pelvic perfusion (Hayes, 2017).

U.S. Food and Drug Administration (FDA)
The GORE® EXCLUDER® Iliac Branch Endoprosthesis (IBE Device) received FDA premarket (PMA) approval February 2016. It is indicated for use with the GORE® EXCLUDER® AAA Endoprosthesis to isolate the common iliac artery from systemic blood flow and preserve blood flow in the external iliac and internal iliac arteries in patients with a common iliac or aortoiliac aneurysm, who have appropriate anatomy that includes:

- Adequate iliac/femoral access
- Minimum common iliac diameter of 17 mm at the proximal implantation zone of the IBE
- External iliac artery treatment diameter range of 6.5-25 mm and seal zone length of at least 10 mm
- Internal iliac artery treatment diameter range of 6.5-13.5 mm and seal zone length of at least 10 mm
- Adequate length from the lowest major renal artery to the internal iliac artery to accommodate the total endoprosthesis length, calculated by adding the minimum lengths of required components, taking into account appropriate overlaps between components

Contraindications to the device include:

- Patients with known sensitivities or allergies to the device materials. All components of the GORE EXCLUDER Iliac Branch Endoprosthesis and the GORE EXCLUDER AAA Endoprosthesis contain ePTFE, FEP, nitinol (nickel-titanium alloy), and gold.
- Patients with a systemic infection who may be at increased risk of endovascular graft infection.

Literature review
van Sterkenburg et al. (2016) reported on a retrospective cohort analysis that analyzed procedural success and early outcome of endovascular treatment of a multicenter cohort of patients (n=46) with common iliac artery (CIA) aneurysms treated with the GORE EXCLUDER. The median diameter of the treated aneurysm was 40.5 (range, 25.0-90.0) mm and the mean procedural time was 198 ± 56 minutes. One implantation was not successful; two type 1b endoleaks were noticed, which resulted in procedural success rate of 93.5%. The two type 1b endoleaks spontaneously disappeared at 30 days and there was no 30-day mortality. Ipsilateral buttock claudication was present in two cases at 30 days and disappeared during follow-up. The incidence of reported erectile dysfunction was low and there was an absence of severe ischemic complications. After a mean follow-up of six months, data on 17 treated aneurysms were available: these showed two with a stable diameter, and 15 showed a mean decrease of 3.9 ± 2.2 mm (P< .001). Re-interventions were done in two patients (7.1%). The six-month primary patency of the internal component of the IBE device was 94%. The authors noted that prospective data with longer follow-up are awaited to establish the role of the device in the treatment algorithm of CIA aneurysms. Limitations of the study include small sample size and retrospective nature of the study.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L35094) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
European Society for Vascular Surgery: this organization published clinical guidelines for the management of abdominal aortic aneurysms (Moll, et al., 2011). Recommendations regarding the management of iliac aneurysms include:

- Coexisting iliac aneurysms should be treated concurrently with AAA. Isolated iliac aneurysms may be treated by either open or, preferentially, endovascular techniques. Intervention should be considered when the iliac diameter exceeds 3 cm. Iliac aneurysms should be repaired once the diameter exceeds 3 cm.

  Level 3a, Recommendation C

- Endovascular treatment options should be considered in all patients and in defined subgroups this will include the consideration for iliac branch graft placement.

  Level 3a, Recommendation C

Level 3A: systematic review (with homogeneity) of case-control studies

Recommendation C: Level 4 studies or extrapolations from level 2 or 3 studies (Extrapolations are where data are used in a situation that has potentially clinically important differences than the original study situation).

References


Implanted Wireless Pulmonary Artery Sensor (e.g., CardioMEMS HF System) (CPT Codes 33289, 93264 and HCPCS Codes C2624)

Implantable intracardiac pressure monitors are intended to complement conventional drug therapy for heart failure (HF) through intermittent monitoring, allowing more timely adjustments to medications, if needed. The CardioMEMS™ HF System (St. Jude Medical, Inc., St. Paul, MN, USA, formerly Champion HF Monitoring System
as well as Heart Sensor; CardioMEMS, Inc., Atlanta, GA) is a 2 x 3.4 x15mm sized device that allows monitoring of pulmonary artery (PA) pressure using a wireless sensor. The sensor has two wire loops extending from either side. It is inserted into the PA through a traditional right heart catheterization procedure. Once deployed, PA pressure measurements can be taken repeatedly and transmitted wirelessly without requiring right heart catheterization or other invasive procedures. The sensor requires no batteries and is intended to be a permanent implant.

To record measurements at home, the patient lies on top of a pillow with sensory equipment embedded. A recording device with a cable-connected remote control is placed within four to five feet of the pillow. The patient reclines on the pillow and is guided to an optimal position by the recording device. When positioning is adequate, the machine prompts the patient to start recording by pushing the remote control. According to the manufacturer, the patient must remain still while pressures are recorded for 18 seconds, during which the machine plays music, intended to relax the patient. When the reading is complete, the machine automatically transmits the information to the CardioMEMS website (St. Jude Medical, 2014).

U.S. Food and Drug Administration (FDA)
Although a number of implantable wireless sensors are in development the CardioMEMS™ HF system is the only device in this group that has received FDA approval. On May 28, 2014 the Food and Drug Administration (FDA) granted CardioMEMS, Inc.’s (formerly Atlanta, GA, now St. Jude Medical, Inc., St. Paul, MN) premarket approval (PMA P100045) for the CardioMEMS HF System which includes the CM2000 implantable PA Sensor/Monitor and transvenous catheter delivery system, the CM1000 Patient Electronics System (GSM), the CM1010 Patient Electronics System (GSM), and CM3000 Hospital Electronics System. According to the PMA, the device is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in patients with New York Heart Association (NYHA) Class III HF who have been hospitalized for HF in the previous year. The FDA approval requires that the manufacturer conduct an additional prospective, multi-center, open-label trial conducted in the United States to examine the safety and effectiveness of CardioMEMS HF System in 663 adults with NYHA Class III Heart Failure (HF) who have experienced a heart failure hospitalization within the past 12 months; of which a total of 420 will be women. Follow-up will be two years post implant with specified safety and effectiveness endpoints. Additionally a prospective, multi-center, open-label substudy conducted in the United States to examine safety and compare the postmarket effectiveness of CardioMEMS HF System to premarket is required by the FDA.

Literature Review
Data is limited in the published peer-reviewed scientific literature regarding the safety and effectiveness of the CardioMEMS HF System.

Hayes published an updated health technology brief for the CardioMEMS Implantable Hemodynamic Monitor for managing patients with heart failure (Hayes, 2019). The review included one multicenter randomized controlled trial (RCT) (the CHAMPION trial; reported in eight publications), which compared CardioMEMS wireless implantable hemodynamic monitor (CM-IHM) with standard monitoring practices in 550 patients with NYHA functional class III HF. One cohort study (n=66) compared CM-IHM with standard monitoring practices, and three retrospective registry analyses (n=3544) evaluated the efficacy of CM-IHM in patients with HF. The findings included:

- For CM-IHM compared with standard management (two studies):
  - HF hospitalizations were statistically significantly reduced in patients managed with CM-IHM (two of two studies); however, in an adjusted analysis the treatment effect was no longer evident in one study.
  - All-cause hospitalizations were statistically significantly reduced in patients managed with CM-IHM (one of one study).
  - Survival and mortality did not differ between groups (one of one study).
  - Statistically significant greater improvements occurred in quality-of-life measures at six and 12 months (one of one study; n=550).

- For efficacy evaluations of CM-IHM in single-arm studies (two studies):
  - HF hospitalizations were statistically significantly reduced at six and 12 months in a large registry analysis of Medicare beneficiaries.
  - All-cause hospitalizations were statistically significantly reduced at six and 12 months in a large registry analysis of Medicare beneficiaries.
Pulmonary artery pressure (PAP) was statistically significantly reduced up to 6 months postimplantation in one large registry analysis.

The report concluded that a very-low-quality body of evidence suggests that management of HF patients with CM-IHM may reduce the incidence of HF-related hospitalization. However, substantial uncertainty remains about the comparative effectiveness of the CM-IHM with standard monitoring and the impact of CM-IHM on long-term health benefits, including mortality, survival, overall patient management, safety, and quality of life. Additional studies are needed to provide comparative evidence for the long-term benefits and harms of CM-IHM.

Abraham et al. (2011) reported results of a randomized controlled trial (RCT): the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial. The outcomes of this trial were reviewed by the FDA for premarket approval of this device. Eligible patients underwent implantation of a wireless pulmonary artery (PA) sensor monitoring system (i.e., CardioMEMS). Five hundred fifty individuals were implanted and randomized to the treatment group (n=270, standard of care HF treatment, plus PA pressure readings) or to the control group (n=280, standard of care HF treatment). Daily PA pressure readings were taken at home by patients in each group and sent to a secure website. In the treatment group clinicians had access to these readings; in the control group clinicians were unable to access pressure readings. Assessment at one, three and six months, and every six-months thereafter included a physical examination, assessment of New York Heart Association class and quality-of-life assessment by use of the 21-question Minnesota Living with Heart Failure questionnaire and review of drugs.

The primary efficacy endpoint was the rate of heart failure-related hospitalizations during the six months after insertion of the pressure sensor in the treatment group versus the control group. The two primary safety endpoints were device-related or system-related complications. The mean follow-up was 15 months. At six months 83 heart-failure-related hospitalizations were reported in the treatment group compared with 120 in the control group (p<0.0001). During the entire follow-up (mean 15 months) the treatment group had a 39% reduction in heart-failure-related hospitalization compared with the control group (p<0.0001). Eight patients had device- or system-related complications (DSRC). Overall freedom from DSRC was 98.6%. Overall freedom from pressure-sensor failures was 100%. Survival rates in the treatment and control groups at six months were similar (p=0.45). Fifteen serious adverse events (AE) were reported, including, infection, bleeding, thrombosis, cardiac arrhythmias, one patient with cardiogenic shock, one atypical chest pain, and one delivery-system failure that required a snare to remove the delivery system. Data in this single clinical trial suggest improved shortterm outcomes; however, additional large blinded RCTs replicating these findings are required before use of a wireless pulmonary artery sensor monitoring system (e.g., CardioMEMS HF system) is incorporated into routine clinical practice.

Professional Societies/Organizations
American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Clinical Practice Guidelines and the Heart Failure Society of America (HFSA) guideline for the management of heart failure does not include the use of implantable intracardiac pressure monitors for treatment of heart failure (Yancy, et al., 2017; Yancy, et al., 2013).

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Local Coverage Determination (LCD): Outpatient Wireless Pulmonary Artery Pressure Monitoring for Heart Failure (L36419). Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
National Institute of Health Care and Excellence (NICE): NICE (2013) guidance on insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure notes that current evidence on the safety and efficacy of the insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure is limited in both quality and quantity. They recommend that this procedure should only be used with special arrangements for clinical governance, consent and audit or research.
European Society of Cardiology (ESC): ESC published guidelines for the diagnosis and treatment of acute and chronic heart failure (Ponikowski, et al., 2016). The guidelines note that monitoring of pulmonary artery pressures using a wireless implantable haemodynamic monitoring system (CardioMems) may be considered in symptomatic patients with HF with previous HF hospitalization in order to reduce the risk of recurrent HF hospitalization. Class of recommendation: IIb; Level of evidence: B

Class of recommendation IIb: Usefullness/efficacy is less well established by evidence/opinion
Level of evidence B: data derived from a single randomized clinical trial or large non-randomized

References

**Acoustic Cardiography (CPT code 93799)**

Acoustic cardiography, also referred to as correlated audioelectric cardiography, is a noninvasive diagnostic tool designed to be used in the evaluation of cardiac conditions such as left ventricular hypertrophy (LVH), acute and age-undetermined myocardial infarction (MI), cardiac arrhythmias, and detection of S3 and S4 heart sounds. An S3 heart sound may be associated with heart failure in patients over age 40. Acoustic cardiography is intended to augment physician auscultation, since S3 and S4 heart sounds may be difficult to hear in some patients. The device acquires, displays, and analyzes 12-lead electrocardiogram (ECG) and heart sound data (Collins et al., 2006; Kobza et al., 2008; Wagner et al., 2002; Warner et al., 2002).

Traditional diagnostic methods include physical examination and auscultation, 12-lead ECG laboratory examinations, measurement of biomarkers of cardiac damage, and imaging.

**U.S. Food and Drug Administration (FDA)**

The Eli 200+ Audicor (Mortara Instrument, Inc., Milwaukee, WI) is an interpretive electrocardiograph device designed to acquire, record and store cardiac data. The device uses Audicor Correlated Audioelectric Cardiography (COR) technology (Inovise Medical, Inc., Newberg, OR) to simultaneously acquire both 12-lead electrocardiogram (ECG) and heart sound data. The Eli 200+ Audicor received U.S. Food and Drug Administration (FDA) clearance to market as a Class II device through the 510(k) process on July 25, 2003. The device was considered a technology evolution and substantially equivalent to the ELI 200, Inovise’s Cardiovise Interpretive Software, and Hewlett Packard’s 1514A ECG/Phono System.

The FDA 510(k) notification of clearance to market the Eli 200+ Audicor included the following indications for use:

- The device is indicated for use to acquire, analyze, display and print ECG and heart sound data (COR).
- The device is indicated for use to provide interpretation of the data for consideration by physicians.
- The device is indicated for use in a clinical setting by a physician or by trained personnel and is not intended as a sole means of diagnosis.
- The interpretations of ECG and heart sound data (COR) offered by the device are only significant when used in conjunction with physician over-read as well as consideration of all other relevant patient data.
- The device is intended for use on adult populations, typically symptomatic.
- The device is not intended to be used as a vital signs physiological monitor.
- The device is intended for evaluation of cardiac conditions such as left ventricular hypertrophy (LVH), acute and age-undetermined myocardial infarction (MI), and detection of S3 and S4 heart sounds.

On October 31, 2003, the Audicor Upgrade System received FDA clearance as a Class II device through the 510(k) process. The Audicor Upgrade System is an add-on device used with Audicor Sensors in the V3 and V4 positions on the chest wall. The system consists of a pocket personal computer (PC) with proprietary software and can be used with several models of existing electrocardiographs to allow physicians access to the COR report, including graphical display of MI and LVH conditions, display of heart sound waveforms, and identification of S3 and S4 heart sounds.

The Zargis Acoustic Cardioscan (Zargis Medical Corporation, Princeton, NJ) received FDA approval through the 510(k) process on May 26, 2004. The system is an electronic auscultatory device intended to acquire, record, and analyze heart sounds. The system consists of an electronic stethoscope, notebook computer, software, printer and an isolation transformer. According to the FDA indications for use, the device acquires and records the acoustic signals of the heart and analyses these signals. The analysis procedure will identify specific heart sounds that may be present, including S1, S2, and suspected murmurs. The approval lists the Audicor system as a predicate device.

**Literature Review**
Published studies have evaluated the use of Cardiovise diagnostic software, a predicate device and component of the Audicor System, for the detection of acute and prior MI (Wagner, et al., 2002; Andresen, et al., 2002). Published studies involving the Audicor system or correlated audioelectric cardiography are limited.

Erne et al. (2017) conducted a prospective cohort study with the aim to investigate whether acoustic cardiography (AUDICOR® 200) immediately post-ECV might provide indices for AF relapse following cardioversion. Acoustic cardiography parameters included Electromechanical Activation Time (EMAT), Left Ventricular Systolic Time (LVST), QRS duration, heart rate and third heart sound intensity (S3 Strength). Data was analyzed from 140 patients who underwent successful cardioversion and in whom AUDICOR results and echocardiographic measurements immediately after (baseline) ECV were available. Patients were followed-up at 4-6 weeks, 3 and 12 months post-ECV, and sinus rhythm maintenance was evaluated using acousticcardiography and Holter electrocardiography. The effect of each baseline AUDICOR parameter on the hazard of AF relapse was investigated using Cox proportional hazards (PH) models. Fifty patients (35.7%) had AF relapse. Of all the AUDICOR parameters, only S3 Strength exhibited consistent predictive value. Increasing S3 Strength increased the hazard of relapse in a univariable Cox PH model (HR=2.52, p=0.003), and in two multivariable Cox PH model constructions (Model I excluded heart rate and Model II excluded EMAT/RR, LVST and LVST/RR) both of which included the parameters as continuous variables (Model I: HR=1.15, p=0.042; Model II: HR=1.14, p=0.045) or the parameters dichotomized according to suggested cut-points (Model I: HR=2.5, p=0.007; Model II: HR=2.09, p=0.031). The study was limited by small size and the lack of randomization.

Wang et al. (2016) reported on results of a prospective cohort study of 474 patients with heart failure (HF) presenting to the emergency department (ED) with dyspnea (n=995). The study also evaluated the impact on patient prognosis. ED physicians who were initially blinded to all laboratory and acoustic cardiography results estimated the probability of acute decompensated heart failure on a scale of 0% to 100% on a visual analog scale. The visual analog scale was repeated after acoustic cardiography results were provided. Patients were followed for 90 days to determine the relationship of the S3 to adverse events. The initial sensitivity, specificity, and accuracy for acute decompensated heart failure as a possible diagnosis were 89.0%, 58.2%, and 71.0%, respectively. Sensitivity, specificity, and accuracy for acoustic cardiography were 40.2%, 88.5%, and

Collins et al. (2009) conducted a multisite study to evaluate the effect of an S3 captured by acoustic cardiography on diagnostic accuracy and confidence in the diagnosis of acute decompensated heart failure in patients presenting to the emergency department (ED) with dyspnea (n=995). The study also evaluated the impact on patient prognosis. ED physicians who were initially blinded to all laboratory and acoustic cardiography results estimated the probability of acute decompensated heart failure on a scale of 0% to 100% on a visual analog scale. The visual analog scale was repeated after acoustic cardiography results were provided. Patients were followed for 90 days to determine the relationship of the S3 to adverse events. The initial sensitivity, specificity, and accuracy for acute decompensated heart failure as a possible diagnosis were 89.0%, 58.2%, and 71.0%, respectively. Sensitivity, specificity, and accuracy for acoustic cardiography were 40.2%, 88.5%, and
68%, respectively. The authors concluded that acoustic cardiography S3 was specific to acute decompensated heart failure, but did not improve diagnostic accuracy, primarily because of the low sensitivity. In addition, the acoustic cardiography S3 provided no significant independent prognostic information.

Maisel et al. (2011) conducted a secondary analysis of the Collins study (2009) to determine if the strength of the S3 can provide diagnostic prognostic information in problematic heart failure subgroups. The analysis included dyspneic ED patients older than age 40 who were not on dialysis. A gold standard acute heart failure diagnosis was determined by two cardiologists who were blinded to acoustic cardiography results. In the 995 enrolled patients, S3 strength was a significant prognosticator in univariate analysis for adverse events. When results were incorporated into the multivariable analysis in stepwise fashion, however, it was not as predictive as other variables, such as B-type natriuretic peptide (BNP) values and ST-depression on ECG. In the subgroup of patients with “gray zone” BNP levels, acoustic cardiography increased diagnostic accuracy of acute heart failure (AHF) from 47% to 69%. Acoustic cardiography also improved S3 detection sensitivity in obese patients compared to auscultation. The authors stated that although acoustic cardiography appears to augment the use of BNP, particularly in problematic subgroups, there were limitations to the study, including the fact that the true diagnostic characteristics when used in real time are unknown, due to the retrospective nature of the study and limited data availability. In addition, cardiologists making the AHF diagnosis were not blinded to BNP results, which would have impacted the diagnosis.

Collins et al. (2006) evaluated the use of an S3 heart sound combined with B-type natriuretic peptide (BNP) levels in the diagnosis of emergency room patients with dyspnea (n=439). The author concluded that an S3 sound is highly specific for heart failure and is ideally suited for use in combination with BNP to improve diagnostic accuracy. The sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy of the electronic S3 for primary heart failure were 34%, 93%, 66%, 7%, and 70%, respectively. The values obtained by physician auscultation were 16%, 97%, 84%, 3%, and 66%, respectively. The addition of an Audicor S3 to intermediate BNP levels improved the positive likelihood ratio from 1.3 to 2.9 and improved the positive predictive value from 53% to 80%. The overall ER misdiagnosis rate was 14%. Of the 48 cases, 44 were a failure to diagnose heart failure when it was present. If the Audicor had been used as the sole diagnostic tool among these 44 ultimately considered to have primary HF, 15 would have been correctly diagnosed. Similarly, if the Audicor tool had been used as the sole diagnostic tool, 14 of the 206 patients correctly diagnosed as nonprimary HF would have been incorrectly diagnosed as primary HF. Although the evaluation of S3 heart sounds in combination with BNP testing may improve diagnostic accuracy in patients with dyspnea of unclear etiology, this study does not demonstrate that the Audicor system provides a benefit, when used alone or in combination with other tests, in terms of improved clinical outcomes.

Marcus et al. (2006) conducted a prospective study to determine the diagnostic test characteristics of the S3 and S4 heart sounds for prediction of left ventricular dysfunction using the Audicor system in patients undergoing elective left-sided heart catheterization (n=90). Patients underwent computerized heart sound phonocardiographic analysis (Audicor system) for assessment of S3/S4 heart sounds, cardiac catheterization for assessment of left ventricular end-diastolic pressure (LVEDP), transthoracic echocardiography for evaluation of left ventricular ejection fraction (LVEF), and blood sampling for BNP. Mean LVEDP was significantly elevated; LVEF was reduced; and median BNP was elevated in those with an S3, S4, or both, compared to patients without a diastolic heart sound. The sensitivities of these heart sounds to detect an elevated LVEDP, reduced LVEF, or elevated BNP were 41%, 52%, 32% for an S3, and 46%, 43%, and 40% for an S4, respectively. The authors concluded that neither the phonocardiographic S3 nor the S4 is a sensitive marker of left ventricular dysfunction. The absence of an S3 or S4 using phonocardiographic testing (Audicor system) is therefore not sufficient to exclude ventricular dysfunction. If present, the phonocardiographic S3 and S4 are specific for an elevated LVEDP, depressed LVEF, and elevated BNP level.

Professional Societies/Organizations

American College of Cardiology/American Heart Association (ACC/AHA): ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (O’Gara, et al., 2013) and do not include the use correlated audioelectric cardiography or acoustic heart sounds as a diagnostic tool.

The ACC/AHA Guideline for the Diagnosis and Management of Chronic Heart Failure in the Adult (Yancy, et al., 2013; Yancy, et al., 2017) notes that other options for diagnostic evaluation of patients with suspected acutely
decompensated HF, such as acoustic cardiography, bioimpedance vector monitoring, or noninvasive cardiac output monitoring are not yet validated.

In addition, this technology is not mentioned in AHA/ACC Recommendations for the Standardization and Interpretation of the Electrocardiogram, Part I (Kligfield, et al., 2007) and II (Mason, et al., 2007).

**American Heart Association (AHA):** The AHA scientific statement, Acute Heart Failure Syndromes: Emergency Department Presentation, Treatment, and Disposition: Current Approaches and Future Aims, includes a discussion of focused areas for future investigation. The authors note that the search for additional tools to improve the diagnostic accuracy for patients with undifferentiated dyspnea and possible acute heart failure syndromes remains a high priority. Electronic detection of third heart sounds (S₃) using acoustic cardiography is included among several tools that have been investigated as both stand-alone and adjunct diagnostic measures, but appear to provide little benefit over existing approaches (Weintraub et al., 2010).

**Centers for Medicare & Medicaid Services (CMS)**
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCDs found.

**Use Outside of the US**

**Australian and New Zealand Horizon Scanning Network ([ANZHSN], 2010):** A Horizon Scanning Technology Prioritizing Summary notes that although comparative evidence indicated that the adjunctive use of acoustic cardiography may be of benefit in the diagnosis of heart failure, the application of this technology in the acute setting was considered impractical.

**References**


A peripheral venous catheter is most commonly used for venous access. Traditional techniques for determining the location of a peripheral vein includes palpatting the skin, and unaided visualization of the skin in ambient light (Perry, 2011). Use of a near-infrared imaging system has been proposed as an alternative method to aid in visualization of the superficial vasculature. The imaging system provides a display of peripheral vasculature in real-time. It is purported to reduce the number of intravenous (IV) attempts, reduce the time it takes to initiate an IV and improve patient satisfaction (Christie Medical, 2013).

U.S. Food and Drug Administration (FDA): The VTS1000 Liquid Crystal Vein Locator (VueTek Scientific™, LLC, Gray, MN) received 510 (k) approval on Feb 18, 2011. The VTS1000 is a noninvasive electronic device to aid in the visualization of superficial vasculature. According to the 510(k) summary it is indicated for use during procedures requiring vascular or peripheral vascular access.
Literature Review

Rothbart et al. (2015) reported on a retrospective study of that examined the use of Accuvein® AV300 vein viewer used to facilitate venous cannulation in children. The study included 238 consecutive pediatric patients preceding surgical interventions. The subjects were allocated to groups [control group (124 patients) and intervention group (114 patients)] in a non-random way - randomization was not feasible because data was acquired retrospectively. In control group, peripheral IV cannulation was performed without supporting device, in intervention group with support of AV300. Time and number of attempts until successful venous cannulation were defined as primary end points. The study found that the median time until successful cannulation was 2 min (range 0.1-20, quartiles: 25%: 1; 75%: 5) in the intervention group and 1 min (range 0.1-18, quartiles: 25%: 0.2; 75%: 2) in the control group (p< 0.01). Median number of attempts was higher in the intervention group (2; range 1-6, quartiles: 25%: 1; 75%: 3) than in the control group (1; range 1-6, quartiles: 25%: 1; 75%: 2, p < 0.01). The rate of cannulations successful at first attempt was 0.45 (51 of 114, 95% CI 0.35-0.54) in the intervention group and 0.73 (90 of 124, 95% CI 0.65-0.81) in the control group (p< 0.01). The authors concluded that they were not able to reduce neither time nor number of attempts until a successful venous cannulation in children using the vein viewer and that laser-supported cannulation cannot be recommended for standard procedures. The study was limited with the lack of randomization.

Van der Woude et al. (2013) reported results of a pragmatic cluster randomized controlled clinical trial using the VascuLuminator in a population of children with dark skin color requiring intravenous (IV) cannulation in the operating room. Eighty-eight patients were included in the study (control, n=45; VascuLuminator, n=43). The availability of the VascuLuminator to anesthesiologists at the operating complex was randomized by computer in clusters of one week. In the VascuLuminator group IV cannulation was aided by the device, whereas the device was not available at the operating room in the control group. Success at first attempt was not significant between the two groups (p=0.27). Median time to successful cannulation was not significant between groups (p=.54). In the subgroup of children a priori anticipated to be difficult to cannulate (i.e., “hard” or “very hard”), there was a trend to higher success at first attempt in the VascuLuminator group (p = 0.03). The authors noted data suggest limited value of the VascuLuminator in facilitating IV cannulation in a subgroup of children with dark skin color who are anticipated to be difficult to cannulate.

Kim et al. (2012) evaluated a group of 111 children who were randomized into one of the two groups (VienViewer, n=54) or control (n=57). There was no significant difference in the overall first attempt success rate using the VeinViewer compared with control (p=0.526). There was no significant difference between the groups for easy (p=0.485), or difficult patients (p=0.026). Limitations to the study cited by the authors included that the procedural time was analyzed only in patients with successful venous access on the first attempt because the time interval after the first failed attempt varied according to the operator and the situation. Further, the amount of training and practice to attain proficiency with the VeinViewer has not been established.

Phipps et al. (2012) randomized 115 preterm and term neonates undergoing placement of peripherally inserted central catheters by use of VeinViewer (n=59) or standard techniques (n=56). Overall, there was a trend to more successful placement using VeinViewer, but no statistical significance (p=0.08). When analysis was limited to the first attempt at cannulation no differences between the two techniques were found (p=0.55). Additionally, infants randomized to the VeinViewer were more mature (30±2 weeks gestational age (GA) versus 28±2 weeks GA; p=0.08). Study limitations included lack of blinding regarding use of VeinViewer compared with standard techniques. Larger studies are needed to demonstrate the effectiveness of this device over standard techniques for attaining peripheral venous access.

Chapman et al. (2011) reported results of a prospective, randomized study of children aged 0 to 17 who required nonemergent peripheral intravenous (PIV) catheter placement. Participants were randomized to standard PIV cannulation or PIV cannulation with the VeinViewer (Christie Medical Holdings, Cypress, CA, formerly Luminetx, Memphis, TN). The primary outcome measure was time to PIV placement. Secondary outcome measures included number of PIV attempts and pain scores as reported by the child, parent or guardian and nurse. A total of 323 patients completed the study. No differences in time to PIV placement, number of PIV attempts or pain scores was noted for the overall study group. However, a planned subgroup analysis of children aged 0 to 2 (n=107) did yield significant results for time to PIV placement (p<0.047), and for nurses’ perception of pain (p=0.01). Data did not support improvement in outcomes for the total study group. Additional randomized
controlled trials (RCT) should be conducted to determine the role of this device for evaluation of potential access sites.

Perry et al. (2011) conducted a prospective RCT to determine whether the use of a near-infrared light venipuncture aid (VeinViewer, Christie Medical Holdings, Cypress, CA, formerly Luminetx, Memphis, TN) would improve the rate of successful first-attempt placement of intravenous (IV) catheters in a high-volume pediatric emergency department (ED). One hundred twenty-three patients were randomized to use of the device (n=62) or the traditional technique of palpation of the overlying skin and unaided visualization of peripheral veins for IV access using only ambient room light (n=61). If a vein could not be cannulated after three attempts, patients crossed over from one study arm to the other, and study nurses attempted placement with the alternative technique. The primary end point was first-attempt success rate for intravenous (IV) catheter placement. After completion of patient enrollment, a questionnaire was completed by study nurses as a qualitative assessment of the device. There was no significant difference in first-attempt success rate between the standard and device groups. Of the 19 study nurses, 14 completed the questionnaire. Seventy percent expressed neutral or unfavorable assessments of the device in nondehydrated patients. Ninety percent of nurses found the device a helpful tool for patients in whom IV access was difficult. Additional RCTs with large patient populations should be conducted to demonstrate the role of the device in these patients.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCDs found.

Use Outside of the US
No relevant information.

Reference

Endothelial Function Assessment (CPT Code 93998)
The endothelium helps to regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation. Alteration in endothelial function precedes the development of morphological atherosclerotic changes and can also contribute to lesion development and later clinical complications (Deanfield, 2007). Noninvasive endothelial function assessment has been proposed as a means to predict the risk of atherosclerosis and cardiovascular disease.

One method involves measurement of the brachial diameter before and after an increase in shear stress induced by reactive hyperemia or flow-mediated dilation (FMD). Special probes that have pneumoelectrical tubing that connect to a computer are placed in an arm stabilizer and the index finger is placed in a probe. A sphygmonanometer cuff is placed on the forearm distal to the brachial artery, inflated and released for a timed
period. This is repeated with higher pressures used to mimic occlusion. Finally the pressures are measured five minutes after the pressure is released. FMD occurs as a result of local endothelial release of nitrous oxide. The information is evaluated by proprietary software and a score indicating the endothelial health is generated. Digital peripheral arterial tonometry (PAT) quantifies reactive hyperemia-induced changes in pulse volume amplitude (PVA) in the finger tip, and is an automated method to non-invasively assess endothelial function (Lee, 2012). According to the manufacturer, EndoPAT™ measures several vascular beds, composed of small vessels and microcirculation. The manufacturer also notes the EndoPAT™ corrects for systemic changes by a simultaneous measurement from the (un-occluded) contra-lateral arm.

U.S. Food and Drug Administration (FDA): The Endo PAT 2000 device (Itamar Medical, Inc., Framingham, MA) received 510(k) approval in November 2003. According to the approval summary it is a non-invasive device, intended for use as a diagnostic aid in the detection of coronary artery endothelial dysfunction (positive or negative) using a reactive hyperemia procedure. The summary also notes "The Endo PAT 2000 has been shown to be predictive of coronary artery endothelial dysfunction in the following patient population: patients with signs or symptoms of ischemic heart disease, who are indicated for coronary artery angiography, but who lack angiographic evidence of obstructive coronary artery disease. The device is intended to be used in a hospital or clinic environment by competent health professionals. The Endo PAT 2000 device is not intended for use as a screening test in the general patient population. It is intended to supplement, not substitute, the physician's decision-making process. It should be used in conjunction with knowledge of the patient’s history and other clinical findings."

The CVProfilor® System, Cardiovascular Profiling System, original applicant Hypertension Diagnostics, Inc. (Eagan, MN) received 510(k) approval (K001948) from the FDA in November, 2000 as a Class II device for the noninvasive measurement of blood pressure and pulse rate. According to the summary "It is classified as a noninvasive blood pressure measurement system providing a signal from which systolic, diastolic, mean, or any combination of the three pressures can be derived through the use of transducers placed on the surface of the body."

Literature Review
Randomized controlled clinical trial data are lacking to demonstrate the clinical utility and effectiveness of endothelial function assessment to predict cardiovascular risk. The majority of studies in the published peer-reviewed literature are prospective cohorts.

Weisrock et al. (2017) conducted a prospective cohort study that evaluated the test-retest reliability of pulse amplitude tonometry (PAT), as a non-invasive way to assess endothelial dysfunction, using the natural logarithmic transformed reactive hyperaemia index (LnRHI). The cohort consisted of 91 patients divided into four groups: heart failure with preserved ejection fraction (HFpEF) (n=25); heart failure with reduced ejection fraction (HFrEF) (n=22); diabetic nephropathy (n=21); and arterial hypertension (n=23). All subjects underwent two separate PAT measurements at a median interval of seven days (range 4-14 days). LnRHI derived by PAT showed good reliability in subjects with diabetic nephropathy (intra-class correlation (ICC) = 0.863) and satisfactory reliability in patients with both HFpEF (ICC = 0.557) and HFrEF (ICC = 0.576). However, in subjects with arterial hypertension, reliability was poor (ICC = 0.125). It appeared that PAT may be a reliable technique to assess endothelial dysfunction in adults with diabetic nephropathy, HFpEF or HFrEF. However, for those with arterial hypertension, the study did not find sufficient reliability, which can possibly be attributed to variations in heart rate and the respective time of the assessments. The study was limited by the lack of randomization, and the sample size of subjects in each group.

Hayes published a technology directory report on peripheral arterial tonometry (PAT), a noninvasive device intended for the evaluation of endothelial dysfunction using indirect measurement of induced reactive hyperemia (RH) (Hayes, 2014; 2017). The review included ten peer-reviewed cross-sectional or prospective cohort studies evaluating RH-PAT, with sample size of 60 to 238 patients. Six studies investigated RH-PAT for: detecting coronary endothelial dysfunction in patients without CAD (one study), for detecting myocardial ischemia in a RH-PAT exercise test (one study), and for detecting or characterizing CAD (four studies). Four studies investigated RH-PAT for predicting cardiovascular adverse events following a surgical procedure. The results varied across studies and applications due to heterogeneity in patient selection criteria, applications, reference standards, and cut-off values. There were no studies evaluating the impact of the use of RH-PAT on health outcomes. The
report concluded that evidence evaluating the clinical validity of reactive hyperemia peripheral arterial tonometry is insufficient to determine its value in the evaluation of coronary artery disease or to predict cardiovascular adverse events.

van den Heuvel et al. (2017) reported on a study of 93 patients to examine the applicability of PAT to detect a low risk of coronary artery disease (CAD) in a chest pain clinic. PAT was performed resulting in reactive hyperaemia (RHI) and augmentation (AIx) indices. Patients were risk classified according to HeartScore, Diamond and Forrester pretest probability (DF), exercise testing (X-ECG), and computed tomography calcium scoring (CCS) and angiography (CTA). Correlations, risk group differences and prediction of revascularisation within 1 year were calculated. The results indicated that PAT cannot detect a low risk of CAD, possibly because RHI and AIx versus X-ECG, CCS and CTA represent independent processes.

To assess whether endothelial dysfunction, as detected by peripheral artery tonometry, can predict late cardiovascular events, Rubinshtein et al. (2010) induced reactive hyperaemia (RH) following upper arm occlusion of systolic blood pressure in 270 outpatients. The natural logarithmic scaled RH index (L_RHI) was calculated from the ratio between the digital pulse volume during RH and at baseline. Follow-up was seven years. Seven-year adverse event rate was 48% in patients with L_RHI < 0.4 vs. 28% in those with L_RHI ≥ 0.4 (p=0.03). Univariate predictors of adverse events were LRHI, advancing age, and prior coronary bypass surgery. Multivariate analysis identified L_RHI < 0.4 as an independent predictor of AE (p=0.03). Study limitations include an uncontrolled study design, and dropout rate of 17%.

Hamburg et al. (2008) reported results of a correlational cohort study of Framingham Third generation Cohort participants (n=1957). A fingertip peripheral arterial tonometry (PAT) device was used to measure digital pulse amplitude. Measurements were taken at baseline and in 30 second intervals for four minutes during reactive hyperemia induced by five minute forearm cuff occlusion. The relation of PAT ratio to cardiovascular risk factors was strongest in the 90-120 second postdeflation interval (overall model R2=0.159). To determine the relation between the hyperemic response over time following cuff deflation and clinical cardiovascular risk factors, stepwise regression models were performed for the PAT ratio for each 30 second interval with age and sex forced in, selecting from systolic blood pressure, diastolic blood pressure, heart rate, body mass index, total/HDL cholesterol, triglycerides, glucose, diabetes, current smoking, hormone replacement therapy, hypertension treatment, lipid-lowering treatment, and prevalent cardiovascular disease. The relation of PAT ratio to cardiovascular risk factors was strongest in the 90-120 second postdeflation interval (overall model R2=0.159). The authors note study findings support further investigations to define clinical utility and predictive value of digital pulse amplitude. The study was limited by uncontrolled design.

Professional Societies/Organizations

American College of Cardiology Foundation/American Heart Association (ACCF/AHA): These organizations published the 2010 Guideline for the Assessment of Cardiovascular Risk in Asymptomatic Adults. The guideline notes that it is unclear whether these measures of peripheral endothelial health provide incremental predictive information when controlling for traditional risk factors. The guideline further notes that due to the limited data available, the writing committee concluded that it was premature to recommend serial FMD measurements to monitor treatment effects. In addition, due to the technical challenges of standardizing measurement of FMD and the relatively modest evidence of incremental change in risk assessment, measurement for risk assessment was not regarded as appropriate for risk assessment in the asymptomatic adult.

American Society of Echocardiography/Society for Vascular Medicine: These societies (Roman, et al., 2006) published a report regarding the clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification. The report notes that the ability of flow-mediated endothelium-dependent brachial artery dilation to provide prognostic information in individuals at intermediate- or low-risk, independent of more standard risk-profiling approaches, remains to be identified.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCDs found.
Use Outside of the US
No relevant information.

References

Intracardiac Ischemia Monitoring System (CPT Codes 0525T, 0526T, 0527T, 0528T, 0529T, 0530T, 0531T, 0532T)
The AngelMed Guardian® system (Angel Medical Systems, Shrewsbury, NJ) is an implantable cardiac device designed to detect rapid ST segment changes that may signify coronary artery occlusion. Once an ST shift (elevation or depression) is detected, the system alerts the patient to seek medical care by delivering a series of vibratory, auditory, and visual warnings. The AngelMed Guardian System consists of three main components:
- Implantable Medical Device (IMD)
- Patient External Device (EXD)
- Programmer

The implantation procedure is similar to a pacemaker implantation procedure. The IMD is implanted in a left pectoral subcutaneous pocket and connects to a standard endocardial bipolar pacing lead, which is placed in the right ventricle. It monitors the intracardiac electrogram (ICEG) in real time to assess for ST segment changes, including ST depression and elevation. The IMD also stores ICEGs for subsequent retrieval by the programmer via wireless telemetry. The ICEG is relatively free of various noise sources that tend to confound body surface ECG recordings; because the recording electrode is within the heart itself and maintains a fixed position within the ventricle as the heart moves within the chest, the ICEG tends to not suffer from muscle noise, axis shifts, or motion artifact. Signals are transmitted wirelessly from the IMD to the patient’s EXD, which is a telemetry device that provides the patient with auditory and visual alerts if the IMD detects an excessive ST shift relative to the...
baseline ST segment, and if the ST shift exceeds a pre-programmed threshold. The Programmer is a portable computer that allows the physician to customize IMD parameters and alarm settings for each patient. It also enables the physician to retrieve and review data collected by the IMD. (Hayes, 2018).

**U.S. Food and Drug Administration (FDA):** a premarket approval was approved by the FDA April 2018 for the AngelMed Guardian System. The Guardian System is indicated for use in patients who have had prior acute coronary syndrome (ACS) events and who remain at high risk for recurrent ACS events. The Guardian System is indicated as an adjunct to patient recognized symptoms.

Contraindications of the device include that the AngelMed Guardian System should not be implanted in:

- Patients with cognitive impairment that would prevent recognition of alarms
- Patients who cannot feel the vibration from the IMD
- Patients with implanted pacemaker, implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) devices
- Patients where a pacemaker lead cannot be placed safely

The approval is based on the results of an unpublished study, ALERTS (AngelMed for Early Recognition and Treatment of STEMI) Phase II, prospective clinical trial that was intended to assess the safety and potential to reduce time to treatment, heart muscle damage and survival benefit in a large group of high-risk cardiac subjects, due to acute coronary syndrome (ACS) or prior bypass surgery. An amendment to the ALERTS trial data analysis protocol was submitted to the FDA after an initial FDA panel meeting in 2016 and the FDA approval is based in part on this additional retrospective post-hoc analysis.

**Literature Review**

There is a lack of evidence in the published peer-reviewed medical literature supporting the clinical utility of an intracardiac ischemia monitoring system for any indication. The one published study was designed to establish intracardiac ischemia monitoring feasibility and did not evaluate the AngelMed Guardian System’s efficacy to improve clinical outcomes.

Fischell et al. (2010) reported on two clinical studies of intracardiac ST-segment monitoring in ambulatory humans to alert them to significant ST-segment shifts associated with thrombotic occlusion. The study included two phase 1 clinical studies, Cardiosaver (n=20) and DETECT (n=17), that assessed device safety and feasibility. The implanted monitor continuously evaluated the patients’ ST segments sensed from a conventional pacemaker right ventricle apical lead, and alerted patients to detected ischemic events. During follow-up (median 1.52 years, range 126 to 974 days), four patients had ST-segment changes of ≥3 SDs of their normal daily range, in the absence of an elevated heart rate. This in combination with immediate hospital monitoring led to angiogram and/or intravascular ultrasonography, which confirmed thrombotic coronary occlusion/ruptured plaque. The median alarm-to-door time was 19.5 min (6, 18, 21, and 60 min, respectively). Alerting for demand-related ischemia at elevated heart rates, reflective of flow-limiting coronary obstructions, occurred in four patients. There were two false-positive ischemia alarms related to arrhythmias, and one alarm due to a programming error that did not prompt cardiac catheterization.

**Professional Societies/Organizations**

Guidelines from the American Heart Association and the American College of Cardiology do not include guidance regarding implantable cardiac intracardiac ischemia monitoring system.

**Centers for Medicare & Medicaid Services (CMS)**

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Local Coverage Determination (LCD):
- Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

**Use Outside of the US**

CE Marking for this product has been issued.
Permanent Cardiac Contractility Modulation System (CPT Codes 0408T, 0409T, 0410T, 0411T, 0412T, 0413T, 0414T, 0415T, 0416T, 0417T, 0418T, HCPCS code C1824)

Cardiac contractility modulation (CCM) is an electrical device-based approach that has been proposed for the treatment of chronic heart failure with reduced and midrange ejection fractions (EFs). The Optimizer Smart System (Impulse Dynamics, Orangeburg, New York) is a CCM device that is proposed for the treatment of moderate to severe heart failure. The system comprises of programmable OPTIMIZER Smart Implantable Pulse Generator (IPG), Model CCM X10; port plug, #2 torque wrench for securing the implanted leads

- OMNI Smart Programmer, model OMNI™ II (with OMNI Smart Software)
- OPTIMIZER Smart Charger, model Mini Charger
- Implantable leads: 2 ventricular leads and 1 atrial lead.

According to the manufacturer’s website, the Optimizer system is a device-based treatment option for the approximately seventy percent of CHF patients with advanced symptoms that have normal QRS duration and are not suitable for Cardiac Resynchronization Therapy (CRT). It is a minimally invasive implantable device designed to treat Chronic Heart Failure (CHF) in patients that are symptomatic despite appropriate medical treatment. The device is based on novel Cardiac Contractility Modulation technology, and delivers non-excitatory electric pulses. CCM signals are nonexcitatory electrical signals applied during the cardiac absolute refractory period that enhance the strength of cardiac muscular contraction (Abraham, et al., 2018).

U.S. Food and Drug Administration (FDA):
The OPTIMIZER Smart System received FDA premarket approval (PMA) March 2019. The device, which delivers Cardiac Contractility Modulation therapy, is indicated to improve 6-minute hall walk distance, quality of life, and functional status of New York Heart Association (NYHA) Class III heart failure patients who remain symptomatic despite guideline directed medical therapy, who are in normal sinus rhythm, are not indicated for Cardiac Resynchronization Therapy, and have a left ventricular ejection fraction ranging from 25% to 45%.

Literature Review
Anker et al. (2019) conducted prospective registry study with the aim to assess the longer-term impact of cardiac contractility modulation (CCM) on hospitalizations and mortality in real-world experience. The study included 140 patients with $25\% \leq \text{LVEF} \leq 45\%$ receiving CCM therapy (CCM REG25-45) for clinical indications. Cardiovascular and heart failure (HF) hospitalizations, Minnesota Living with Heart Failure Questionnaire (MLHFQ) and NYHA class were assessed over 2 years. Mortality was tracked through 3 years and compared with predictions by the Seattle Heart Failure Model (SHFM). Separate analysis was performed on patients with $35\% \leq \text{LVEF} \leq 45\%$ (CCM REG35-45) and $25\% \leq \text{LVEF} < 35\%$ (CCM REG25-34). Hospitalizations decreased by 75% (from 1.2/patient-year the year before, to 0.35/patient-year during the 2 years following CCM, $P<0.0001$) in CCM-REG25-45 and by a similar amount in CCM-REG35-45 ($P<0.0001$) and CCM-REG25-34. MLHFQ and NYHA class improved in all three cohorts, with progressive improvements over time ($P<0.002$). Three-year survival in CCM-REG25-45 (82.8%) and CCM-REG24-34 (79.4%) were similar to those predicted by SHFM (76.7%, $P=0.16$; 78.0%, $P=0.81$, respectively) and was better than predicted in CCM REG35-45 (88.0% vs. 74.7%, $P=0.046$). The limitations of the study include lack of randomization and no separate control group.

Abraham et al. (2018) conducted a randomized controlled study to confirm a subgroup analysis of the prior FIX-HF-5 (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure) study to evaluate that cardiac contractility modulation (CCM) improved exercise tolerance (ET) and quality of life in patients with ejection fractions between 25% and 45%. The study included 160 patients with NYHA functional class III or IV symptoms, QRS duration <130 ms, and ejection fraction $\geq 25\%$ and $\leq 45\%$ that were randomized to continued medical therapy (control, $n=86$) or CCM (treatment, $n=74$; 68 underwent device implantation) unblinded for 24 weeks. Peak rate of oxygen consumption (peak $V_O_2$) (primary endpoint), Minnesota Living With Heart Failure questionnaire, NYHA functional class, and 6-min hall walk were measured at baseline and at 12 and 24 weeks. Bayesian repeated measures linear modeling was used for the primary endpoint analysis with 30% borrowing from the FIX-HF-5 subgroup. Safety was assessed by the percentage of patients free of device-related adverse events with a pre-specified lower bound of 70%. The difference in peak $V_O_2$ between groups was 0.84 (95% Bayesian credible interval: 0.123 to 1.552) ml $O_2$/kg/min. Minnesota Living With Heart Failure questionnaire ($p < 0.001$), NYHA functional class ($p < 0.001$), and 6-min hall walk ($p = 0.02$) were all better in the treatment versus control group. There were seven device-related events, yielding a lower bound of 80% of patients free of events. The safety/adverse events included five events of lead dislodgements, one deep vein thrombosis, and one generator erosion resulting in pocket stimulation that required pocket revision and replacement of pacemaker leads. The composite of cardiovascular death and HF hospitalizations was reduced from 10.8% to 2.9% ($p = 0.048$). Limitation of the study include limited follow-up duration of the current study which limits the ability to evaluate the long-term effects of CCM on mortality and hospitalizations.

Müller et al. (2017) reported on a prospective, two-year, multi-site evaluation of CCM in patients with heart failure. The study included 143 subjects with heart failure and reduced ejection fraction that were followed via clinical registry for 24 months recording NYHA class, Minnesota living with heart failure questionnaire (MLWHFQ) score, 6 min walk distance, LVEF, and peak VO2 at baseline and 6 month intervals as clinically indicated. Serious adverse events, and all cause as well as cardiovascular mortality were recorded. Data are presented stratified by LVEF (all subjects, LVEF <35%, LVEF $\geq$35%). One hundred and six subjects from 24 sites completed the 24 month follow-up. Baseline parameters were similar among LVEF groups. NYHA and MLWHFQ improved in all three groups at each time point. LVEF in the entire cohort improved 2.5, 2.9, 5.0, and 4.9% at 6, 12, 18, and 24 months, respectively. Insufficient numbers of subjects had follow-up data for 6 min walk or peak VO2 assessment, precluding comparative analysis. Serious adverse events (n = 193) were observed in 91 subjects and similarly distributed between groups with LVEF <35% and LVEF $\geq$35%, and similar to other device trials for heart failure. There were 18 deaths (seven cardiovascular related) over two years. Overall survival at two years was 86.4% (95% confidence intervals: 79.3, 91.2%). The study is limited by the lack of randomization and control group.

Professional Societies/Organizations
American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Clinical Practice Guidelines and the Heart Failure Society of America (HFSA) guideline for the management of heart failure does not include the use of cardiac contractility modulation (CCM) for treatment of heart failure (Yancy, et al., 2017; Yancy, et al., 2013).

Centers for Medicare & Medicaid Services (CMS)
• National Coverage Determinations (NCD): No NCD found
• Local Coverage Determinations (LCDs): Local Coverage Determination (LCD): Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
National Institute of Health Care and Excellence (NICE): NICE published an interventional procedures guidance for cardiac contractility modulation device implantation for heart failure (NICE, 2019). The guidance includes the following recommendations:
• The evidence on cardiac contractility modulation device implantation for heart failure raises no major safety concerns. However, the evidence on efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research
• Further research should ideally be in the form of randomized controlled trials. These should report details of patient selection, duration and timing of stimulation, and duration of effect of stimulation. Outcomes should include ejection fraction, oxygen consumption, New York Heart Association classification and patient-reported outcomes, including quality of life.

European Society of Cardiology (ESC): ESC published guidelines for the diagnosis and treatment of acute and chronic heart failure (Ponikowski, et al., 2016). The guidelines note that currently, the evidence is considered insufficient to support specific guideline recommendations for other therapeutic technologies, including cardiac contractility modulation and further research is required.

References


Thoracic Electrical Bioimpedance for the Measurement of Cardiac Output (CPT code 93701)

Electrical bioimpedance (also referred to as thoracic electrical bioimpedance [TEB], transthoracic bioimpedance, plethysmography, impedance cardiography [ICG], or bioimpedance cardiography) has been investigated as a noninvasive means of providing continuous assessment of cardiac output and other hemodynamic parameters. A small electric current is applied to the chest through electrodes placed on the neck and sides of the chest. Resistance to the current (impedance) is measured through sensors also placed on the neck and sides of the chest. The pulsatile flow of blood causes fluctuations in the current, and the device calculates cardiac output from the impedance waveform. Electrical bioimpedance has been investigated in a number of different clinical settings, including hospital; ambulatory; and specialty care and for a variety of purposes including diagnosis, assessment, prognosis determination, and management (Albert, 2006).

The use of TEB has been proposed for multiple clinical purposes. These have included differentiation of cardiogenic from pulmonary causes of dyspnea, optimization of atrioventricular (AV) delay, determination of need for inotropic therapy, response to cardiac medications, identification of rejection in patients after heart transplantation, management of fluid and hemodynamics in cardiac patients, evaluate for hypotension in dialysis patients, measuring normal hemodynamic changes during pregnancy and postpartum, assessing fluid retention after major thoracic surgery and management of hypertension (San-Frutos, et al., 2011; Cagini, et al., 2011; Bayya, et al., 2011; Tonelli, et al., 2011; Wang, et al., 2006). However, there is a lack of controlled studies in the published medical literature that validate clinical applications of thoracic bioimpedance or provide comparisons to other noninvasive cardiac diagnostic techniques, such as echocardiography.
Definitive patient selection criteria for TEB have not been established due to conflicting evidence regarding the impact of cardiac output monitoring on patient management and clinical outcomes. Numerous factors may interfere with the accuracy of electrical bioimpedance measurements, including: acute lung injury; significant pulmonary edema; pleural effusion; hemothorax; chest tubes parallel to the aorta; extensive chest wall edema due to crystalloid infusions; dilatation of the aorta; severe mitral regurgitation; severe aortic regurgitation; complete bundle block during cardiopulmonary bypass; presence of a minute ventilation sensor function pacemaker; post-kidney transplant or radical cystectomy; or inability to place electrodes properly. Electrical bioimpedance measurement may also be inaccurate if the patient is moving, agitated, restless, shivering, or hyperventilating (Summers, et al., 2003).

U.S. Food and Drug Administration (FDA)
A number of electrical bioimpedance devices have been approved through the 510(k) process of the U.S. Food and Drug Administration (FDA) as Class II devices for the noninvasive monitoring of cardiac output and other hemodynamic parameters. The predicate devices upon which clearance was based are previous cardiac output monitors employing impedance plethysmography. The FDA does not necessarily require clinical data or outcome studies in making a determination of substantial equivalency for the purpose of device approval under section 510(k). There are several FDA-approved devices including, but not limited to: BioZ Portable (Model BZ-125), BioZ®.com (Model 4110), BioZ.PC (Models BZ 500 and 501) and BioZDX (Model 5100) (SonoSite, Bothell, WA); PhysioFlow® Enduro (Vasocom, Inc., Bristol, PA); Cheetah Starling™ SV(Cheetah Medical, Newton Center, MA);

Literature Review
Heart Failure (HF): The role of electrical bioimpedance in the evaluation of patients with acute heart failure syndromes is still under investigation. There are several prospective and retrospective studies that evaluated the use of electrical impedance for heart failure.
Malfatto et al. (2012) evaluated the reliability of echocardiography, brain natriuretic peptide (BNP), and thoracic electrical bioimpedance (TEB) in predicting pulmonary capillary wedge pressure (PCWP) in 29 patients (72±4 years, New York Heart Association class 3.5±0.9, ejection fraction 28%±6%) who underwent hemodynamic evaluation for worsening HF. Echocardiography was performed immediately before the hemodynamic study. During clinical stability, PCWP, plasma BNP, and TEB were simultaneously assessed. Among TEB variables, thoracic conductance (thoracic fluid content [TFC]=1/kΩ) was used. For detection of PCWP ≥15 mm Hg, TFC≥35/kΩ had high specificity (97%) and sensitivity (86%) and negative (92%) and positive (97%) predictive value, while E/E’ and BNP levels had poorer specificity. After infusion of the inodilator levosimendan, changes in TFC and PCWP were of the same order of magnitude and mutually related. The study did not provide data on the clinical impact on patient management or improved health outcome. The authors reported limitations of this study are the small number of patients included, and the single-center origin of data.

Kamath et al. (2009) studied the utility of ICG in patients hospitalized with heart failure. The BioImpedance CardioGraphy in Advanced Heart Failure study was a prospective substudy of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness. A total of 170 subjects underwent blinded ICG measurements using BioZ; of these, 82 underwent right heart catheterization. ICG was compared with invasively measured hemodynamics by simple correlation and compared overall ICG hemodynamic profiles. ICG measurements were associated with subsequent death or hospitalization within six months. There was modest correlation between ICG and invasively measured CO (r=0.4–0.6 on serial measurement). Thoracic fluid content measured by ICG was not a reliable measure of pulmonary capillary wedge pressure. There was poor agreement between ICG and invasively measured hemodynamic profiles (κ≤0.1). No ICG variable alone or in combination was associated with outcome. The authors reported that there does not appear to be specific utility for ICG in patients hospitalized with advanced heart failure.

In a cohort study, Castellanos et al. (2009) studied whether the combination of BNP and ICG could be used in a nonacute clinical setting to risk stratify and predict HF-related events in stable outpatients. Patients undergoing routine outpatient echocardiography underwent ICG and BNP testing and were followed for one year for HF-related events (emergency department visit or hospitalization due to HF or all-cause death). A total of 524 patients were analyzed, resulting in 57 HF-related events; 16 emergency department visits, 17 hospitalizations, and 24 all-cause deaths. Using Cox regression analyses, BNP and systolic time ratio index (STRI) by ICG proved to be the strongest predictors of future HF-related events. Patients with a BNP>100 pg/ml and STRI >0.45 sec-1 had a significantly lower event-free survival rate than those with a high BNP and low STRI (67%
versus 89%, \( P=0.001 \)). In patients with LV dysfunction only, if both BNP and STRI values were high, the relative risk of a HF-related event increased by 12.5 (95% C.I. 4.2–36.7), when compared with patients with a low BNP and low STRI (\( P<0.001 \)). A limitation of this study is it was performed at a single hospital with a homogenous population therefore results of the study can not be generalized to the broad population.

In the “PRospective Evaluation of Cardiac Decompensation in Patients with Heart Failure by Impedance Cardiography Test (PREDICT) Multicenter Trial,” researchers studied whether noninvasive thoracic ICG parameters could predict short-term risk, defined as all-cause death or emergency department (ED) visit or hospitalization due to worsening heart failure. Data were collected every two weeks for 26 weeks in 212 patients. A total of 29% of all patients had events. Multivariate analysis identified six clinical and ICG variables that independently predicted an event within 14 days of assessment. The clinical variables included visual analog score, New York Heart Association functional class, and systolic BP. The ICG parameters included velocity index, thoracic fluid content index, and left ventricular ejection time. The three ICG parameters combined into a composite score were a powerful predictor of an event during the next 14 days. The visits with a high-risk composite score had a 2.5 times greater likelihood, and those with a low-risk score had a 70% lower chance of a near-term event compared with visits at intermediate risk. The researchers caution that their findings are not to be used to titrate therapeutic agents or monitor their effectiveness. It is still not clear whether impedance cardiography-directed modifications improve clinical outcomes beyond that expected if physicians responded appropriately to clinical signals in the absence of ICG data. The clinical importance of these findings is currently being tested in a large-scale trial (Packer, et al., 2006).

**Hypertension:** There is limited evidence in the peer-reviewed literature to suggest that determination of hemodynamic parameters by ICG may improve blood pressure (BP) control in patients with hypertension. The studies do not address the long-term patient health outcomes with ICG monitoring. Additional studies are needed to indicate that it is the ICG determinations and not the differences in patients or the treatment algorithm that lead to lower BP (Wang, et al., 2006).

In a randomized, prospective, controlled trial (n=128), Krzesinski et al. (2012) studied the effectiveness of antihypertensive therapy based on hemodynamic assessment by impedance cardiography in patients with arterial hypertension. Patients were randomized into empiric or hemodynamic groups in which treatment choice considered impedance cardiography results. Evaluation of treatment effects was performed after 12 weeks and included office blood pressure measurement and ambulatory blood pressure monitoring. The authors reported that all final blood pressure values were lower in the hemodynamic group, significantly for office systolic blood pressure (empiric versus hemodynamic: 136.1 versus 131.6 mmHg; \( p=0.036 \)) and diastolic blood pressure (87.0 versus 83.7 mmHg; \( p=0.013 \)), as well as night-time systolic blood pressure (121.3 versus 117.2 mmHg; \( p=0.023 \)) and diastolic blood pressure (71.9 versus 68.4 mmHg; \( p=0.007 \)). Therapy based on impedance cardiography significantly increased the reduction in office systolic blood pressure (11.0 versus 17.3 mmHg; \( p=0.008 \)) and diastolic blood pressure (7.7 versus 12.2 mmHg; \( p=0.008 \)); as well as 24-hour mean systolic blood pressure (9.8 versus 14.2 mmHg; \( p=0.026 \)), day-time systolic blood pressure (10.5 versus 14.8 mmHg; \( p=0.040 \)), and night-time systolic blood pressure (7.7 versus 12.2 mmHg; \( p=0.032 \)). The reported limitation of this study is the lack of long-term patient health outcomes of ICG monitoring. Additionally, the obtained results should be applied with caution in women and in patients with significant chronic diseases since both groups were minorities in this study.

In a randomized controlled trial, the investigators for the Consideration of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels (CONTROL) study group (Smith, et al., 2006), studied whether ICG-guided treatment could aid physicians in reducing BP more effectively than standard care in a population of uncontrolled hypertensive patients receiving 1–3 medications in a primary care setting. Between November 2002 and November 2004, eleven primary care centers screened 262 patients with a diagnosis of essential hypertension, ages 18–75, on 1–3 antihypertensive medications with systolic BP 140–179 millimeters of mercury (mm Hg) and/or diastolic BP 90–109 mm Hg. Exclusion criteria were: greater than three antihypertensive medications, history of heart failure, ejection fraction < 40%, atrial fibrillation, severe valvular or renal disease, nephrotic syndrome, cirrhosis, and a cerebrovascular event within three months. Patients were also excluded if they had abnormal laboratory findings that are not further described, nor were any laboratory values reported in the study. Technical limitations of ICG also caused exclusion for height < 47 or > 75 inches, weight < 66 or > 341
pounds, hypersensitivity to sensor gel or adhesive, skin lesion at a sensor site, or the presence of activated minute-ventilation pacemaker.

One-hundred eighty-four patients were randomized in a 3:2 ratio to either standard care or ICG-guided care. After randomization, 18 patients were excluded for BP < 140/90 mm Hg upon remeasurement, and two patients withdrew early from the study. No information was provided about the method of randomization. The authors did not indicate the number of patients lost in each study arm. Each of the 164 analyzable patients in the study (95 in the standard arm and 69 in the hemodynamic arm) had a total of five study visits during which BP and ICG measurements were made. Following a baseline visit, they underwent a two-week washout period during which all antihypertensive medications were discontinued. They received a post-washout visit at which physicians prescribed medications consistent with published guidelines, their usual practice patterns, and patient clinical characteristics. This was followed by three monthly visits at which BP was measured and ICG data were obtained on all patients, but ICG findings were not revealed in the standard arm to treating physicians or patients. In the hemodynamic arm, physicians were encouraged to use, but not required to follow, a hemodynamic treatment strategy. Data are not provided on adherence to the strategy or differences in outcomes within the hemodynamic group based upon adherence. Patients in both arms were educated about medication compliance and received a follow-up phone call from a nurse between visits. ICG data were discussed with the patient by the treating physician in the hemodynamic arm only. Patients were asked how many of their prescribed pills they had taken at each visit as an estimate of compliance. The authors reported very high compliance overall, including 100% of pills taken in both arms of the trial at the fifth visit. Pill count audits were not done. Information was not provided regarding how long a patient had been under treatment for hypertension prior to study entry. A large percentage of both groups (42% of standard care group and 45% of hemodynamic care group) were on only one antihypertensive medication at baseline. At baseline, standard care patients’ BP (in mm Hg) was 147 ± 9/87 ± 10 and hemodynamic care patients’ BP was 148 ± 12/89 ± 8. After washout, standard care BP was 156 ± 13/92 ± 9 and hemodynamic care was 155 ± 13/94 ± 9. The final BP for patients in the standard care group was 136 ±15/82 ± 10, and for the hemodynamic care group the final BP was 129 ± 14/76 ± 11 (p<0.01). There were no statistically significant differences reported in any hemodynamic measures between the groups at baseline or after washout. The authors reported generalized information as to how hemodynamic data was used. Specific information as to how a particular hemodynamic measurement was used to change patient treatment was not provided. For example, “In the hemodynamic arm, the initial selection of antihypertensive medications appears to have been influenced by the hemodynamic data, because these patients were more likely to be prescribed a vasodilating agent to reduce systemic vascular resistance (SVR) index,” and “the hemodynamic treatment strategy influenced medication use when SVR index was considered high, because patients in the hemodynamic arm were more likely to have received an angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blocker (ARB), or calcium channel blocker (CCB), as was suggested. This study does not address the long-term patient health outcomes of ICG use in uncontrolled hypertensive patients.

**Dyspnea:** Limited evidence is available that evaluates the clinical impact on patient management and/or improved health outcomes from the use of electrical bioimpedance monitoring for differentiation of cardiogenic from pulmonary causes of acute dyspnea. Well-designed controlled studies are needed to establish the value of ICG in assessing patients with dyspnea.

In a prospective study, Lo et al. (2007) compared ICG results in differentiating cardiac from noncardiac causes of dyspnea to ED physician diagnoses. A total of 52 patients were included in the study. Compared with the final diagnoses, the overall diagnostic accuracy for ED physicians was 69% (36/52) versus 83% (43/52) for ICG. ED physicians diagnosed 13 of 20 patients correctly with a final diagnosis of cardiac-caused dyspnea, and 23 of 32 for noncardiac-caused dyspnea. If the ED physician diagnosed both cardiac and noncardiac causes in the same patient, the authors favored diagnosis by ED physicians according to the treatment at the ED. ICG correctly diagnosed 15 of 20 patients with cardiac cause, and 28 of 32 with noncardiac cause. The authors reported that ICG had superior sensitivity (75%/60%), specificity (88%/66%), positive predictive value (79%/52%), and negative predictive value (85%/72%) over ED physicians, respectively, in the final diagnosis of cardiac versus noncardiac causes of dyspnea. The reported limitations of this study include a small sample size and retrospective criteria for ICG diagnosis. The authors stated that a prospective trial is needed to provide greater confidence in which hemodynamic parameters of ICG have the greatest value in assessing patients in the ED.
In a prospective study, Peacock et al. (2006) studied the rate of change in diagnosis and therapy resulting from the availability of ICG data during the initial evaluation of ED patients 65 years of age or older presenting with dyspnea. Eighty-nine patients were enrolled. Congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) were the most common final diagnoses, occurring in 43 (48%), and 20 (22%), respectively. ICG data changed the working diagnosis in 12 (13%) and medications administered in 35 (39%). The authors reported that it is possible that a physician had the right diagnosis and treatment plan before reviewing ICG results and that ICG data resulted in inappropriate therapies. The authors stated a larger outcomes-based study is needed.

Ischemic Heart Disease: Gujjar et al (2010) compared cardiac output (CO) measured by TEB with that measured by multi-gated radionuclide equilibrium cardiography (RNEC). A total of 32 patients with proven or suspected ischemic heart disease, but without overt cardiac failure, edema or arrhythmias were studied. Reported limitations are that this study was restricted to outpatients with relatively well preserved cardiac functions. Hence the comparison may not be generalized to other clinical situations. Additionally, the percentage error of 42% is moderately higher than an acceptable 30% recommended for such studies comparing physiologic measurements by two different methods. The authors reported that this comparative study found a moderate correlation between TEB and RNEC methods of CO measurement. They stated that further studies are needed to examine the relative utility of TEB in comparison with RNEC as well as other methods of CO measurement before considering its use in patients with ischemic heart disease.

Optimization of AV Delay: Adjustment of AV delay has been proposed as a means of improving cardiac output in patients with dual chamber pacemakers and heart failure. Studies have not identified an optimal AV delay in patients with heart failure. Therefore, it is difficult to know the significance of the reported correlation between echocardiographic and ICG determination measurements of cardiac output. Studies that support the beneficial long-term health outcomes using ICG data have not been performed (Wang, et al., 2006, Jordan, et al., 2002).

In a descriptive study, Heinroth et al. (2007) presented data from the routine use of ICG-based cardiac output measurements to guide the optimization of AV- and interventricular (VV)-interval timing of cardiac resynchronization therapy (CRT) devices. Forty-six patients with heart failure (left ventricular ejection fraction <35%, New York Heart Association [NYHA] III–IV) and left bundle branch block (>130 milliseconds [ms]) in sinus rhythm were evaluated 3–5 days after implantation of a CRT device by means of ICG. Cardiac output was measured without pacing and with biventricular pacing using a standard protocol of VV- and AV-interval modification from -60 to +60 ms and 80–140 ms, respectively, in 20 ms steps. Mean CO without pacing was 3.66 ± 0.85 L/min and significantly increased to 4.40 ± 1.1 L/min (p<0.05) with simultaneous biventricular pacing and an AV interval of 120 ms. ’Optimizing’ both VV and AV intervals further increased cardiac output to 4.86 ± 1.1 L/min (p<0.05). Maximum cardiac output was measured in most patients with left ventricular pre-excitation. The proportion of nonresponders to CRT was reduced by 56% following AV- and VV-interval modification using ICG guidance. The authors reported that further work is needed to determine the utility of ICG-derived data in combining AV and VV intervals to ideally suit any given patient.

Rejection in Patients after Heart Transplantation: ICG in conjunction with endomyocardial biopsy for detection of rejection in patients after heart transplantation has been proposed. Preliminary findings in a case series study of 35 patients (Weinhold, et al., 1993) with heart transplants reported that a decrease in acceleration index was 71% sensitive and 100% specific for rejection. The study did not provide data on the clinical impact on patient management or improved health outcome after treatment. No other study has confirmed these preliminary findings (Wang, et al., 2006; Jordan, et al., 2002).

Professional Societies/Organizations
American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Clinical Practice Guidelines and the Heart Failure Society of America (HFSA) guideline for the management of heart failure states that other options for diagnostic evaluation of patients with suspected acutely decompensated heart failure, such as noninvasive cardiac output monitoring are not yet validated (Yancy, et al., 2013). The 2017 focused updated of the ACCF/AHA/HFSA Guideline for the Management of Heart Failure does not address thoracic electrical bioimpedance for the measurement of cardiac output (Yancy, et al., 2017).

Centers for Medicare & Medicaid Services (CMS)
• National Coverage Determinations (NCDs): National Coverage Determination (NCD) for Cardiac Output Monitoring by Thoracic Electrical Bioimpedance (TEB) (20.16), November 2006. The Coverage Policy is broader in scope than the NCD. Refer to the CMS NCD table of contents link in the reference section.

• Local Coverage Determinations (LCDs): No LCDs found.

Use Outside of the US

European Society of Cardiology (ESC): The 2012 European Society of Cardiology (ESC) guideline for the diagnosis and treatment of acute and chronic heart failure states, “Management adapted in response to monitoring thoracic impedance (as an indirect measure of intrathoracic fluid) has not been shown to improve outcomes. The optimum approach to non-invasive remote monitoring is uncertain, and RCTs performed to date have given inconsistent results and do not yet support a guideline recommendation” (McMurray, et al., 2012). ESC published guidelines for the diagnosis and treatment of acute and chronic heart failure (Ponikowski, et al., 2016). The 2016 ESC guideline for the diagnosis and treatment of acute and chronic heart failure does not address thoracic electrical bioimpedance for the measurement of cardiac output (Ponikowski, et al., 2016).

References
7. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al.; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012 Jul;33(14):1787-847.

Coding/Billing Information Cardiovascular

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Cardiovascular Services Considered Experimental/Investigational/Unproven:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>33289</td>
<td>Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision and interpretation, and pulmonary artery angiography, when performed.</td>
<td></td>
</tr>
<tr>
<td>34717</td>
<td>Endovascular repair of iliac artery at the time of aorto-iliac artery endograft placement by deployment of an iliac branched endograft including pre-procedure sizing and device selection, all ipsilateral selective iliac artery catheterization(s), all associated radiological supervision and interpretation, and all endograft extension(s) proximally to the aortic bifurcation and distally in the internal iliac, external iliac, and common femoral artery(ies), and treatment zone angioplasty/stenting, when performed, for rupture or other than rupture (eg, for aneurysm, pseudoaneurysm, dissection, arteriovenous malformation, penetrating ulcer, traumatic disruption), unilateral (List separately in addition to code for primary procedure)</td>
<td></td>
</tr>
<tr>
<td>34718</td>
<td>Endovascular repair of iliac artery, not associated with placement of an aorto-iliac artery endograft at the same session, by deployment of an iliac branched endograft, including pre-procedure sizing and device selection, all ipsilateral selective iliac artery catheterization(s), all associated radiological supervision and interpretation, and all endograft extension(s) proximally to the aortic bifurcation and</td>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>34839</td>
<td>Physician planning of a patient-specific fenestrated visceral aortic endograft requiring a minimum of 90 minutes of physician time</td>
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<tr>
<td>34841</td>
<td>Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)</td>
<td></td>
</tr>
<tr>
<td>34842</td>
<td>Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery]s)</td>
<td></td>
</tr>
<tr>
<td>34843</td>
<td>Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery]s)</td>
<td></td>
</tr>
<tr>
<td>34844</td>
<td>Endovascular repair of visceral aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) by deployment of a fenestrated visceral aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery]s)</td>
<td></td>
</tr>
<tr>
<td>34845</td>
<td>Endovascular repair of visceral aorta and infrarenal abdominal aorta (eg, aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including one visceral artery endoprosthesis (superior mesenteric, celiac or renal artery)</td>
<td></td>
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<tr>
<td>Code</td>
<td>Description</td>
<td>Considered</td>
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<tr>
<td>34846</td>
<td>Endovascular repair of visceral aorta and infrarenal abdominal aorta (e.g., aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including two visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])</td>
<td>Medical Coverage Policy: 0504</td>
</tr>
<tr>
<td>34847</td>
<td>Endovascular repair of visceral aorta and infrarenal abdominal aorta (e.g., aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including three visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])</td>
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</tr>
<tr>
<td>34848</td>
<td>Endovascular repair of visceral aorta and infrarenal abdominal aorta (e.g., aneurysm, pseudoaneurysm, dissection, penetrating ulcer, intramural hematoma, or traumatic disruption) with a fenestrated visceral aortic endograft and concomitant unibody or modular infrarenal aortic endograft and all associated radiological supervision and interpretation, including target zone angioplasty, when performed; including four or more visceral artery endoprostheses (superior mesenteric, celiac and/or renal artery[s])</td>
<td></td>
</tr>
<tr>
<td>93264</td>
<td>Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional</td>
<td></td>
</tr>
<tr>
<td>93701</td>
<td>Biopolar-field-derived physiologic cardiovascular analysis</td>
<td>Medical Coverage Policy: 0504</td>
</tr>
<tr>
<td>93799</td>
<td>Unlisted cardiovascular service or procedure</td>
<td>Experimental/Investigational/Unproven when used to report acoustic cardiography</td>
</tr>
<tr>
<td>93998</td>
<td>Unlisted noninvasive vascular diagnostic study</td>
<td>Experimental/Investigational/Unproven when used to report unilateral or bilateral endothelial function assessments, using peripheral vascular response to reactive hyperemia, noninvasive (e.g., brachial artery ultrasound, peripheral artery tonometry)</td>
</tr>
<tr>
<td>99199</td>
<td>Unlisted special service, procedure or report</td>
<td>Experimental/Investigational/Unproven when used to report near-infrared guidance for vascular access</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>0254T</td>
<td>Endovascular repair of iliac artery bifurcation (e.g., aneurysm, pseudoaneurysm, arteriovenous malformation, trauma, dissection) using bifurcated endograft from the common iliac artery into both the external and internal iliac artery, including all selective and/or nonselective catheterization(s) required for device placement and all associated radiological supervision and interpretation, unilateral (Code deleted 12/31/2019)</td>
<td></td>
</tr>
<tr>
<td>0266T</td>
<td>Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intraoperative interrogation, programming, and repositioning, when performed)</td>
<td></td>
</tr>
<tr>
<td>0267T</td>
<td>Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intraoperative interrogation, programming and repositioning, when performed)</td>
<td></td>
</tr>
<tr>
<td>0268T</td>
<td>Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intraoperative interrogation, programming, and repositioning, when performed)</td>
<td></td>
</tr>
<tr>
<td>0269T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intraoperative interrogation, programming, and repositioning, when performed)</td>
<td></td>
</tr>
<tr>
<td>0270T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intraoperative interrogation, programming, and repositioning, when performed)</td>
<td></td>
</tr>
<tr>
<td>0271T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intraoperative interrogation, programming, and repositioning, when performed)</td>
<td></td>
</tr>
<tr>
<td>0272T</td>
<td>Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day);</td>
<td></td>
</tr>
<tr>
<td>0273T</td>
<td>Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway</td>
<td></td>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>0408T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes</td>
<td></td>
</tr>
<tr>
<td>0409T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only</td>
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<tr>
<td>0410T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only</td>
<td></td>
</tr>
<tr>
<td>0411T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only</td>
<td></td>
</tr>
<tr>
<td>0412T</td>
<td>Removal of permanent cardiac contractility modulation system; pulse generator only</td>
<td></td>
</tr>
<tr>
<td>0413T</td>
<td>Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)</td>
<td></td>
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<tr>
<td>0414T</td>
<td>Removal and replacement of permanent cardiac contractility modulation system pulse generator only</td>
<td></td>
</tr>
<tr>
<td>0415T</td>
<td>Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)</td>
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<tr>
<td>0416T</td>
<td>Relocation of skin pocket for implanted cardiac contractility modulation pulse generator</td>
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</tr>
<tr>
<td>0417T</td>
<td>Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system</td>
<td></td>
</tr>
<tr>
<td>0418T</td>
<td>Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter; implantable cardiac contractility modulation system</td>
<td></td>
</tr>
<tr>
<td>0525T</td>
<td>Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; complete system (electrode and implantable monitor)</td>
<td></td>
</tr>
<tr>
<td>0526T</td>
<td>Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; electrode only</td>
<td></td>
</tr>
<tr>
<td>0527T</td>
<td>Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging督导和解释；导管和植入监测系统</td>
<td></td>
</tr>
</tbody>
</table>
supervision and interpretation; implantable monitor only

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1824</td>
<td>Generator, cardiac contractility modulation (implantable)</td>
</tr>
<tr>
<td>C2624</td>
<td>Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components</td>
</tr>
</tbody>
</table>


**Pulmonary**

**Computer-Aided Detection of Chest Radiographs (CPT Codes 0174T, 0175T)**
Computer-aided detection (CAD) systems for computed tomography or digital chest x-rays are software programs that subtract one lung from another to reveal subtle asymmetric opacities, and perform temporal subtraction of prior imaging from the current exam. The basic concept of computer-aided detection (CAD) is to provide computerized image recognition to assist and improve radiologist’s interpretation. Through algorithms, CAD technology provides radiologists with regions of interest (ROI) for their interpretation. Although CAD is used most often in mammography, many different types of CAD technologies and/or devices are being developed for detection of various lesions in medical imaging, including conventional x-ray, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound.

Proponents of computer-aided detection with chest x-ray state that diagnostic accuracy is improved with the use of a CAD program and that CAD can expedite screening of at-risk individuals at an earlier and more curable stage of lung cancer. Potential risks of using CAD with chest x-rays may include the generation of false-positive and false-negative results leading to over- and under-diagnosis. Abnormalities (e.g., scars from smoking, areas of inflammation, or other noncancerous conditions) can mimic lung cancer on x-ray. Subsequent additional testing may cause anxiety for the patient or may lead to unnecessary biopsy or surgery and increase medical costs. Also, the use of CAD programs in screening for lung cancer may detect small tumors that would never become life-threatening, putting a patient at risk for unnecessary treatments for cancer, such as chemotherapy or radiation.

**U.S. Food and Drug Administration (FDA)**
Deus Technologies received FDA premarket approval for its RapidScreen™ CAD system in July 2001. Its intended use is “to identify and mark regions of interest on digital or digitized frontal chest radiographs. It identifies features associated with solitary pulmonary nodules from 9–30 millimeters (mm) in size, which could represent early-stage lung cancer. The device is intended for use as an aid only after the physician has performed an initial interpretation of the radiograph. The device is of little value when used for patients who are not at high risk for lung cancer.”
In 2007, Dues Technologies manufacturer Riverain Medical Group (Miamisburg, OH) received approval for a new trade name. The device, as modified, will be marketed under the trade name OnGuard™ and is indicated “to identify and mark ROIs on frontal chest radiographic films from adult males with an increased risk for lung cancer to bring ROI to the attention of the radiologist after the initial reading has been completed. Thus the system assists the radiologist in minimizing observational oversights by identifying areas on the original chest films that may warrant a second review.” In March of 2012, Riverain’s OnGuard software was renamed ClearRead Detect™. Currently, Riverain Medical’s ClearRead Detect™ CAD System is the only FDA-approved CAD systems with a Product Device Description of “Analyzer, Medical Image” for chest x-rays (Product Code MYN). Other CAD systems (for example, mammography or lung computed tomography) are listed under this same device description.

The FDA approved EDDA Technology’s (Princeton Junction, NJ) “IQQA® Chest Software Package” in October 2004 under the Product Device Description of Picture Archiving and Communications System (PACS). It uses a real-time interactive pulmonary nodule analysis system for chest digital radiographic image softcopy reading. Intended use states it is “used during the review of digital chest radiographic images. Combining image viewing, evaluation and reporting tools, the software is designed to support the physician in the identification of lung lesions (e.g. nodules), as well as the confirmation, evaluation and documentation of such physician-identified lesions. The IQQA-Chest software package supports a workflow based on automated segmentation for the visual identification of possible lesions. The tools also allow for regional analysis of possible lesions in terms of size, shape and position, thus aiding the physician in the characterization of physician-identified suspicious lesions.” Philips Medical Systems (Hamburg, Germany) has licensed EDDA Technology’s IQQA® Chest software and markets it under the name xLNA (x-ray lung node assessment) Enterprise.

**Literature Review**

There is insufficient evidence in the published, peer-reviewed scientific literature addressing the accuracy and clinical utility of CAD of chest x-rays. Well-designed clinical trials are lacking. Studies are primarily retrospective analyses of registry data and there is concern regarding unacceptable false-positive rates. Retrospective registry studies address multiple variables that may impact accuracy such as the experience and training of radiologist using the CAD program, type of chest x-ray utilized (e.g., temporal subtraction, dual energy subtraction) and region of interest identification parameters in the algorithms themselves (e.g., nodules size, bone suppression, and nodule-in-center or nodule-in-circle criterion). Additionally, screening populations and timing for the use of CAD in the diagnostic work-up vary in studies. The clinical utility of CAD of chest x-rays for lung cancer screening is not established. The FDA wording regarding RapidScreen™ CAD systems notes that the device is of little value when used for patients who are not at high risk for lung cancer (Dellios, et al., (2017); Kligerman, et al., 2013; De Boo, et al., 2011; Meziane, et al., 2012; Szucs-Farkas, et al., 2010; Balkman, et al., 2010; Moore, et al., 2010; White, et al., 2009; Li, et al., 2008; Van Beek, et al., 2008; Bley, et al., 2008; Kakeda, et al., 2004).

**Professional Societies/Organizations**

Guidelines are lacking from professional organizations that include computer-aided detection of chest radiographs,

**Centers for Medicare & Medicaid Services (CMS)**

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L35094) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

**Use Outside of the US**

No relevant information.

**References**


Cryoablation of Lung Tumors (CPT Code 32994)

Pulmonary tumor cryoablation involves the destruction of tumor tissue using extreme cold. This is also known as cryoablation, cryosurgery, or cryotherapy. In this procedure a small thin wand-like needle, known as a cryoprobe, is inserted through the skin of the chest and between the ribs. Under computerized tomography (CT) guidance, the probe is advanced into the lesion of the lung and any tumor extensions to the pleura and/or chest wall. Compressed argon gas is passed through the probe and into the tumor, which freezes it and destroys the tissue. Treatment with the probe usually takes several minutes and may include repositioning the probe within the lesion so that overlapping ablations treat the entire tumor.

Literature Review
Randomized controlled clinical trial data are lacking in the published peer-reviewed scientific literature to demonstrate the safety and effectiveness of pulmonary tumor ablation by cryoablation. Studies are limited by uncontrolled design and small patient populations. Additional well-designed high quality studies are necessary to inform on health outcomes. Further, published professional consensus is necessary before this treatment can be translated into routine clinical practice.

Moore et al. (2015) reported on a retrospective study that evaluated long-term survival in 45 patients with early stage non-small cell lung cancer (NSCLC) treated with cryoablation treatment. The study findings included five year survival rate 67.8% ± 15.3; the cancer-specific survival rate was 56.6% ± 16.5; and the 5-year progression-free survival rate was 87.9% ± 9. The combined local and regional recurrence rate was 36.2%. Major complications occurred 6.4% of patients that included two cases of hemoptysis and a prolonged placement of a chest tube requiring mechanical sclerosis in one patient. There were no deaths in the first 30 days after treatment.

Hayes published a technology directory report regarding cryoablation for treatment of non-small cell lung cancer (NSCLC) (Hayes, 2015; 2018). The review included one randomized controlled trial (RCT), six nonrandomized comparative studies, and one uncontrolled study, with sample size of 36 to 346 patients. The body of evidence concerning cryoablation for NSCLC is moderate in size and low in overall quality. Results of the available studies provide preliminary evidence that cryoablation is a reasonably safe and effective treatment for NSCLC. While the results of some of the studies were somewhat conflicting or inconclusive, there is some evidence of improved survival when cryoablation is used alone or with other therapies. Additional well-designed studies with long-term follow-up are needed to define the clinical role of cryoablation relative to other common therapies for NSCLC such as surgery, RFA, chemotherapy, radiation therapy, and immunotherapy.

Yashiro et al. (2013) reported results of a prospective study of 71 consecutive patients with 210 pulmonary tumors treated with 102 sessions of percutaneous cryoablation of lung tumors. A mean of 1.4 sessions was performed per case. A maximum of four cryoprobes was used on one lesion; the number and diameter of the probes were based on estimated tumor size. Every procedure was performed using a triple freeze/thaw protocol. High-pressure argon gas was used for freezing. There was no procedural mortality. Of 210 tumors, technical success was achieved for 167 (79.5%). At a median follow-up of 454 days, local progression occurred in 50 tumors (23.8%). One-, 2-, and 3-year local progression-free rates were 80.4%, 69.0%, and 67.7%, respectively, and technique effectiveness rates were 91.4%, 83.0%, and 83.0%, respectively. Existence of a thick vessel (diameter≥3 mm) no more than 3 mm from the edge of the tumor was assessed as an independent factor (HR, 3.84; 95% CI, 1.59–9.30; P = .003) associated with local progression by multivariate analysis. Although results are promising, study limitations include uncontrolled design, and small patient numbers.

Kawamura et al. (2006) conducted a nonrandomized uncontrolled study to evaluate cryoablation of 35 pulmonary metastatic tumors in 20 patients who were not surgical candidates. In all cases cryoablation was performed percutaneously under CT guidance with local anesthesia. A total of 22 sessions of cryoablation were performed. Pneumothorax occurred in 11 of the 22 sessions, primarily after the completion of the ablation procedure. A chest tube was inserted in one case, transient needle aspiration was performed in three cases, and in seven cases no additional treatment was given. Phrenic nerve palsy occurred during one session. Mean hospital stay after treatment was 2.6 days, although for the initial five sessions, it was 5.4 days. There were no treatment-related deaths or conversion to surgical intervention. The follow-up period was 9 to 28 months. Local recurrence occurred in 7 (20%) of tumors. Five patients underwent repeat cryoablation without complications. Study limitations which preclude the ability to apply results to other populations include uncontrolled randomized design and small patient populations.

Professional Societies/Organizations
National Comprehensive Cancer Network™ (NCCN™): The NCCN (2019) guidelines do not contain detailed information on cryoablation for NSCLC. Cryotherapy is mentioned as follows (NCCN, 2019):

- Resection is the preferred local treatment modality (other modalities include radiotherapy ablation, cryotherapy, and stereotactic ablative radiotherapy).

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
• Local Coverage Determinations (LCDs): Local Coverage Determination (LCD):
• Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
European Society for Medical Oncology (ESMO): ESMO published clinical practice guidelines for metastatic non-small cell lung cancer (Novello, et al., 2016). The guidelines note that in case of symptomatic major airways obstruction or postobstructive infection, endoscopy debulking by laser, cryotherapy or stent placement may be helpful (III, C).

Levels of evidence and grades of recommendation
III Prospective cohort studies
C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs), optional

References

Coding/Billing Information Pulmonary

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Pulmonary Services Considered Experimental/Investigational/Unproven:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>32994</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>0174T</td>
<td>Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images,</td>
<td></td>
</tr>
</tbody>
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chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>0175T</td>
<td>Computer aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation</td>
</tr>
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**Gastroenterology**

**Fecal Calprotectin Testing (FC) (CPT Code 83993)**

In general chronic diarrhea is defined as three or more loose or watery stools daily lasting for four or more weeks (Bonis and Lamant, 2017). Common causes include irritable bowel syndrome (IBS), inflammatory bowel disease, malabsorption syndromes (such as lactose intolerance and celiac disease), and chronic infections (particularly in patients who are immunocompromised). There is no firm rule as to what testing should be done. The history and physical examination may point toward a specific diagnosis for which testing may be indicated. Fecal calprotectin levels are increased in intestinal inflammation and may be useful for distinguishing inflammatory from noninflammatory causes of chronic diarrhea.

This fecal calprotectin laboratory test measures the level of calprotectin in stool. Calprotectin is a calcium and zinc binding protein that is found predominantly in neutrophils. The concentration of calprotectin is higher in feces compared to plasma and can be measured by enzyme-linked immunosorbent assay (ELISA) using less than five grams of stool. Although the normal range has been defined for FC, an optimal cutoff point for distinguishing inflammatory bowel disease (IBD) from other diagnoses has not been defined (von Roon et al. 2007). It has been studied as a surrogate marker of intestinal inflammation in inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis), colorectal cancer, diverticular disease, and polyposis of the colon. It has also been studied as a marker to predict response to treatment and relapse of disease.

**U.S. Food and Drug Administration (FDA)**

PhiCal™ Fecal Calprotectin Immunoassay (Genova Diagnostics, Inc., Ashville, NC) received 510 (k) device approval in 2006. The immunoassay is a lab test that measures the amount of fecal calprotectin in a patient’s stool sample. The PhiCal test is indicated for use as an in vitro diagnostic to aid in the diagnosis of inflammatory bowel diseases (IBD) (Crohn's disease and ulcerative colitis), and to differentiate IBD from irritable bowel syndrome (IBS) when used in conjunction with other diagnostic testing and the total clinical picture.

BUHLMANN fCAL® ELISA (BUHLMANN Laboratories AG, Lexington, Kentuck) received 510 (k) approval 2018. It is an in vitro diagnostic assay that is intended for the quantitative measurement of fecal calprotectin in human stool. The test aids in the diagnosis of inflammatory bowel disease (IBD), specifically Crohn’s disease (CD) and ulcerative colitis (UC) and aids in the differentiation of IBD from irritable bowel syndrome (IBS) in conjunction with other laboratory and clinical findings.

**Literature Review**

Randomized controlled clinical trial data are lacking regarding the clinical utility of fecal calprotectin testing to inform diagnosis, or predict relapse or response to treatment for IBD or any indication. Although patient numbers included in published studies are large, a number of study limitations have been identified by authors including uncontrolled and heterogeneous study design, and heterogeneous patient populations. Further, in some studies it is unknown whether FC samples were obtained before commencing treatment, which may be a major confounder in reports of diagnostic accuracy (Henderson, et al., 2013). In the study by Henderson (2013) the authors note “The assessment of methodological quality determined that there were deficiencies in all the studies evaluated, but especially with regard to important aspects, such as the use of a representative spectrum.
of patients, an acceptable reference standard (upper and lower endoscopy), and the poor reporting of current treatment modalities in use during FC sampling."

**Inflammatory Bowel Disease (IBD):** El-Matary et al. (2017) reported on a retrospective cohort study that examined the impact of fecal calprotectin (FCal) measurements on decision-making and clinical care of children with IBD. FCal, clinical activity indices, and blood markers were measured in 77 (115 fecal samples) children with diagnoses of IBD. Pearson correlation coefficient analysis was performed to examine association between FCal and other markers. Then decisions based on FCal measurements were prospectively documented and participants were evaluated three to six months later. FCal positively correlated with clinical activity indices (r = 0.481, P < 0.05) and erythrocyte sedimentation rate (r = 0.40, P < 0.05) and negatively correlated with hemoglobin (r = -0.40, P < 0.05). Sixty-four out of 74 (86%) positive FCal measurements (≥250 μg/g of stools) resulted in treatment escalation with subsequent significant clinical improvement while in the FCal negative group, 34 out of 41 (83%) measurements resulted in no change in treatment and were associated with remission on follow-up. The study was limited by lack of randomization, retrospective design, and small sample size in particular for those with colonoscopy.

Abej et al. (2016) reported on a prospective cohort study performed to determine the relationship between fecal calprotectin (FCAL) and imaging studies and other biochemical inflammatory markers and the impact of FCAL measurements on decision-making in IBD patient management in usual clinical practice. The study included 240 persons with IBD. The correlation between FCAL values and other markers for disease activity such as serum albumin (alb), hemoglobin (Hg), and C-reactive protein (CRP) and diagnostic imaging or colonoscopy were examined. FCAL ≥250 mcg/g of stool was considered a positive result indicating active IBD. The results of 183 stool samples (76.3%) were returned. The return rate in the pediatric and adult cohorts was 91% (n = 82) and 67.3% (n = 101), respectively (P<0.0001). Positive FCAL was associated with colonoscopy findings of active IBD (P < 0.05), low albumin (P < 0.05), anemia (P < 0.01), and elevated CRP (P < 0.01). There was no significant difference for FCAL results by outcomes on small bowel evaluation among the 21 persons with small bowel CD. Most persons (87.5%) with normal FCAL and no change in therapy remained in remission during subsequent 3 months. Of 11 subjects with a positive FCAL who underwent imaging, only 6 had active disease on imaging; a positive FCAL was not significantly associated with radiologic evidence of active disease (P = 0.31).this study was limited by lack of controls, and the small number who underwent imaging and endoscopy.

Bar-Gil Shitrit et al. (2016) reported on a study that prospectively assessed the value of fecal calprotectin and lactoferrin in 68 patients with Crohn’s disease (CD) to predict capsule endoscopy (CE) findings. Stool samples for calprotectin and lactoferrin and blood samples were collected for relevant parameters. Correlation between fecal markers and CE findings was assessed and receiver operating characteristic (ROC) curves were built to determine the predictive values of fecal markers for the diagnosis of CD. Fecal calprotectin data was available for all the patients and lactoferrin data for 38. CE findings compatible with CD were found in 23 (33%) patients and 45 (67%) were negative for CD. The average age of the CD group was 34 compared to 46 in the non-CD group (p = .048). Median calprotectin and lactoferrin in the CD group and in the control group were 169 mg/kg vs. 40 (p = .004) and 6.6 mg/kg versus 1 (p = .051), respectively. The area under the ROC curve was 0.767 for calprotectin and 0.70 for lactoferrin. A fecal calprotectin concentration of 95 mg/kg and fecal lactoferrin of 1.05 mg/kg had a sensitivity, specificity, positive predictive value and negative predictive value of 77 and 73%, 60 and 65%, 50 and 50%, and 84 and 84% in predicting CE findings compatible with CD. The study is limited by small number of participants and lack of controls.

Several meta-analyses of prospective and registry data have been performed to examine the predictive capacity of fecal calprotectin in individuals with IBD (e.g., Crohn’s disease, ulcerative colitis). Reported results have been inconsistent with a wide variation in sensitivity and specificity of FC for included studies, ranging from 61-100% and 71-100%, respectively for diagnosis of IBD and other intestinal disorders. Sensitivity and specificity to predict relapse are 43-80% and 48-73%, respectively (Heida, et al., 2017; Henderson, et al., 2013; Kostakis, et al., 2012; Mao, et al., 2012; Jellema, et al, 2011; Laharie, et al., 2011; van Rheenen, et al., 2010; von Roon, et al., 2007).

In several studies (Hukkinen, et al., 2016, Henderson, et al., 2013; van Rheenen, et al., 2010), results regarding specificity of FC testing in children were significantly different compared with those for adults (96% and 68-97%, respectively). In addition, recent studies and meta-analysis have been published regarding the use of fecal
calprotectin in management of IBD (Bressler, et al., 2015; Wright, et al., 2015; Kennedy, et al., 2015; Mosli, et al., 2015; Menees et al., 2015; Lin, et al., 2014, Sandborn, et al., 2016; Chey, et al., 2015). These studies examine the accuracy of the test, but do not indicate the clinical utility of fecal calprotectin in the management of IBD. The tests did not substantiate the use of this test in altering the management of the condition, or reducing or eliminating other testing for the condition.

Hayes published a directory report for fecal calprotectin (FC) assay for monitoring postoperative recurrence (PER) of Crohn Disease (CD) (2013, 2018). It was found that overall quality of the body of evidence pertaining to the use of FC testing systems for the evaluation of postoperative endoscopic recurrence (PER) in patients with CD was considered to be low with one study rated as good quality; five as fair quality; and, five as poor quality. The major individual study limitations included small sample sizes; study design; lack of blinding; no follow-up; unclear, extended, or varying lengths time between FC stool sample collection and colonoscopy; lack of correction for multiplicity in analysis; multiple endoscopic procedures per patient unaccounted for in the analysis; and nonuniform postoperative treatment. The study concluded that the available evidence indicates that FC testing generally has high negative predictive value (NPVs) and moderate sensitivity but low-to-moderate specificity and positive predictive value (PPVs) for the prediction of PER in patients with CD. With a high NPV, patients and clinicians can have a high assurance that a negative result on an FC test suggests that PER will not occur, thus potentially avoiding or delaying invasive endoscopic procedures. The study noted that however, NPVs and sensitivity values varied across some studies; thus, additional research is needed to define uniform and optimal cutoffs for FC testing to predict and monitor PER of CD. In addition, no direct evidence was available regarding the clinical utility of FC testing to change management or improve outcomes in patients with CD following ileocolic resection. Additional good-quality, blinded studies of sufficient size, design, and duration are required to evaluate the clinical utility of FC testing for monitoring PER of CD.

Hayes published a directory report for the use of fecal calprotectin (FC) assay for monitoring disease activity in Crohn disease (CD) (Hayes, 2013; 2018). The review found that in general, FC testing provides moderate-to-high sensitivity, specificity, PPV, NPV, and diagnostic accuracy for the prediction of disease activity using endoscopic or clinical indices in patients with CD and that noo studies directly addressed measures of clinical utility. The conclusions of the report included that:

- The available evidence suggests that FC testing is safe and may have promise for monitoring disease activity due to the moderate-to-high diagnostic sensitivity and accuracy of this test to predict disease activity in patients with CD. However, no direct evidence was available regarding the clinical utility (i.e., change in patient management or improved clinical outcomes) of FC testing for monitoring disease activity in patients with CD. In addition, the specificity, positive predictive value (PPVs), and negative predictive value (NPVs) varied across studies, and additional studies are required to define uniform cutoffs for FC testing to predict and monitor CD activity.
- Across 12 studies assessing FC testing for the prediction of endoscopic disease activity, sensitivity ranged from 70% to 94.1% and specificity ranged from 40% to 97%. PPV and NPV ranged from 48.5% to 98% and 40% to 96.6%, respectively. Four studies reported diagnostic accuracy, which ranged from 71% to 87%.
- In three studies, FC testing had 50% to 80% sensitivity and 74.4% to 88% specificity for monitoring changes in clinical disease activity. PPV and NPV ranged from 27.6% to 76% and 71% to 96.8%, respectively.
- In one study, FC testing had a moderately high specificity (82%), moderate NPV (75%), and very low sensitivity (37%) for detection of clinical loss of response (LOR) to infliximab in patients undergoing maintenance therapy.
- There do not appear to be any safety concerns with the use of FC testing to predict and monitor CD activity, although the potential risk for false-positive results could result in unnecessary endoscopic procedures.
- Additional good-quality, blinded studies of sufficient size, design, and duration in well characterized patient populations are required to evaluate the clinical utility of FC testing for monitoring disease activity in patients with CD.

Although several clinical trials reflect abnormal or elevated FC levels in individuals with inflammatory bowel disease compared with controls, the clinical utility of fecal calprotectin testing to impact management and
improve overall health outcomes has not been demonstrated. Large randomized controlled trials are necessary to establish the role of FC testing when compared to available diagnostic tests.

**Colorectal Cancer:** Similar to IBD, RCT data are lacking in the published, peer-reviewed scientific literature to evaluate the clinical utility of FC testing for screening and diagnosis of colorectal cancer (CRC) in adults and children. Although levels of fecal calprotectin may be elevated in individuals with CRC compared with healthy control subjects, several meta-analyses of prospective and retrospective studies reflect inconsistent sensitivity and specificity with values of 36-75% and 64-84% respectively (von Roon, et al., 2007; Shitrit, et al., 2007). The role of FC testing as a means to diagnose CRC has not been established.

**Other Intestinal Conditions:** FC testing has also been proposed for other conditions such as irritable bowel syndrome, colonic polyposis, and diverticular disease (Tursi, et al., 2014; Licata, et al., 2012; Pezzilli, et al., 2008; Parsons, et al., 2014). Randomized controlled trial data are lacking in the published peer-reviewed scientific literature demonstrating the ability to impact care management or improve patient health outcomes with FC testing for these conditions. Further, there is a lack of published literature reflecting that this is considered a standard of care option for these indications. At this time there is insufficient evidence to determine the role and clinical utility of such testing.

**Professional Societies**

**American College of Gastroenterology (ACG):** ACG published updated guidelines for management of Crohn’s Disease in adults (Lichtenstein, et al., 2018). The guidelines include the following recommendation:

- Diagnosis: Fecal calprotectin is a helpful test that should be considered to help differentiate the presence of IBD from irritable bowel syndrome (IBS) (strong recommendation, moderate level of evidence).
- In patients who have symptoms of active Crohn’s disease, stool testing should be performed to include fecal pathogens, Clostridium difficile testing, and may include studies that identify gut inflammation such as a fecal calprotectin and may include studies that identify gut inflammation such as a fecal calprotectin. (summary statement, no level of evidence)
- Fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity. (summary statement, no level of evidence)

  **Level of evidence:**
  Moderate: (further research would be likely to have an impact on the confidence in the estimate of effect)

  **Recommendation grading:**
  Strength of a recommendation graded as “strong” when the desirable effects of an intervention clearly outweigh the undesirable effects.

  **Summary statements are descriptive and do not have associated evidence-based ratings.**

**American Gastroenterological Association (AGA):** the AGA published a clinical care pathway for Crohn’s disease. In the section for assessing inflammatory status, fecal calprotectin is listed along with other lab testing that includes CBC, CRP, CMP, and ESR. There is no evidence level included in the clinical care pathway.

**Infectious Diseases Society of America (IDSA):** the IDSA published clinical practice guidelines for the diagnosis and management of infectious diarrhea. The guidelines note regarding the clinical relevance of calprotectin in a person with acute diarrhea that “There are insufficient data available to make a recommendation on the value of fecal calprotectin measurement in people with acute infectious diarrhea.” (Shane, et al., 2017)

**Centers for Medicare & Medicaid Services (CMS)**

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCDs found.

**Use Outside of the US**

**British Society of Gastroenterology (BSG):** BSG published guidelines for the investigation of chronic diarrhoea in adults (Arasaradnam, et al., 2018). The recommendations include
• Recommend an initial screening blood test (full blood count, ferritin, tissue transglutaminase/EMA and thyroid function test) as well as stool tests for inflammation (faecal calprotectin) should be undertaken in primary care (Grade of evidence level 3, Strength of recommendation strong).

• Faecal calprotectin is recommended to exclude colonic inflammation in those suspected with IBS and under the age of 40 (Grade of evidence level 1, Strength of recommendation strong).

• A faecal calprotectin cut-off of 50 μg/g faeces (assay-dependent) is recommended to distinguish functional bowel disorder from organic/inflammatory bowel disease (Grade of evidence level 1, Strength of recommendation strong).

• In patients with typical symptoms of functional bowel disease, normal physical examination and normal screening blood and faecal tests (calprotectin), a positive diagnosis of IBS can be made (Grade of evidence level 2, Strength of recommendation strong).

• In younger patients (under 40 years) with a normal faecal calprotectin and in whom functional bowel disease is suspected, we recommend a flexible sigmoidoscopy with biopsy (Grade of evidence level 3, Strength of recommendation strong).

Grade of evidence:
Level 1a–c ranges from systematic reviews with homogeneity, individual randomised controlled trials (RCTs)
Level 2a–c ranges from systematic reviews of cohort studies, low quality RCTs and outcomes research
Level 3a–b ranges from systematic reviews with heterogeneity and individual case control studies

European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)/North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN): In joint recommendations From these organizations fecal calprotectin (FC) and fecal leukocytes (FL) are described as markers of bowel inflammation that have been shown to correlate with clinical measures of disease activity in patients who have Crohn’s disease. They note that they may help clinicians ascertain the nature and severity of disease, in particular if prior measurements are available for comparison. Although FC and FL have also been shown to have potential to predict relapse, there is insufficient evidence to recommend routine use of these markers for surveillance of Crohn’s disease (Rufo et al., 2012).

National Institute for Health and Care Excellence (NICE): NICE published guidance for fecal calprotectin diagnostic tests for inflammatory diseases of the bowel (2013; 2017). Recommendations include:

• Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:
  ➢ Cancer is not suspected, having considered the risk factors (for example, age) described in the NICE guideline on suspected cancer
  ➢ Appropriate quality assurance processes and locally agreed care pathways are in place for the testing.

• Fecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment, if:
  ➢ Appropriate quality assurance processes and locally agreed care pathways are in place for the testing.

World Gastroenterology Organisation (2015): The global guideline for irritable bowel syndrome (IBS), lists fecal inflammation marker (e.g., calprotectin) in the IBS Level I diagnostic cascade.

References


41. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ. 2010 Jul 15;341:c3369.


Transanal Radiofrequency Therapy for Fecal Incontinence (e.g., SECCA Procedure) (CPT Code 46999)

Fecal incontinence is the inability to control the passage of gas, liquid and/or solid feces due to the loss of the coordinated function of the muscles and/or nerves of the rectum, anal canal, and pelvic floor. Treatment of minor incontinence (i.e., incontinence to flatus and occasional seepage of liquid stool) may be controlled by changes in diet and dietary habits, medication (e.g., bulking agents, antidiarrheal drugs), and bowel training (e.g., Kegel exercises, biofeedback). In the case of major incontinence (i.e., frequent loss of solid waste material) or incontinence unresponsive to conservative measures, surgical intervention may be indicated. In the event of an isolated sphincter defect, the standard surgical treatment is sphincteroplasty. Other surgical procedures include repair of rectocele or rectal prolapse and, in severe cases, fecal diversion (i.e., colostomy) (Kim, et al., 2009; Lefebure, at al., 2008; Rao, 2004; Wexner and Sands, 2003; Takahashi, et al., 2002).

Transanal radiofrequency therapy (e.g., Secca® procedure) is a proposed alternative therapy for the treatment of fecal incontinence for patients who have not responded to medical therapy and are not good surgical candidates or have failed surgical intervention. The Secca procedure is noninvasive, typically takes 30–45 minutes, and is performed in an outpatient setting under local anesthesia and sedation. It is also proposed that there are fewer complications following the Secca procedure compared to invasive surgical procedures.

Radiofrequency therapy is based on the theory that “collagen deposition and subsequent scarring may increase one’s ability to recognize and retain stool and permit improved continence” (Parisien and Corman, 2005). An anoscopy device uses four electrodes to deliver controlled radiofrequency energy to the sphincter muscles surrounding the anal canal. The energy creates precise, submucosal burn lesions, triggering collagen contraction. The lesions are subsequently resorbed, remodeling the tissue. The remodeling is proposed to improve barrier function of the anal sphincter (Efron, et al., 2003; Takahashi, et. al., 2002).

U.S. Food and Drug Administration (FDA)
The Secca® System (Curon Medical Inc., Sunnyvale, CA) was approved by the FDA as a 510(k) Class II device for general use for electrosurgical coagulation and “for use specifically in the treatment of fecal incontinence in those patients with incontinence to solid or liquid stool at least once per week and who have failed more conservative treatment” (FDA, 2002).

Literature Review
The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review for treatments for fecal incontinence (Forte, et al., 2016). The review found only case series studies for SECCA procedure, no randomized controlled trials or observational studies were found. It was found that evidence was insufficient regarding this procedure.
There is insufficient evidence in the published peer-reviewed scientific literature to support the effectiveness of transanal radiofrequency therapy (e.g., Secca procedure) for the treatment of fecal incontinence. Studies are primarily in the form of prospective case series with small patient populations (n=8–50). With the exception of one, five-year study (Takahashi-Monroy, et al., 2008) follow-ups were short-term, ranging from 6–12 months. Various questionnaires (e.g., Fecal Incontinence Severity Index, Fecal Incontinence-related Quality of Life questionnaire, Vaizey scale) were utilized to measure quality of life (e.g., coping, depression, embarrassment) outcomes and results were inconsistent. Typically there were no significant improvements in physical component outcomes, such as anorectal manometry parameters, pudendal nerve motor latency, endoanal ultrasound results, and the thickness of internal anal sphincters. Some studies reported numerous complications while others reported no complications (Ruiz, et al., 2010; Kim, et al., 2009; Lefebure, et al., 2008; Takahashi-Monroy, et al., 2008; Felt-Bersma, et al., 2007; Efron, et al., 2003; Takahashi, et al., 2003). Studies comparing the use of transanal radiofrequency therapy to established medical and surgical treatment options are lacking.

Professional Societies/Organizations

**American College of Gastroenterology (ACG):** in the ACG clinical guideline for management of benign anorectal disorders (Wald, et al., 2014) for the treatment of fecal incontinence it is noted regarding the Secca procedure, that there is insufficient evidence to recommend radiofrequency ablation treatment to the anal sphincter (SECCA) at this time (no recommendation, insufficient evidence).

**American Society of Colon and Rectal Surgeons:** In their practice parameters for the treatment of fecal incontinence, the American Society of Colon and Rectal Surgeons (Tjandra, et al., 2007) discussed the medical (e.g., fiber intake, antidiarrheal agents, enemas, laxatives, suppositories, anal plug) and surgical (e.g., sphincter repair, injectable therapy, sacral nerve stimulation, dynamic graciloplasty, artificial bowel sphincter, stoma) treatment options for this condition. Based on studies by Takahashi et al. (2003) (n=10) and Efron et al. (2003) (n=50), the ASCRS stated that the Secca procedure may be useful for selected patients with moderate fecal incontinence.

**Centers for Medicare & Medicaid Services (CMS)**
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCDs found.

**Use Outside of the US**

**National Institute for Health and Care Excellence (NICE):** In an interventional procedure guidance document, NICE (2011) (United Kingdom) stated that endoscopic radiofrequency therapy of the anal sphincter for the treatment of fecal incontinence raised no major safety concerns, but the procedure should only be carried out in units specializing in the assessment and treatment of fecal incontinence. NICE noted that further research is needed to clearly define the appropriate patient group for this procedure. The guidance was based on three case series with small patient populations (n=19–50).

**References**
Optical microscopy, also known as confocal laser endomicroscopy (CLE), is an emerging endoscopic technology that permits high-resolution assessment of gastrointestinal mucosal histology at a cellular and sub-cellular level. CLE and endocytoscopy can be performed with probe-based systems that are passed through the working channel of an endoscope. A confocal miniprobe is a flexible probe-based system (Cellvizio, Mauna Kea Technologies, Paris, France) that is used as an alternative to a confocal laser endomicroscope. In probe-based confocal laser endomicroscopy (pCLE), both the laser scanning unit and light source are outside the body of the patient, which makes the confocal miniprobe a "passive" conduit. The miniprobes are very flexible and can be passed through the working channel of a standard endoscope. The indications for confocal laser endomicroscopy (CLE) are still being defined. In general, the technology is used to target biopsies of abnormal tissue and to avoid taking biopsies of normal tissue. A use of this technology that is being investigated is the differentiation of benign from malignant biliary strictures with probe-based CLE (Meining, [UpToDate], 2018).

U.S. Food and Drug Administration (FDA)
In 2012 the Cellvizio® 100 Series System and Cellvizio® System with Confocal Miniprobes received 510(k) premarket approval for the GastroFlex M™ series of Confocal Miniprobes™ which are intended to allow imaging of the internal microstructure of tissues in the upper gastrointestinal tract including biliary and pancreatic ducts, accessed by an endoscope or endoscopic accessories. The Cellvizio 100 Series is a confocal laser imaging system with a variety of fiber optic probes that is intended to allow confocal laser imaging of the internal microstructure of tissues in anatomical tracts, i.e. gastrointestinal or respiratory, accessed through an endoscope.

Literature Review
Fugazza et al. (2016) systematic review is to analyze the current literature on confocal laser endomicroscopy (CLE) and to evaluate the applicability and diagnostic yield of CLE in patients with gastrointestinal and pancreatobiliary diseases. The review included 102 prospective and retrospective clinical studies that evaluated...
the sensitivity, specificity, or accuracy of CLE. Regarding the use of CLE in biliary duct, it was found that the addition of CLE to histological examination results in a significant increase in diagnostic reliability. Currently, biliary strictures are staged using a combination of endoscopic ultrasound and advanced imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), or EUS, with endoscopic retrograde cholangiopancreatography (ERCP) typically used for tissue sampling, including biopsy and cytological brushing. The current sensitivity of each of these methods is quite low, ranging from 20% to 60%. The present meta-analysis demonstrated that combining CLE with ERCP yields high sensitivity (90%) in the assessment of biliary strictures. The authors conclude that although CLE has several promising applications, its use has been limited by low availability, high cost, and the necessity of specific operator training. The review noted that in order to implement CLE in routine clinical practice there is a need for further clinical trials with a particular focus on cost-effectiveness and medicoeconomic analyses, as well as standardized institutional training.

Meining et al. (2011) reported on a prospective observational multicenter study of 102 patients with indeterminate pancreaticobiliary strictures. Clinical information, ERCP findings, tissue sampling results, and pCLE videos were collected prospectively. A presumptive diagnosis was provided based on probe-based confocal laser endomicroscopy (pCLE) during the procedure before pathology results were available. Patients received at least 30 days of follow-up until definitive diagnosis of malignancy was established or one-year follow-up if index tissue sampling was benign. The main outcome measurements were diagnostic accuracy, sensitivity, specificity of ERCP-guided pCLE compared with ERCP with tissue acquisition. Eighty-nine patients were able to be evaluated with CLE, with 40 patients were proven to have cancer. CLE had a sensitivity of 98% and a specificity of 67% for diagnosing malignancy.

Professional Societies/Organizations
American Society for Gastrointestinal Endoscopy (ASGE): the ASGE published a technology evaluation status report on confocal laser endomicroscopy (ASGE, 2014). The report notes that on probe-based confocal laser endomicroscopy (pCLE) allows in vivo real-time visualization of biliary strictures via a dedicated probe passed through a cholangioscope or catheter for ERCP. pCLE can provide real-time microscopic images of the biliary epithelium, thereby providing histological information that is not otherwise available during ERCP.

The report identified several issues pertaining to CLE that deserve further investigation:
- Further studies evaluating the applicability and practicality of CLE, especially in community settings are needed. Although it appears that the current studies of CLE seem promising, these have primarily been in academic centers and their generalizability in nonacademic practices is unknown.
- Additional studies evaluating the learning curve of CLE image interpretation, use of CLE devices, and additional time needed to perform the procedure are needed.
- The clinical efficacy of the technology and its cost-effectiveness compared with other available advanced imaging technologies needs further study.
- Improvements in CLE imaging and image interpretation are needed. Combining CLE imaging with newer molecular markers and the development of computer-based algorithms may be possible avenues for further research in this area.

The report concluded that CLE is an emerging technology that in the bile duct and within pancreatic cysts, it can provide surrogate real-time histological information that has previously been unavailable. The limitations of CLE include the high cost of the equipment and probes, the lack of proven efficacy compared with other widely available advanced imaging techniques, and the need for either intravenous or topical fluorescent contrast agents. The report notes that before the technology can be widely accepted, many further studies are needed to determine its clinical efficacy and evaluate its cost-effectiveness and its utilization in both academic and community settings.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Multiple LCDs found. Refer to the LCD table of contents link in the reference section.

Use Outside of the US
No relevant information
References

Wireless Gastrointestinal Motility Monitoring System (SmartPill®) (CPT Code 91112)
The SmartPill Gastrointestinal (GI) Monitoring System® (The SmartPill Corporation, Buffalo, NY) has been proposed as an alternative testing method for the diagnosis of gastric conditions and intestinal motility disorders such as gastroparesis and chronic constipation. The system records pH and pressure measurements from the entire length of the gastrointestinal tract for use by physicians to aid in the evaluation of gastrointestinal motility diseases and conditions. Sensors on board an ingestible capsule measure pH and pressure as the capsule travels the length of the GI tract. Measurements are transmitted from the capsule within the GI tract via radiofrequency signal to a patient worn receiver and subsequently downloaded for analysis and review. Next, software performs data analyses providing the physician with a printable report containing regional gut transit times: gastric emptying or transit time (GET), small bowel transit time (SBTT), combined small and large bowel transit time (SLBTT), colonic transit time (CTT) and whole gut transit time (WGTT). The capsule is expelled naturally from the body.

U.S. Food and Drug Administration (FDA)
The SmartPill GI Monitoring System® was approved in 2006 by the U.S. by the Food and Drug Administration (FDA) under the 510(k) process. Indications for use state SmartPill is used in evaluating patients with suspected gastroparesis. In October 2009, the SmartPill was FDA-approved for the evaluation of colonic transit in patients with chronic constipation, to aid in differentiating slow and normal transit constipation. It is not indicated for use in children.

Literature Review
Hayes (2017; 2018) published a directory report for wireless capsule systems for diagnosis of gastroparesis and monitoring of gastrointestinal motility. The review included 13 studies of wireless capsule systems for detection of GI motility disorders that were reported in 14 publications with three cross-sectional comparative studies, seven prospective case-control studies, and three retrospective pretest/posttest studies. Wireless motility capsule (ten studies) or wireless capsule endoscopy (three studies) were compared to reference standards (i.e., gastric scintigraphy, small bowel barium transit, and radiopaque markers). The findings of the report note that although 13 studies were identified that compared wireless capsule systems with other methods for detection of GI motility disorders, these studies provide limited evidence concerning the accuracy of the wireless capsule systems and no reliable evidence that use of these systems improves patient outcomes.

The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review for wireless motility capsule (WMC) versus other diagnostic technologies for evaluating gastroparesis and constipation (Stein, et al., 2013). The review noted WMC appears to be accurate in detection of gastroparesis and slow-transit constipation and may provide increased diagnostic gain as compared with standard motility testing. While the strength of evidence (SOE) is low, the data were relatively consistent and suggested that this
modality is no less sensitive than conventional testing. The review noted that the evidence is insufficient to
determine whether use of WMC will improve outcomes of care.

Published studies in the peer-reviewed scientific literature are observational or retrospectively conducted with
small populations. Although well-established motility testing methods exist, studies are not designed to provide
comparison of the accuracy—including sensitivity, specificity, positive and negative predictive values—of the
SmartPill to conventional tests as the reference standard in same symptomatic patient population. As a result no
strong conclusions can be made regarding the clinical utility of this technology (Hasler, et al., 2018; Kuo, 2011;

Professional Societies/Organizations
**American College of Gastroenterology (ACG):** The ACG Practice Guideline on Gastroparesis (Camilleri et al.
2013) notes that wireless capsule motility testing is an alternative approach for assessment of gastric emptying;
however, further validation is required before it can be considered an alternate to scintigraphy for the diagnosis
of gastroparesis. This is noted to be a ‘Conditional recommendation, moderate level of evidence’.

**American Gastroenterological Association (AGA):** The AGA Medical Position Statement ‘Diagnosis and
Treatment of Gastroparesis’ (Parkman, et al., 2004) states that GES of a radiolabeled solid meal is the best
accepted method to test for delayed gastric emptying. The AGA Medical Position Statement Guidelines on
Constipation (AGA, 2013) supports the use of special tests such as CTT, anorectal manometry, balloon-
expulsion tests or defecography in refractory patients. Neither guideline addresses the use of SmartPill.

**American and European Neurogastroenterology and Motility Societies:** These organizations published
guidelines with consensus recommendations on the indications and optimal methods for the use of transit
measurements in clinical practice (Rao, et al., 2011b). The guidelines note that, “The WMC (wireless motility
capsule) is a validated and standardized test. It is recommended for assessment of colonic transit time in
subjects with constipation and those with suspected colonic disorders. It also provides measurements of regional
and whole gut transit.”

**American Society of Colon and Rectal Surgeons (ASCRS):** The ASCRS practice parameter for the
evaluation and management of constipation notes that anorectal physiology and colon transit time investigations
may help to identify the underlying etiology and improve the outcome in patients with refractory constipation. The
practice position notes the measurement of colon transit time using radio-opaque markers in patients with
suspected slow-transit constipation is inexpensive, simple, and safe (Ternent, et al., 2007).

**North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHN):** The
NASPGHN recommendations on evaluation and treatment of constipation in infants and children (2006) notes
that an evaluation of colonic transit time with radiopaque markers may be helpful in children with a history of
infrequent bowel movements who have no objective findings of constipation.

**Centers for Medicare & Medicaid Services (CMS):**
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Multiple LCDs found. Refer to the LCD table of contents link in
  the reference section.

**Use Outside of the US**
National Institute for Health and Care Excellence (NICE): NICE published guidelines regarding assessing motility
of the gastrointestinal tract using a wireless capsule. The guidelines note that:
- The evidence on assessing motility of the gastrointestinal tract using a wireless capsule raises no major
  safety concerns.
- There is evidence of efficacy in measuring gastrointestinal function but uncertainty about the clinical
  benefit of this, and about patient selection; therefore, this procedure should be used only with special
  arrangements for clinical governance, consent and audit or research.

**References**


**High Resolution Anoscopy (HRA) (CPT Codes 46601, 46607)**

During an anoscopy the perianal area and distal rectum are examined. High resolution anoscopy has been proposed as a method to identify anal lesions in high-risk populations, and for use in screening for anal cytology. High resolution anoscopy uses an anoscope as well as a colposcope or operating microscope for more detailed examination. After application of a 3% acetic acid solution and Lugol’s iodine, the canal is inspected with the colposcope. Areas with acetowhiteness are examined for abnormal patterns and targeted biopsies are performed on areas suspicious for high-grade squamous intraepithelial lesion (HSIL). Correlation of biopsy results with anal cytology results has been variable (Lee, 2010).

**Literature Review**

Hayes published a directory report for high-resolution anoscopy (HRA) for the evaluation of anal lesions (2014; 2018). The report concluded that HRA exhibits high sensitivity and moderate specificity for detecting abnormal lesions in high-risk populations. The findings included that HRA is more sensitive than cytology in detecting potentially harmful lesions. There were few studies found that evaluated the capacity of HRA to detect high grade anal intraepithelial neoplasia and findings were too inconsistent to accurately make any determination regarding the validity of HRA for this use.

Randomized controlled clinical trial data are lacking to demonstrate improved health outcomes with the use of high-resolution anoscopy to detect anal cytology. However, there is support by a number of professional societies/organizations related to its use as diagnostic tool in individuals with a suspicious anal lesion, including high-grade suspicious intraepithelial lesion (HSIL) and anal dysplasia found in prior cytology/biopsy.

A case series by Chang (2002) reported on a prospective study of high resolution anoscopy directed surgery in 37 patients with high-grade squamous intraepithelial lesion. Twenty-nine patients tested positive for human immunodeficiency virus (HIV), eight patients tested negative. Mean follow-up was 32.3 months for HIV-positive patients and 28.6 months in HIV-negative patients. No HIV-negative patient developed recurrent high-grade squamous intraepithelial lesions. Twenty-three of the 29 HIV positive patients had persistent or recurrent high-grade squamous intraepithelial lesions (HSIL) (p<.003). Six patients underwent reoperation for HSIL; four recurred by six months. No patients developed incontinence, stenosis, postoperative infection, or significant bleeding after surgical treatment. Study limitations include small patient population and uncontrolled study design.

**Professional Societies/Organizations**
American Society of Colon and Rectal Surgeons (ACRS):
The ACRS published updated (Steele, et al., 2012) published practice parameters for anal squamous cell cancers (2018). The guidelines note that HRA may be considered as a screening option for patients at high risk for cancer when performed by clinicians with appropriate training in the procedure. Recommendation: Weak recommendation based on moderate-quality evidence, 2B.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
Ontario Health Technology Assessment Series (OHTAS): OHTAS (2007) notes that high resolution anoscopy rather than routine anoscopy-guided biopsy is considered to be the diagnostic standard.

Reference

13C-Spirulina Gastric Emptying Breath Test (GEBT) (CPT codes 91299, 0106U)
Gastroparesis is a syndrome of objectively delayed gastric emptying in the absence of a mechanical obstruction and cardinal symptoms of nausea, vomiting, early satiety, bloating, and/or upper abdominal pain. In patients with suspected gastroparesis and no evidence of a mechanical obstruction on imaging or upper endoscopy, an assessment of gastric motility is necessary to establish the diagnosis of gastroparesis. Delayed gastric emptying on scintigraphy is required to establish the diagnosis of gastroparesis (Camilleri, [UpToDate], 2018). A more recent developed test, the 13C-Spirulina Gastric Emptying Breath Test (GEBT) (Cairn Diagnostics, Brentwood, TN) has been proposed as an alternative approach for the assessment of gastric emptying. While these tests have the advantage of avoiding radiation associated with scintigraphy, further studies are needed before they can be routinely recommended for evaluation of delayed gastric emptying (Camilleri, [UpToDate], 2018).
A kit containing the specially labeled test meal and all components necessary to administer the test meal and collect breath samples is provided to the test administration site by Cairn Diagnostics. The collected breath samples are returned to Cairn's CLIA-certified clinical laboratory for analysis by gas isotope ratio mass spectrometry (GIRMS). The patient will eat a special test meal, and then additional breath samples are collected at specified times. Once the test meal is consumed, the carbon-13 in the Cairn GEBT test meal gives rise to carbon-13 labeled CO₂, or ¹³CO₂, which can be measured in the breath samples.

Literature Review
Szarka conducted a study to validate ¹³C-Spirulina platensis gastric emptying (GE) breath test (GEBT) with a standardized meal. The study included 38 healthy volunteers and 129 patients with clinically suspected delayed gastric emptying (GE) who underwent measurements at 45, 90, 120, 150, 180, and 240 minutes after a 238 kcal meal labeled test with 100 mg [¹³C]-S platensis and 0.5 mCi ⁹⁹mTc. The authors established normal ranges for scintigraphy with the test meal, intra-individual and inter-individual coefficients of variation (COVs), and the ability of the GEBT breath percent dose excreted *1000 values to predict scintigraphic half-life and to categorize GE as delayed, normal, or accelerated. In healthy group, the 10th and 90th percentiles of half-life for scintigraphic GE with this meal were 52 and 86 minutes; intra-individual COVs for scintigraphy and the GEBT were, respectively, 31% and 27% at 45 minutes, 17% and 21% at 90 minutes, 13% and 16% at 120 minutes, 10% and 13% at 150 minutes, and 8% and 12% at 180 minutes. The inter-individual COVs at each time for the [¹³C] GEBT and scintigraphy were typically approximately 1%-4% lower than intra-individual COVs. Individual breath samples at 45, 150, and 180 minutes predicted GE category; at 80% specificity, 45- and 180-minute combined were 93% sensitive to identify accelerated GE, and 150- and 180-minute combined were 89% sensitive for delayed GE.

U.S. Food and Drug Administration (FDA)
13C-Spirulina Platensis Gastric Emptying Breath Test (Gastric Emptying Breath Test, [GEBT]) (Advanced Breath Diagnostics LLC, Brentwood TN) received premarket approval (PMA) April 2015. The Gastric Emptying Breath Test (GEBT), to be used with the GEBT test meal, is intended for use in the measurement of the rate of gastric emptying of solids and as an aid in the diagnosis of delayed gastric emptying (gastroparesis) in adult humans who are symptomatic for gastroparesis. Contraindications include:
- Individuals with known hypersensitivity to Spirulina, egg, milk or wheat allergens should avoid the GEBT.
- Because the GEBT is an indirect multi-compartmental method of measuring gastric emptying, GEBT results may be inaccurate in individuals compromised with significant small bowel, pancreatic, liver and/or lung disease. Consequently GEBT should not be administered to patients with pulmonary dysfunction (e.g. COPD) and/or small bowel malabsorption.

Approval was based on the observation in a study of 115 patients who underwent simultaneous scintigraphy and spirulina 13C breath test. At 80 percent specificity, the 13C-spirulina breath test samples at 150 and 180 minutes had a combined sensitivity of 89 percent for delayed gastric emptying.

Professional Societies/Organizations
American College of Gastroenterology (ACG): ACG published clinical guidelines for management of gastroparesis. The recommendations include, "Alternative approaches for assessment of gastric emptying include wireless capsule motility testing and ¹³C breath testing using octanoate or spirulina incorporated into a solid meal; they require further validation before they can be considered as alternates to scintigraphy for the diagnosis of gastroparesis. (Conditional recommendation, moderate level of evidence)"

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCDs found.

Use Outside of the US
No relevant information

References


Rectal control system for vaginal insertion (e.g., Eclipse System) (HCPCS code A4563)
Fecal incontinence is defined as the involuntary loss of solid or liquid feces. Initial management includes supportive care and medical therapy. Subsequent management may include injectable anal bulking agents, biofeedback, and sacral nerve stimulation. A method to treat fecal incontinence has been proposed that includes a vaginal insert with a pressure-regulated pump to temporarily occlude the rectum. The Eclipse system (Pelvalon, Sunnyvale, CA) consists of includes two main components, an insert and a pump. The insert is used intra-vaginally, is insertable/removable by the patient, and includes a balloon that when inflated, exerts a force posteriorly (trans-vaginally) against the wall in the rectum resulting in a decrease in the lumen of the rectum. It is theorized that the compression of the rectal space results in decreased frequency of fecal incontinence events.

U.S. Food and Drug Administration (FDA)
The Eclipse System received Food and Drug Administration (FDA) 510(k) Premarket Notification clearance (K150558) on November 15, 2015. It is Class II device and is a vaginal bowel control therapy intended to treat women with fecal incontinence.

Literature Review
There is a lack of randomized studies regarding this treatment. The published studies include a prospective cohort study with small numbers. Studies are needed to evaluate its efficacy in the long-term.

Richter et al. (2015) conducted a prospective, non-comparative study of the effectiveness and safety of a vaginal bowel-control device and pump system for fecal incontinence treatment. The study included 61 patients with a minimum of four fecal incontinence episodes over 2 weeks that were fit with the intravaginal device. Treatment success, defined as a 50% or greater reduction of incontinent episodes, was assessed at 1 month. Participants were invited into an optional extended-wear period of another 2 months. Secondary outcomes included symptom improvement measured by the Fecal Incontinence Quality of Life, Modified Manchester Health Questionnaire, and Patient Global Impression of Improvement. The results included at one month, intention-to-treat success was 78.7% (48/61, P<.001); per protocol success, 85.7% (48/56, P<.001) and 85.7% (48/56) considered bowel symptoms "very much better" or "much better." There was improvement in all Fecal Incontinence Quality of Life (P<.001) and Modified Manchester (P<.007) subscales. The success rate at 3 months was 86.4% (38/44; 95% confidence interval 73-95%). There were no serious adverse events. The study was limited due to the lack of randomization, small number of patients and short follow-up timeframe.

Varma et al. (2016) reported on secondary analysis of the above study (Richter, et al., 2015) to examine the impact of a vaginal bowel control system on parameters of bowel function, including frequency, urgency, stool consistency, and evacuation. The study included 56 patients. Subjects completed a 2-week baseline diary of bowel function before and after treatment completed at one month. Fecal urgency, consistency of stool (Bristol score), and completeness of evacuation were recorded for all bowel movements. Use of the insert was
associated with an improvement in bowel function across all 4 categories. Two thirds (8/12) of subjects with a high frequency of daily stools (more than 2 per day) shifted to a normal or low frequency of stools. Analysis of Bristol stool scale scores demonstrated a significant reduction in the proportion of all bowel movements reported as liquid (Bristol 6 or 7), from 36% to 21% (p = 0.0001). On average, 54% of stools were associated with urgency at baseline compared with 26% at 1 month (p < 0.0001). Incomplete evacuations with all bowel movements were reduced from 39% to 26% of subjects at 1 month (p = 0.0034).

**Professional Societies/Organizations**

Professional society guidelines in support of this treatment for fecal incontinence are lacking.

**Centers for Medicare & Medicaid Services (CMS)**

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCDs found.

**Use Outside of the US**

No relevant information

**References**


**Coding/Billing Information Gastroenterology**

**Anoscopy, High Resolution (HRA)**

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<td>46601</td>
<td>Anoscopy; diagnostic, with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, including collection of specimen(s) by brushing or washing, when performed</td>
</tr>
<tr>
<td>46607</td>
<td>Anoscopy; with high-resolution magnification (HRA) (eg, colposcope, operating microscope) and chemical agent enhancement, with biopsy, single or multiple</td>
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**Fecal Calprotectin**

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:
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<td>83993</td>
<td>Calprotectin, fecal</td>
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### ICD-10-CM Diagnosis Codes

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<th>Codes</th>
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<td>R19.7</td>
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### Additional Services Considered Experimental/Investigational/Unproven:

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<tr>
<td>46999</td>
<td>Unlisted procedure, anus</td>
<td>Considered Experimental/Investigational/Unproven when used to report transanal radiofrequency therapy for fecal Incontinence (e.g., SECCA procedure)</td>
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<tr>
<td>91112</td>
<td>Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report</td>
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<tr>
<td>91299</td>
<td>Unlisted diagnostic gastroenterology procedure</td>
<td>Considered Experimental/Investigational/Unproven when used to report 13C-Spirulina Gastric Emptying Breath Test (GEBT)</td>
</tr>
<tr>
<td>0106U</td>
<td>Gastric emptying, serial collection of 7 timed breath specimens, non-radioisotope carbon-13 (13C) spirulina substrate, analysis of each specimen by gas isotope ratio mass spectrometry, reported as rate of 13CO2 excretion</td>
<td></td>
</tr>
<tr>
<td>0397T</td>
<td>Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)</td>
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<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>A4563</td>
<td>Rectal control system for vaginal insertion, for long term use, includes pump and all supplies and accessories, any type each</td>
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**Neurology**

Quantitative Sensory Testing (QST) (CPT Codes 0106T, 0107T, 0108T, 0109T, 0110T; Current perception threshold/sensory nerve conduction test (sNCT) HCPCS Code G0255)

QST is a psychophysical test used to assess and quantify small and large-fiber sensory nerve function by the use of touch, thermal (i.e., hot and cold), pain, and/or vibratory sensations. QST, a noninvasive study, is proposed to be able to detect early, subtle changes in small and large sensory nerve fibers. It has been proposed as a complementary diagnostic and monitoring tool to be used with traditional testing (e.g., Semmes-Weinstein monofilaments, Rydel Seiffert graduated tuning fork) for the detection of sensory nerve abnormalities for conditions such as diabetic neuropathy, carpal tunnel syndrome, multiple sclerosis and vitamin B deficiencies. QST has also been proposed for multiple other indications including: identifying HIV-associated peripheral neuropathy, use before and after lumbar discectomy to analyze sensory nerve dysfunction in the lower-extremities, following greater saphenous vein stripping to evaluate postoperative sensory changes, and prior to and following spinal cord stimulation for patients with chronic neuropathic pain due to either failed back surgery...
syndrome or complex regional pain syndrome, evaluation of sexual dysfunction, peripheral nerve dysfunction, painful bladder syndrome, and radiculopathy.

Several limitations of QST have been documented including a potential for bias if the patient is cognitively impaired or desires an abnormal result. QST has no localizing value because it is reflective of the integrity of the entire sensory neuraxis from receptors to brain. Abnormal QST values may occur because of peripheral nerve or central nervous system dysfunction. The test may lack objectivity due to patient status (e.g., distraction, boredom, inattentiveness, fatigue, drowsiness), which may be enhanced by the time it takes to complete the test (e.g., one to two hours). The inclusion of the patient’s reaction time to a stimulus may distort the actual sensory threshold. Electrode size, site of stimulation, method and rate of change of the stimulation, method of obtaining patient’s response, and variations in testing devices make reproducibility of the test results difficult. There is also a lack of standardization for testing procedures and reporting outcomes, therefore test execution may differ with different examiners. Due to these variables, it is proposed that quantitative sensory testing (QST) lacks the objectivity of conventional nerve conduction studies (Pavlaković, et al., 2010; Backonja, et al., 2009; Siemionow, et al., 2006; Chong, et al., 2004; Shy, et al., 2003).

The various testing methods and devices used for QST to determine sensory abnormalities include:

- Electrical current testing such as current perception threshold testing or sensory nerve conduction testing (sNCT) which assesses sensory function. Examples of these devices include the Medi-DX 7000 (Neuro-Diagnostic Associates, Laguna Beach, CA) and the Neumeter® CPT or s-NCT (Neurotron, Inc., Baltimore, MD).
- Pressure-specified sensory testing evaluates nerve function by detection of light, status, and moving touch. Devices include the NK Pressure-Specified Sensory Device™ (PSSD) (NK Biotechnical Engineering Co., Minneapolis, MN).
- Thermal testing is used to assess a distinction between predominantly C fiber and A-delta fiber activity by the application of cold and heat. Examples of thermal devices by Medoc Advanced Medical Systems LTD (Minneapolis, MN) include the Contact Heat-Evoked Potential Stimulator (CHEPS), GSA Genito, TSA-2001 Sensory Analyzer, and the TSA-2001 Sensory Analyzer.
- Vibration perception threshold testing, or vibratory testing, assesses large myelinated nerve fiber dysfunction and measures sensory thresholds. The VSA-3000 Vibratory Sensory Analyzer (Medoc Advanced Medical Systems, Eilat, Israel) and the Bio-thesiometer (Bio-Medical Instruments, Newbury, OH) are examples of these devices.
- Voltage-actuated sensory nerve conduction threshold (V-sNCT) testing is used to evaluate the sensitivity, specificity and predictive value of A-delta fibers to assess localize pain sources. These devices include the Neural-Scan (Neuro-Diagnostic Associates [NDA], Inc., Laguna Beach, CA).
- Pain-fiber nerve conduction testing (pf NCV), also referred to as pain fiber nerve testing, has been proposed as a method of evaluating the severity, location and distribution of pain associated with conditions such as radiculopathy and/or neuropathy. According to the American Association of Sensory Electrodiagnostic Medicine (AASEM, 2015), this type of nerve testing is noninvasive, employs the use of a device, such as the Axon II, Neural Scan, and is conducted using a voltage actuated stimulus (sensory nerve conduction) and a potentiometer to measure the amplitude of the action potential.

**U.S. Food and Drug Administration (FDA):** QST systems and devices are approved by the FDA 510(k) process and are classified either as a Class II device or an unclassified device.

**Literature Review**
Hayes published a technology directory report regarding quantitative sensory testing for the diagnosis of lower extremity peripheral neuropathy (Hayes 2014; updated 2018). The review included 29 prospective or retrospective cohort, cross-sectional, matched-group, or case-control studies that evaluated QST for detection of neuropathy or foot ulcer and/or amputation susceptibility. There were no studies identified that relied on QST to guide patient management. Findings of the report noted that all of the available studies of QST are of poor to very poor quality and the amount and consistency of evidence concerning QST for the diagnosis of neuropathy varies widely, depending on the type of QST and the indication for testing. Some evidence suggests that vibration QST has moderate to high accuracy for the diagnosis of neuropathy and that monofilament QST and vibration QST have moderate to high accuracy for the diagnosis of loss of protective sensation as reflected in
susceptibility to foot ulcer and/or amputation as a consequence of neuropathy. It was noted that there is insufficient evidence to evaluate monofilament QST for the diagnosis of neuropathy or to evaluate thermal QST, ball bearing QST, 2-point discrimination QST, or tactile circumferential QST for the diagnosis of neuropathy or susceptibility to foot ulcer and/or amputation. The report concluded that the best available studies do not provide consistent evidence that quantitative sensory testing (QST) has high accuracy for the diagnosis of neuropathy or loss of protective sensation.

The clinical significance of QST has not been demonstrated in clinical trials (Georgopoulos et al., 2019; Griffioen, et al., 2018; Marcuzzi, et al., 2016; Atherton, et al., 2007; Soomekh, et al., 2006; Chong, et al., 2004; Shy, et al., 2003). Additionally, evidence in the published peer-reviewed scientific literature does not support the clinical utility of QST. Randomized controlled clinical trial data are scarce; studies are primarily in the form of nonrandomized comparative studies and case series with heterogeneous small patient populations, using a variety of different devices. QST has not been recommended as a stand alone test. Limitations of the studies include: weak study methodology; inability to verify data; lack of a control group; numbers of patients lost to follow-up; numbers of patients who did not complete all of the testing; lack of comparisons to conventional neurological tools; variations in testing parameters, equipment and protocol; and lack of randomization (Eisenberg, et al., 2006; England, et al, 2005/2008; Centers for Medicare and Medicaid Services, 2003).

Professional Societies/Organizations
American Academy of Orthopaedic Surgeons (AAOS). The evidenced-based guideline for management of carpal tunnel syndrome does not include the use of QST or CPT for diagnosis of carpal tunnel syndrome (AAOS, 2016).

American Academy of Neurology (AAN): In a report on QST based on a review of 350 articles, the AAN (Shy, et al., 2003; reaffirmed 2019) noted QST is a potentially useful tool for measuring sensory impairment for clinical and research studies. However, QST results should not be the sole criteria used to diagnose pathology. The AAN indicated that malingering and other nonorganic factors can affect the outcomes of the test results. They also noted that well-designed studies to compare the various types of QST devices and methodologies are indicated and should include patients with abnormalities detected solely by QST.

In a report on distal symmetric polyneuropathy (England, et al., 2005; reaffirmed 2008), the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation stated that QST was not recommended as a diagnostic tool because the sensitivities and specificities varied widely among the studies, and the tests have inherent variability. QST is difficult to standardize, and reproducibility of results ranged from poor to excellent.

American Association of Electrodiagnostic Medicine (AAEM): The AAEM (Chong, et al., 2004) conducted a review of the literature on QST to assess the “methodology, reliability, reproducibility, limitations, and potential clinical applications” of these studies. The authors noted the following conclusions:

- QST is a reliable psychophysical test of large- and small-fiber sensory modalities.
- QST tests the integrity of the entire sensory axis from receptors to brain. Abnormalities do not localize dysfunction to the central or peripheral nervous system, or any particular location along the peripheral nervous system.
- QST is highly dependent on the full cooperation of the patient and may be falsely abnormal if the patient is biased toward an abnormal result or is cognitively impaired. No algorithm can reliably distinguish between psychogenic and organic abnormality.
- QST has been shown to be reasonably reproducible over a period of days or weeks in normal subjects. Since longitudinal QST studies of patients in drug trials are usually done over a period of several months to a few years, reproducibility studies on the placebo-controlled group should be included.
- The reproducibility of thermal thresholds may not be as good as that of vibration threshold.
- For individual patients, more studies are needed to determine the maximum allowable difference between two QSTs that can be attributed to experimental error.
- Different commercially available QST instruments have different specifications (thermode size, stimulus characteristics), testing protocols, algorithms, and normal values. Only QST instruments and their
corresponding methodologies that have been shown to be reproducible should be used for research and patient care.

- The results of QST can only be interpreted properly if machine calibration and testing protocol are strictly followed.
- The literature does not allow a conclusion to be made regarding whether any QST instrument is better than another.

Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCD): Sensory Nerve Conduction Threshold Tests (sNCTs) (160.23). Refer to the CMS NCD table of contents link in the reference section.
- Local Coverage Determinations (LCDs): No LCD found.

Use Outside of the US

European Federation Of Neurological Societies (EFNS): In their 2009 guidelines (Cruccu, 2009) on the assessment of neuropathic pain, EFNS stated that studies using qualitative sensory testing (QST) lack blinding, involve a broad spectrum of patients and controls, and only four of 50 new studies were prospective. The variability of methods, results, and patient populations (e.g., diabetic neuropathy, spinal cord injury, radiculopathy) prevent any conclusions from being drawn. The Society stated that qualitative sensory testing (QST) may be used to document the sensory profile, but the test “cannot be considered sufficient to separate differential diagnoses”. “Quantitative sensory testing (QST) is helpful to quantify the effects of treatments on allodynia and hyperalgesia and may reveal a differential efficacy of treatments on different pain components”. They “do not recommend the systematic measure of thermal stimuli except for pathophysiological research or treatment trials. A simple and sensitive tool to quantify pain induced by thermal stimuli in clinical practice is still lacking”.

International Association for the Study of Pain (IASP®): In guidelines on neuropathic pain assessment (Haanpää, 2011), the Special Interest Group on Neuropathic Pain of the IASP (NeuPSIG) explains that QST is biased towards thermal, including nociceptive, testing, which means that it excludes assessment of large fiber function. According to NeuPSIG, more studies with complete somatosensory profiles are needed. Results of available studies have been inconsistent and conflicting. Since QST abnormalities are found in non-neuropathic pains, these tests cannot be taken as a conclusive demonstration of neuropathic pain. Furthr, NeuPSIG notes QST can be used in clinic along with bedside testing, but it cannot allow for estimation of the level of the lesion within the neuraxis. The relevance of QST to predict therapeutic outcome has yet to be established in prospective studies.

References


Physiologic Recording of Tremor Using Accelerometer/Gyroscope (CPT Code 95999)

Accelerometers and gyroscopes are devices that may be used to objectively record and monitor motion and electrical activity of muscles to measure tremor in individuals with movement disorders. Recent studies have examined the clinical utility of these devices as an adjunct in diagnosis and measurement of functional ability and recovery in individuals with dyskenetic disorders.

U.S. Food and Drug Administration (FDA)
The FDA approved the Kinesia™ device (Cleveland Medical Service, Cleveland, OH) in April 2007 for the monitoring and recording of motion and electrical activity of muscle to quantify kinematics of movement disorders such as tremor for research and diagnostic purposes. The Tremorometer® (FlexAble Systems, Inc., Fountain Hills, AZ) received substantial equivalency FDA 510 (k) approval in January 2001. It is a system designed to improve the measurement and quantification of tremor in human patients regardless of the etiology.

Literature Review
Controlled clinical trial data are lacking to inform the utility of these devices, including the translation of measurements into meaningful outcomes. Cheung et al. (2011) performed a systematic literature review; reviewing 54 studies that used accelerometers to classify human movement and to appraise their potential to determine the level of activity of older persons in hospital settings. Outcome measures criteria were comparisons of derived classifications of postural movements and mobility against those made by using observations. A number of limitations to the study were noted including the number and type of accelerometers used for measurement, varied age of study participants (varied from teenager to >60 yrs). Most studies were limited by small sample size; 54% had 10 subjects or less. Methods for validating data were also varied. Of the accelerometer studies included in this review, only 17 were conducted on patients and the remaining were conducted on healthy subjects (n=37 studies). The authors note that the literature review indicates that only a limited number of studies have applied accelerometry to measure activities in patients, of which six studies were of older patients. These studies were limited by smaller sample sizes and use of multiple accelerometer devices attached to different body positions. The activity classification algorithms validated in small sample size studies with <6 patients are insufficient for clinical use. A suitable algorithm for application in geriatric rehabilitation settings needs to be generic and accurate in older patients with different levels of mobility impairment.

Gebruers et al. (2010) reported results of a systematic review assessing the clinical applicability of different accelerometer based measurement techniques in persons with stroke. Twenty-five articles were selected for inclusion; there were 4 randomized controlled trials (RCT). The authors noted that although the available evidence may suggest that accelerometers yield valid and reliable data about individuals with stroke, data are young, limiting the ability to draw consistent conclusions. Further research is necessary to investigate predictive value and responsiveness.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCDs found.

Use Outside of the US
No relevant information.

References
There are scarce data in the published, peer-reviewed scientific literature regarding the current clinical use of adrenal-to-brain transplantation in humans for any indication. In a systematic review of the literature, the Agency for Healthcare Research and Quality ([AHRQ], 2003) noted that there is a lack of efficacy and substantial morbidity associated with the procedure for the treatment of Parkinson disease (PD). The AHRQ also concluded that adrenal medullary transplants are no longer performed to treat PD.

There is ongoing research in animal and human models relative to the use of fetal mesencephalic transplantation as a replacement source of dopamine-producing cells. In this procedure, fetal brain cells (i.e., neurons) that produce dopamine are implanted in the putamen or head of the caudate area of the brain, which is the area controlling movement. In theory, the transplanted neurons can replace the loss of normal dopamine-producing cells. These fetal cells may be human or xenogeneic (i.e., derived from a different species).

Clinical improvement was demonstrated in small numbers of individuals with PD undergoing transplantation of fetal tissue in several nonrandomized studies; however, results have not been replicated in double-blind sham-surgery controlled clinical trials (Olanow, 2003; Freed, 2001). Transplantation of fetal substantia nigra into the stratum has failed to show significant efficacy and has been associated with the side effect of transplant-induced off-medication dyskinesias. More recently, implanted dopamine neurons have been found to contain Lewy bodies, suggesting that they are dysfunctional and may have been affected by the PD pathological process (Olanow, 2009).

The data is scarce regarding the safety and effectiveness of xenogeneic fetal cells for any indication in humans. Schumacher et al. (2000) reported results of a case series study of 12 individuals with Parkinson disease who underwent unilateral implantation of embryonic porcine ventral mesencephalic tissue (Schumacher, 2000). In the medication-off state, total Unified Parkinson's Disease Rating Scale scores improved by 19% (p=.01). At the time of study publication there were no reported permanent complications. Limitations of the study include small size, uncontrolled study design, and short-term follow-up.

U.S. Food and Drug Administration (FDA)
The FDA Center for Biologics and Research regulates the transplantation of fetal/embryonic cells. Companies supplying cell and tissue-based products must register and list their products with the FDA.

Professional Societies/Organizations
American Academy of Neurology (AAN): The AAN in an evaluation of surgery for Parkinson's disease (Hallet, et al., 1999) recommended that adrenal-to-brain transplantation not be performed because of unacceptable risk to the patient. They further noted that the procedure was no longer being studied. Regarding fetal mesencephalic transplantation the AAN notes that, while the procedure is promising, it remains experimental due to lack of controlled clinical trials. The authors determined that there were small, nonrandomized case studies which noted
functional improvement in some patients; however, unacceptably high levels of morbidity and mortality were associated with the procedure. Review of pathologic reports found that few transplanted cells survived long term, suggesting that benefit of the procedure would be of short duration.

The authors also reviewed the documented studies of fetal mesencephalic transplantation. Studies were small and nonrandomized. There was variation between the studies in the techniques utilized, the site of transplantation, the number of mesencephalons used, and the immune-suppressive regimen provided. In all of the studies some of the patients demonstrated improvement in motor function. The summary notes that while the procedure is promising because it appears effective and has low morbidity and mortality, it is considered experimental because of the absence of controlled studies.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCDs found.

Use Outside of the US
No relevant information

References

External Heart Rate and 3-Axis Accelerometer Monitoring to Diagnose Nocturnal Epilepsy (CPT Codes 0381T, 0382T, 0383T, 0384T, 0385T, 0386T)

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures (Abou-Khalil, 2012). Standard evaluation and diagnosis of seizures and epilepsy includes an in-depth clinical history; an electroencephalogram and other brain imaging may be used to supplement the history, help classify the type of seizure and determine underlying pathology. A number of epileptic seizure syndromes exist including several which are characterized by the occurrence of seizures at night, while the individual is sleeping and unattended. Nocturnal seizures often occur in children. Use of external heart rate and 3-axis accelerometer monitoring has been proposed as a method to detect/diagnose nocturnal epilepsy. Three-axial accelerometer measures the movement (acceleration) in three orthogonal directions fixed to a sensor by way of soft bands generally affixed to the wrists and/or ankles.
U.S. Food and Drug Administration (FDA)

Embrace (Empatica Inc.) was initially cleared through the FDA 510(k) Premarket Notification process (K172935) on January 26, 2018. A second clearance (K181861) was issued on December 20, 2018. The Embrace is a prescription only device that is indicated for use as an adjunct to seizure monitoring of adults and children age six and up in home or healthcare facilities during periods of rest. The device is worn on the wrist and senses Electrodermal Activity (EDA) and motion data to detect patterns that may be associated with generalized tonic clonic seizures in patients with epilepsy or at risk of having epilepsy. When a seizure event is detected, Embrace sends a command to a paired wireless device that is programmed to initiate an alert to a designated caregiver. The System records and stores data from Accelerometer, EDA, and Temperature sensors for subsequent review by a trained healthcare professional.

Literature Review

Published, peer-reviewed data are limited regarding the effectiveness of accelerometer monitoring to diagnose epilepsy, including nocturnal epilepsy (Velez, et al., 2016; Beniczky, 2013; Van de Vel, 2013). Studies are limited by uncontrolled design, small participant numbers and short-term follow-up.

Beniczky et al. (2013) reported outcomes of a prospective study designed to assess the clinical reliability of a wrist-worn, wireless accelerometer sensor for detecting generalized tonic–clonic seizures in 73 consecutive patients. The wireless wrist accelerometer correctly detected 35 seizures (89.7%). The mean sensitivity per patient (with seizure) was 91%. Twenty-eight seizures occurred during sleep and eleven seizures occurred when the patient was awake. The device had a similar accuracy for detecting nocturnal and daytime seizures. One hundred forty-nine seizures other than generalized tonic-clonic seizures were recorded (simple partial, 37; complex partial/psychomotor, 31; focal tonic, 6; hypermotor, 6; absence, 1; myoclonus, 60; psychogenic nonepileptic seizure, 8). Study limitations include uncontrolled design, small study numbers and short-term follow-up.

Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCD found

Use Outside of the US

No relevant information

References


Coding/Billing Information Neurology

Note: 1) This list of codes may not be all-inclusive.
    2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.
Neurology Services Considered Experimental/Investigational/Unproven:

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<td>95999</td>
<td>Unlisted neurological or neuromuscular diagnostic procedure</td>
<td>Considered Experimental/Investigational/Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s)</td>
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<td>0106T</td>
<td>Quantitative sensory testing (QST), testing and interpretation per extremity; using touch pressure stimuli to assess large diameter sensation</td>
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<tr>
<td>0107T</td>
<td>Quantitative sensory testing (QST), testing and interpretation per extremity; using vibration stimuli to assess large diameter fiber sensation</td>
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<td>Quantitative sensory testing (QST), testing and interpretation per extremity; using cooling stimuli to assess small nerve fiber sensation and hyperalgesia</td>
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<td>Quantitative sensory testing (QST), testing and interpretation per extremity; using heat-pain stimuli to assess small nerve fiber sensation and hyperalgesia</td>
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<td>0110T</td>
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<td>0381T</td>
<td>External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
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<td>0382T</td>
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<td>External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
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review and interpretation by a physician or other qualified health care professional

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<td>0386T</td>
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<td>G0255</td>
<td>Current perception threshold/sensory nerve conduction test, (sNCT) per limb, any nerve</td>
</tr>
<tr>
<td>S2103</td>
<td>Adrenal tissue transplant to brain</td>
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**Obstetrics/Gynecology**

**Laparoscopic Radiofrequency Ablation (RFA) of Uterine Fibroids (CPT codes 58674)**

Laparoscopic RFA has been proposed for the treatment of uterine fibroids (UF). In this minimally invasive procedure a laparoscopic ultrasound probe is used to determine the location and size of fibroids. An electrode array delivers alternating radiofrequency energy to drive a current through the tissue to be ablated, causing controlled, local heating, resulting in targeted tissue destruction. Treatment options for symptomatic UF include medication, hysterectomy, myomectomy, hysteroscopy, uterine artery embolization (UAE), radiofrequency ablation (RFA), and magnetic resonance imaging–guided ultrasound surgery (MRgFUS).

**U.S. Food and Drug Administration (FDA):** The Acessa System (Halt Medical, Inc., Brentwood, CA) was given 510(k) approval in November 2012. According to the approval summary this system is indicated for use in percutaneous, laparoscopic coagulation and ablation of soft tissue, including treatment of symptomatic uterine fibroids under laparoscopic ultrasound guidance. The FDA specifically notes the Acessa System must be used under laparoscopic ultrasound guidance. Laparoscopic ultrasound equipment is not included with the Acessa System.

In October 2018, the next generation of the Acessa System, received 510(k) FDA approval for the Acessa ProVu System. It is indicated for use in percutaneous, laparoscopic coagulation and ablation of soft tissue, including treatment of symptomatic uterine fibroids under laparoscopic ultrasound guidance. The Acessa ProVu System includes optional electromagnetic guidance for enhancing the ultrasonic image of the Acessa ProVu Handpiece and for predicting its future path on a computer monitor screen which also shows the ultrasound B-scan image.

**Literature Review**

Peer-reviewed published clinical trial data are include two randomized controlled trials (Brucker, 2014; Hahn, et al., 2015; Kramer, et al., 2016; Rattray, et al., 2018) and several nonrandomized, uncontrolled prospective studies, also with small participant numbers. Chudnoff et al. (2013), Guido et al. (2013) and Berman et al. (2014) reported 12-, 24- and 36-month follow-up of the same nonrandomized prospective interventional trial involving 135 women with symptomatic uterine fibroids. The only comparator evaluated in the eligible studies was laparoscopic myomectomy (LM) in two studies (Brucker, et al., 2014; Hahn, et al., 2015; Kramer, et al., 2016; Rattray, et al., 2018). These studies are generally limited by uncontrolled, nonrandomized study design, small size and lack of comparison to other treatment methods. Several randomized controlled studies are ongoing.

Hayes evaluated the safety and efficacy the Acessa System for treatment of uterine fibroids (Hayes, 2014; 2019). The review included six clinical studies reported in 11 publications that evaluated the efficacy and safety of RFVTA with the Acessa System for treatment of symptomatic UF. The only comparator evaluated in the eligible studies was laparoscopic myomectomy (LM) (in two studies). Follow-up periods ranged from three months to three years.

The review noted regarding effectiveness:
• Symptom severity (six studies): Evidence suggests that RFVTA generally resulted in statistically significant improvements from baseline in symptomatology. RFVTA did not result in any statistically significant differences in UF-related symptom severity or quality of life (QOL) compared with LM; however, comparative analyses were limited to two studies and were not always conducted statistically.
• General QOL (four studies): Comparatively, one study performed a between-group analysis at 12 months and found no statistically significant differences between scores of the SF-36 Health Survey (SF-36) (RAND Corp.) among patients who received RFVTA or LM. Other evaluations demonstrated statistically significant improvements from baseline at three months (one study) and 36 months (one study). A third study found changes from baseline were statistically significant on the mental component of the SF-36 at six weeks but not 12 weeks; changes from baseline were statistically significantly improved on the physical component at both six and 12 weeks.
• Recovery (six studies): Time to return to normal activity ranged from 3.4 to 20.5 days for those treated with RFVTA. Differences were not assessed statistically in the only comparison of RFVTA and LM at the 3-month follow-up. Missed work varied among studies, ranging from 4.1 to 11 days. Compared with LM, treatment with RFVTA resulted in statistically significantly less days missed from work at three months according to one study (11.1 versus 18.5; P=0.0193). A second comparative study did not assess statistical differences between RFVTA (10 days) and myomectomy (17 days).
• Uterine volume (three studies): Reductions in mean uterine volume were statistically significant in two studies, ranging from 24.3% to 41.8% at 12 months follow-up (P<0.05). Of these studies, one study also noted significant uterine reduction at three months (15.7%; P<0.001). A third study evaluated uterine volume reduction at 12 months and found no statistically significant difference from baseline (21% change from baseline; P=0.192).
• Fertility and pregnancy outcomes (two studies): No studies evaluated success in achieving pregnancy among women attempting to conceive after RFVTA. Two studies reported pregnancies among patients who underwent RFVTA compared with LM. One RCT reported that no pregnancies had occurred as of three months follow-up. A second RCT reported three pregnancies in patients undergoing RFVTA and six pregnancies in patients undergoing LM; however, no analysis was performed regarding the proportion of patients who achieved pregnancy out of the proportion of patients who were attempting to conceive.

Regarding safety: Safety: Patients reporting any adverse event ranged from 4% to 32%. Adverse events reported in the eligible studies were uncommon and included hypermenorrhea, uterine cramping, nausea, vomiting, migraine, hematoma at trocar site, vertigo, abdominal pain, urinary tract infection, abdominal wall injury, pelvic abscess, laceration of sigmoid colon, vaginal bleeding, severe lower abdominal pain, uterine serosal burn, abnormal vaginal discharge, skin infection, bloating, constipation, intestinal inflammation, flu-like symptoms, sinus infection, sore gums, swollen throat glands, upper respiratory infection, skin blisters, arthritis, and skin irritation. In the eligible studies, one patient experienced severe bleeding during a cesarean section and early postpartum period which was deemed as possibly related to treatment with RFVTA.

Regarding quality of evidence: The overall low-quality body of evidence was due to individual study quality, lack of evidence comparing RFVTA with other minimally invasive techniques, and lack of evaluation of the safety of RFVTA in women who wish to maintain fertility and achieve pregnancy. Of the eligible studies, one was of fair quality, four were of poor quality, and one was of very poor quality. Additional limitations noted in the studies included lack of randomization, lack of active comparators, small sample sizes, lack of power analyses, high attrition rates, censored data for patients lost to follow-up, limited follow-up, and limited statistical analyses.

The review noted that large, well-controlled trials comparing RFVTA with other minimally invasive, uterine-sparing procedures are needed especially evaluating the safety and effectiveness of RFVTA among women wishing to maintain fertility.

Systematic review and meta-analysis
Lin et al. (2019) conducted a meta-analysis to assess the short-term (three and six months) and long-term (12, 24, and 36 months) symptom relief and quality of life improvement, procedure-related adverse event rate, reintervention rate, and days missed from work after laparoscopic radiofrequency ablation. Both comparative and non-comparative studies consisting of uterine fibroid symptoms and quality of life scores were included. Eight studies (one RCT, seven non-comparative) with a total of 581 patients were included in the review. Based on
validated questionnaires, quality of life improved significantly until 36 months after laparoscopic radiofrequency ablation therapy, with a maximum improvement (Health-Related Quality of Life [HRQL] questionnaire score of +41.64 [95% confidence interval (CI), 38.94-44.34] and a transformed Symptom Severity Score [tSSS] of -39.37 [95% CI, 34.70-44.04]) at 12 months after laparoscopic radiofrequency ablation. All subscales of quality of life improved significantly, and most of the changes remained stable in long-term follow-up. The overall reintervention rate was 4.39% (95% CI, 1.60%-8.45%), and the median uterine volume reduction was 69.17 cm³ (95% CI, 35.87-102.46 cm³). The overall procedure-related adverse events rate was 1.78% (95% CI, 0.62%-3.53%), and patients missed an average of 4.35 days (95% CI, 2.55-6.15 days) of work. Limitations of the studies include that most of the studies were noncomparative studies. The author notes that there were differences in study types, inclusion and exclusion criteria, and study methodology.

Sandberg et al. (2018) conducted a systematic review and meta-analysis to compare uterine-sparing treatment options for fibroids in terms of reintervention risk and quality of life. The review included randomized controlled trials (RCT) and cohort studies (both noncomparative and comparative). The main outcome measures included: reintervention risk after uterine-sparing treatment for fibroids after 12, 36, and 60 months; and quality of life outcomes, based on validated questionnaires. Two separate analyses were performed for the procedures that used an abdominal approach (myomectomy, uterine artery embolization [UAE], artery ligation, high-intensity focused ultrasound [HIFU], laparoscopic radiofrequency ablation [RFA]) and for the procedures managing intracavitary fibroids (hysteroscopic approach, including hysteroscopic myomectomy and hysteroscopic RFA). The review included 85 articles for analysis (17,789 women). Stratified by treatment options, reintervention risk after 60 months was 12.2% (95% confidence interval [CI] 5.2%-21.2%) for myomectomy, 14.4% (95% CI 9.8%-19.6%) for UAE, 53.9% (95% CI 47.2%-60.4%) for HIFU, and 7% (95% CI 4.8%-9.5%) for hysterectomy. For the other treatment options, no studies were available at 60 months. For quality of life outcomes, symptoms improved after treatment for all options. Laparoscopic RFA included eight studies, with 652 patients.

Havryliuk et al. (2017) reported on a systematic review and meta-analysis for the purpose of determining whether recommendations can be made regarding best practice based on review and analysis of the literature that addressed clinical outcomes associated with interventions for the management of symptomatic uterine fibroids. Outcomes of interest were patient baseline characteristics, fibroid characteristics, procedural details, complications, and long-term follow-up. The review included hysterectomy trials compared with those from uterine-preserving fibroid studies (myomectomy, uterine artery embolization (UAE), laparoscopic radiofrequency ablation (lap-RFA), and magnetic resonance-guided focused ultrasound). For lap-RFA, the long-term follow-up averaged 27 months in four cohorts with 209 patients. For lap-RFA the analysis in the review indicated that Lap-RFA is associated with low complication rates, minimal estimated blood loss, and low reintervention rates. In addition, patients reported major improvement in their Health-Related Quality of Life (HRQL) and symptom severity scores compared to reports of more traditional interventions, such as hysterectomy, myomectomy, and UAE. The authors note that the study is limited by the inherent heterogeneity among studies and that although some of the included studies were randomized controlled trials, most were not. The review concluded that currently available data regarding certain fibroid characteristics, such as size, location, or number are insufficient to assign specific cutoffs that favor one treatment modality over another and recommended further comprehensive prospective research, ideally in the form of well-powered randomized controlled trials, to validate the specific treatment modality preferred for specific anatomical variances of fibroids.

Taheri et al. (2019) conducted a systematic review to examine the change in uterine and fibroid volumes associated with uterine artery embolization (UAE), focused ultrasound (FUS), and radiofrequency ablation (RFA). Eighty-one relevant papers were included: 52 related to UAE, 11 to RFA, 17 to FUS, and one compared UAE and FUS. The report noted the published uterine volume and fibroid volume changes in the studies at one to 36 months. The pooled fibroid volume reductions at six months seen with RFA were 70%, UAE 54% and FUS 32%. All three types of nonresective treatment result in fibroid volume reduction with fibroid volume reduction most marked with RFA; with UAE resulting in the next most volume reduction. The authors note that additional larger cohort studies, including those that are randomized and/or comparative, would enable definitive conclusions.

In a systematic review prepared for AHRQ, Hartmann et al. (2017) reported that the strength of evidence for radiofrequency ablation in the management of uterine fibroids is insufficient to inform care.
Studies
Rattray et al (2018) conducted a study to compare laparoscopic ultrasound-guided radiofrequency ablation of fibroids (Lap-RFA) and laparoscopic myomectomy in terms of 1) health care utilization and 2) serious complication rates. Secondary objectives were comparison of subject responses to validated symptom and quality-of-life questionnaires. The randomized, prospective, multicenter, longitudinal, non-inferiority interventional comparative evaluation included 45 participants (Lap-RFA, n=23; myomectomy, n=22) who were premenopausal with symptomatic uterine fibroids and desired uterine conservation. Health care resource utilization was measured during the procedure day and at one week, one and three months post-surgery. Symptom severity and quality of life were based on patients’ responses to the Uterine Fibroid Symptom Severity and Quality-of-Life Questionnaire, EuroQol-5D-visual analog scale general health status and menstrual impact questionnaires, and time from work. Hospitalization time (primary endpoint) was 6.7±3.0 hours for the Lap-RFA group and 9.9±10.7 hours for the myomectomy group (p=0.0004). Intraoperative blood loss was lesser for Lap-RFA subjects: 25.2±21.6 versus 82.4±62.5 mL (p=0.0002). Lap-RFA procedures took less time than myomectomy procedures: 70.0 versus 86.5 minutes (p=0.018), and Lap-RFA required -34.9% (130 fewer) units of surgical equipment. At three months, both cohorts reported the same significant symptom severity reduction (−44.8%; p<0.0001). Lap-RFA subjects also took less time from work: 11.1±7.6 versus 18.5±10.6 days (p=0.0193). One myomectomy subject was hospitalized overnight after experiencing a 20-second asystole during the procedure. One Lap-RFA subject underwent a re-intervention. Limitations include the small number of participants. The authors noted that the lack of long-term data was a limitation; the data was based on outcomes to three months post-intervention and, therefore, the durability of the symptom improvement and pregnancy outcomes could not be evaluated for either procedure.

Brucker et al. (2014) reported outcomes of a randomized, prospective single-center international clinical trial involving 51 women comparing radiofrequency volumetric thermal ablation (RFVTA) (n=26) and laparoscopic myomectomy (LM) (n=25) for symptomatic uterine fibroids. Primary outcomes were the mean hospital discharge times and perioperative outcomes. The predominant symptom reported by the patients in both groups was heavy menstrual bleeding followed by urinary frequency, pelvic discomfort and pain, backache, localized pain, dysmenorrhea, urinary retention, increased abdominal girth, dyspareunia, uterine pain, and sleep disturbance. There were no significant differences based on Fisher exact test between the two groups with regard to any of these symptoms, although the authors note this could be because of the relatively small number of patients in each group. Surgeons were blinded to the treatment until all fibroids were mapped by laparoscopic ultrasound. The mean hospitalization times were 10.0±5.5 hours for the RFVTA group and 29.9±14.2 hours for the LM group (p=.16). Intraoperative blood loss was 16 mL for the RFVTA procedures and 51 mL for the LM procedures. The percentage of fibroids imaged by laparoscopic ultrasound that were treated/excised was 98.6% for RFVTA and 80.3% for LM. Two complications were reported: vertigo (n=1; RFVTA) and port site hematoma (n=1; LM). The mean time between arrival in post-anesthesia recovery and discharge from the hospital was 8.2 hours for the RFVTA group and 28.0 hours for the LM group (p<0.001). Mean hospitalization time was 10.0 hours and 29.9 hours for the RFVTA and LM groups, respectively, p<0.001. The authors note that short-term follow-up is a limitation to the study and plan five-year follow-up for pregnancy outcomes, symptom improvement, and overall treatment satisfaction as evaluated on the basis of participants’ responses to validated questionnaires. The study is limited by small study participant numbers.

Hahn et al. (2015) published one year results of the above study (Brucker, et al., 2014) with objective to analyze, compare and describe the study’s three, six and twelve month outcomes in terms of pain medication use, recovery from surgery, and subjects’ subjective responses to validated questionnaires. The results included: post-surgery, ablation and myomectomy subjects took pain medications for 4 days (range: 1–46) and 7 days (range: 1–83 days) respectively (p=0.60); ablation and myomectomy patients missed 10.0 workdays (range: 2–86 days) and 17.0 workdays (range: 7–30 days) (p=0.28); resumed normal activities in 20.5 days (range: 5–103 days) versus 28.0 days (range: 10–42 days) (p=0.86) respectively. The mean symptom severity scores decreased (improved) by −7.8 for the ablation subjects and by −17.9 for the myomectomy subjects (p=0.16). Health-related quality of life improved (increased) by 7.5 and 13.1, respectively, for the two groups (p=0.46). Two myomectomy subjects had pregnancies that ended in a Cesarean delivery and a vaginal delivery of healthy infants. Two pregnancies in the RFVTA group ended in full-term vaginal deliveries of healthy infants. The authors concluded that early postoperative recovery and twelve-month results indicate similar efficacy, quality of life, and safety for both treatment groups. The subjects will be continued to be followed for five years.
Kramer et al. (2016) reported on 24 month data from the above study (Brucker, et al., 2014). The outcomes included this analysis were patients’ responses to validated questionnaires and long-term safety. The study included 51 patients with 21 and 22 patients in the RFVTA and laparoscopic myomectomy groups, respectively that completed 24 months of follow-up. There was improvement reported in the severity of symptoms from baseline by participants in both the RFVTA (P<0.001) and laparoscopic myomectomy groups (P=0.001). The study observed a significant improvement in health-related quality of life in the laparoscopic myomectomy group (P=0.040); and a non-significant improvement was noted in the RFVTA group (P=0.083). A trocar-site hematoma occurred in one patient in the laparoscopic myomectomy group. There were further surgical interventions recorded in three patients in the RFVTA group but it was noted that these were unrelated to fibroid symptoms.

Jacoby et al., (2019) conducted a single-arm, unblended, uncontrolled trial to assess surgical outcomes, clinical effectiveness, and gynecologist experience of introducing laparoscopic radiofrequency ablation (RFA) of leiomyomas into surgical practice. The study included 26 women who were premenopausal with symptomatic uterine leiomyomas, uterus size ≤16 weeks size, and all leiomyomas ≤10 cm with no more than 6 total leiomyomas and who underwent the RFA treatment. Intraoperative complications, blood loss, operative time, and adverse events were assessed. Gynecologists reported the operative difficulty and need for further training after each case. Participants reported leiomyoma symptoms preoperatively and at 6 and 12 weeks after surgery. The mean operating time was 153 ± 51 minutes, and mean estimated blood loss was 24 ± 40 cc. There were no intraoperative complications and no major adverse events. Menstrual bleeding, sexual function, and quality of life symptoms improved significantly from baseline to 12 weeks, with a 25 ± 18-point, or 47%, decrease in the Leiomyoma Symptom Severity Score. The study was limited by the low number of participants.

Berman et al. (2019) conducted a case series to analyze pregnancy delivery and safety outcomes after patient receipt of percutaneous, laparoscopic intra-abdominal ultrasound-guided radiofrequency ablation (Lap-RFA) for symptomatic uterine myomas. Evidence was obtained from two randomized, controlled trials (level I), six cohort studies (level II-2), and in commercial settings (level II-3). The study included premenopausal adult women with symptomatic uterine myoma types 1 through 6 with Lap-RFA procedure conducted under general anesthesia with laparoscopic and intra-abdominal ultrasound guidance. Safety unknowns included the safety of a full-term pregnancy for mother and baby, rates of spontaneous abortion, preterm delivery, postpartum hemorrhage, placental abnormalities, intrauterine growth restriction, and vaginal versus cesarean delivery. A total of 28 women conceived a total of 30 times after Lap-RFA, either as part of a clinical study or in commercial settings. The number of myomas treated per patient ranged from one to seven. The diameter of treated myomas ranged from 0.9 to 11.0 cm. Most patients had one or two myomas, and most myomas were ≤5.5 cm in maximal diameter. The 30 pregnancies resulted in 26 full-term live births (86.7%), all healthy infants, with an equal distribution of vaginal and cesarean deliveries. Four (13.3%) spontaneous abortions occurred. No cases of preterm delivery, uterine rupture, placental abruption, placenta accreta, or intruterine growth restriction were reported. One event each of placenta previa and postpartum hemorrhage were reported. The authors concluded that conception and safe, full-term pregnancy appear to be achievable after Lap-RFA of symptomatic myomas, however, additional large, rigorous, multivariate prospective studies that adjust for confounders and report pregnancy outcomes after symptomatic myoma treatment are needed.

Chudnoff et al. (2013) reported one year results of a prospective, multicenter, interventional clinical trial (i.e., HALT trial) with primary outcome measures of change from baseline to 12 months and ongoing qualitative follow-up of women for three years in a cohort of 135 premenopausal symptomatic women with uterine myomas, uteri 14 weeks of gestation-sized or less with no single myoma exceeding 7 cm, and objectively confirmed heavy menstrual bleeding. Primary intervention was outpatient laparoscopic ultrasound-guided radiofrequency volumetric thermal ablation using the Acessa system (Halt Medical, Brentwood, CA). Bleeding outcomes and validated quality-of-life and patient satisfaction scales and objective measurements of uterine and myoma volume were conducted at 3, 6, and 12 months. Mean alkaline hematin and associated menstrual blood loss decreased from baseline levels by 31.8%, 40.7%, and 38.3%, respectively, at three-, six-, and 12-month intervals (p <.001 for all). Symptom severity and health-related quality of life improved (p<.001). There was one serious adverse event (0.7%) requiring readmission 5 weeks post-procedure and one surgical reintervention for persistent bleeding. Ninety-four percent of the women reported satisfaction with the treatment (p<.001). The study was limited by uncontrolled design, short-term follow-up and a lack of comparison to other treatment methods.
In a follow-up to the study by Chudnoff et al. (2013), Guido et al. (2013) reported two-year outcomes of 124 subjects who participated in the HALT trial, of whom 112 were evaluable. Outcome measures included: subject responses to validated questionnaires, treatment-emergent adverse events, and surgical re-intervention for fibroids at 24 months post-procedure. Significant changes from baseline were noted in symptom severity (p< .001) and health-related quality of life scores (p< .001). There was a significant improvement in the mean health state score between baseline and 3 months after treatment (p < .001). Measurements at subsequent intervals showed no continued improvement. Six patients underwent surgical reintervention for fibroid-related bleeding between 12 and 24 months. The authors also reported on one patient who had an episode of bleeding post Cesarean section requiring receipt of six units of blood, which the study authors noted as possibly related to the RFA procedure. Limitations to the study include uncontrolled design, lack of comparator, short-term follow-up and small total patient numbers.

In a thirty-six month follow-up study, Berman et al. (2014) reported subject responses to validated questionnaires and surgical repeat intervention to treat myomas outcomes for a cohort of 104 evaluable patients (104/135) who participated in the HALT trial. Change in mean symptom severity (p< .001) and Health-Related Quality of Life questionnaire scores (p< .001) were improved from the baseline. Patient-reported Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire subscores demonstrated statistically significant improvement from baseline to 36 months (p< .001) in all categories (i.e., Concern, Activities, Energy/Mood, Control, Self-consciousness, and Sexual Function). The cumulative repeat intervention rate was of 11% at 36 months. Although results are promising, study limitations include uncontrolled, nonrandomized design, lack of comparison to other treatment methods, and small study participant numbers.

Robles et al. (2013) assessed outcomes of a prospective study assessing the laparoscopic radiofrequency volumetric thermal ablation (RFVTA) system among 114 screened women with symptomatic myomas. Thirty-five women completed the 12-month follow-up period. Uterine fibroid symptom and health-related quality-of-life (UFS-QOL) questionnaires were completed at zero, three-, six-, and 12-months. There was a significant reduction in average symptom severity score over the study period (p<0.001), and reductions in symptom severity scores from baseline to each of the follow-up visits, and from the 3-month visit to the 12-month follow-up visit were significant (p<0.001). There was a significant increase in average health-related quality of life (HRQL) scores from baseline to 12 months (p<0.001) and in the HRQL scores from baseline to each of the follow-up visits (p<0.001). After discharge, none of the participants was admitted to hospital for procedure-related complications. Within the study period, none of the participants required hysterectomy or any myoma treatment after RFVTA. No transfusions were required. Nine adverse events among eight women were reported as definitely not device- or procedure-related. Study limitations which limit the ability to routine clinical practice include lack of randomization and control, small study population, short-term follow-up of 12 months and lack of comparison to other treatment methods.

Thirty-one women with symptomatic uterine fibroids underwent outpatient laparoscopic, ultrasound-guided, radiofrequency volumetric thermal ablation using the Halt 2000 System. Postoperative follow-up occurred at three, six, and 12 months. The primary outcome measures were patient safety, frequency of adverse events, repeat intervention rate, symptom severity and health-related quality-of-life scores from the validated Uterine Fibroid Symptom and Quality-of-Life Questionnaire. Secondary outcome measures were uterine volume changes over time. Mean symptom severity scores improved significantly compared with baseline at three, six, and 12 months. Mean health-related quality-of-life scores reached statistical significance over time. Mean uterine volume decreased at three six, and 12 months. There were no procedure-related repeat hospitalizations, repeat treatments or procedures related to fibroid symptoms following treatment. The study is limited by lack of randomization and control, short-term follow-up, small sample size and lack of comparison to other treatment methods. Larger multicenter studies are needed to confirm these results (Garza, 2011).

**Professional Societies/Organizations**

**American Association of Gynecological Laparoscopists (AAGL):**

The AAGL published practice guidelines for the diagnosis and management of submucous leiomyomas (2012) which note with currently available evidence, embolic and ablative therapies, including leiomyoma ablation with radiofrequency electricity are not appropriate for women with submucous myomas who have current infertility or who wish to conceive in the future. The guidelines do not address embolic or ablative therapies related to submucous myomas for individuals without infertility or who do not desire future conception.
Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCD found.

Use Outside of the US

Canadian Agency for Drugs and Technologies in Health (CADTH): CADTH published a systematic review of the clinical and cost-effectiveness for uterine-preserving interventions for the management of symptomatic uterine fibroids. The review assessed the treatment effects of various uterine-preserving interventions in women with symptomatic uterine fibroids including myomectomy, uterine artery embolization (UAE), uterine artery occlusion (UAO), magnetic resonance-guided focused ultrasound (MRgFU), and radiofrequency volumetric thermal ablation (RFVTA). These interventions were compared either with the conventional surgical intervention (hysterectomy), or with other uterine-preserving interventions. It was concluded that radiofrequency volumetric thermal ablation (RFVTA) improved abnormal uterine bleeding and quality of life (QOL) compared with baseline assessments. In comparison with myomectomy (in one study), RFVTA resulted in fewer complications, including intraoperative blood loss and a shorter length of stay; however, RFVTA was associated with more reinterventions.

Society of Obstetricians and Gynaecologists of Canada (SOGC): SOGC published evidenced-based guidelines for the management of uterine leiomyomas (Vilos, et al., 2015). The recommendations note that, "Of the conservative interventional treatments currently available, uterine artery embolization has the longest track record and has been shown to be effective in properly selected patients. (II-3) Newer focused energy delivery methods are promising but lack long-term data. (III)". The newer methods included in this statement includes radiofrequency ablation of uterine fibroids.

Quality of evidence assessment:
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

References


Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency (CPT code 0404T)

Radiofrequency transcervical uterine fibroid ablation with ultrasound guidance has been proposed for the treatment of uterine fibroids. The Sonata® Sonography-Guided Transcervical Fibroid Ablation System (Gynesonics; Redwood City, CA), has been developed to provide transcervical radiofrequency ablation (RFA) for treatment of uterine fibroids, the Sonata system combines a miniaturized, reusable, intrauterine ultrasound probe and a single-use RFA handpiece that contains an introducer and needle electrode array; the device is introduced into the uterus via a transcervical approach and the ablation is initiated by foot control. The Sonata System is designed to treat patients in an outpatient setting, depending on anesthetic requirements (general anesthesia, conscious sedation, or spinal anesthesia) (Hayes, 2018). The Sonata system was previously known as the VizAblate System.

U.S. Food and Drug Administration (FDA):

The FDA granted a 510(k) marketing clearance for the Sonata Sonography-Guided Transcervical Fibroid Ablation System in August 2018. The Sonata Sonography-Guided Transcervical Fibroid Ablation System is intended for diagnostic intrauterine imaging and transcervical treatment of symptomatic uterine fibroids, including those associated with heavy menstrual bleeding.

Literature Review

Chudnoff et al. (2019) reported on a prospective, multicenter, single-arm interventional trial to evaluate the 12-month safety and effectiveness of transcervical ablation for the treatment of symptomatic uterine leiomyomas in 147 patients (the Sonata trial). Transcervical ablation was performed on 1-10 leiomyomas per patient with leiomyoma diameters ranging from one to five cm with treated leiomyomas including all nonpedunculated types. Coprimary endpoints assessed at 12 months were reduction in menstrual blood loss and absence of surgical reintervention. Additional assessments included symptom severity, quality of life, patient satisfaction, reductions in uterine and leiomyoma volumes, and safety. The study met coprimary endpoints at 12 months (N=143; full analysis set), with 64.8% of patients (95% CI 56.3-72.6%) that experienced 50% or greater reduction in menstrual bleeding and 99.3% of patients (95% CI 95.1-99.9%) were free from surgical reintervention. The mean pictorial blood loss assessment chart score decreased by 38.9%, 48.4%, and 51.1% at three, six, and 12 months, respectively (P<.001), and 95.1% of patients experienced a reduction in menstrual bleeding at 12
months. There were mean improvements in symptom severity and health-related quality of life of 32.1 points and 43.7 points, respectively, at 12 months (all \( P<.001 \)). Mean maximal leiomyoma volume reduction per patient was 62.4% (\( P<.001 \)). More than half of patients returned to normal activity within 1 day, 96.3% of patients reported symptom improvement at 12 months, and 97% expressed satisfaction with the treatment at 12 months. There were no device-related adverse events. The study was limited by the lack of randomization and lack of a comparator.

Garza-Leal et al. (2019) reported on long-term (> 5 years) clinical outcomes of transcervical radiofrequency ablation of uterine fibroids, the VITALITY study, a retrospective, single-arm, long-term data-collection study, one arm of the above FAST-EU trial. The study included 23 women with heavy menstrual bleeding secondary to fibroids were treated with transcervical radiofrequency ablation guided by integrated intrauterine sonography (using the Sonata® System). This study was within one center of the 12-month Fibroid Ablation Study-EU clinical trial. Symptoms were assessed using the Uterine Fibroid Symptom and Quality-of-Life's Symptom Severity Score (SSS) and Health-Related Quality of Life (HRQoL) subscales. Patients were queried regarding pregnancy and surgical reinterventions. Seventeen women (73.9%) provided long-term follow-up information, with a mean of 64.4 months ±4.5 months (range: 57-73 months). From baseline, mean SSS decreased significantly from 64.9 ± 16.9 to 27.6 ± 36.1, and mean HRQoL improved significantly from 27.2 ± 22.4 to 76.0 ± 32.6 (\( p = 0.002 \), and \( p = 0.0001 \), respectively). There were no surgical reinterventions through the first 3.5 years post-treatment. There was an 11.8% incidence of surgical reinterventions over 5.4 years of average follow-up, with 2 hysterectomies occurring after 3.5 and 4 years postablation, respectively. Freedom from surgical reintervention at 1, 2, and 3 years was 100%, and, at 4 and 5 years, was 88.2% ± 7.8%. There was a single pregnancy occurring within the first year of treatment leading to a normal-term delivery by elective repeat cesarean section. The study is limited by the lack of randomization and small number of participants.

Taheri et al. (2019) conducted a systematic review to examine the change in uterine and fibroid volumes associated with uterine artery embolization (UAE), focused ultrasound (FUS), and radiofrequency ablation (RFA). Eighty-one relevant papers were included: 52 related to UAE, 11 to RFA, 17 to FUS, and one compared UAE and FUS. The report noted the published uterine volume and fibroid volume changes in the studies at one to 36 months. The pooled fibroid volume reductions at six months seen with RFA were 70%, UAE 54% and FUS 32%. All three types of nonresective treatment result in fibroid volume reduction with fibroid volume reduction most marked with RFA; with UAE resulting in the next most volume reduction. The authors note that additional larger cohort studies, including those that are randomized and/or comparative, would enable definitive conclusions.

Initial evidence on the safety and efficacy of transcervical intrauterine ultrasound-guided RFA for the treatment of uterine fibroids included a study of the VizAblate system: the single-arm FAST-EU trial of the VizAblate System conducted at 7 centers outside the U.S. (Bongers et al., 2015; Brölmann et al., 2015; Huirne and Brooks, 2018). VizAblate is the previous version of the Sonata System; the two systems are similar.

Professional Societies/Organizations
Professional organization guidelines for transcervical intrauterine ultrasound-guided RFA for treatment of uterine fibroids are lacking.

Centers for Medicare & Medicaid Services (CMS)
• National Coverage Determinations (NCD): No NCD found
• Local Coverage Determinations (LCDs): No LCD found

Use Outside of the US
No relevant information

References


**Coding/Billing Information Obstetrics/Gynecology**

**Note:**
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Obstetrics/Gynecology Services Considered Experimental/Investigational/Unproven:**

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>58674</td>
<td>Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency</td>
</tr>
<tr>
<td>0404T</td>
<td>Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency</td>
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**Urology**

**Transurethral Radiofrequency Tissue Micro-Remodeling (CPT code 53860)**

Radiofrequency energy (RF) is used for a variety of disorders. Researchers have proposed the use of RF technique to shrink and stabilize the endopelvic fascia, thus improving the support for the urethra and bladder neck. A radiofrequency device has been specifically designed for the treatment of urinary stress incontinence that can be performed as outpatient procedures under general anesthesia. The Renessa® procedure (Novasys Medical Inc., Newark, California) induces collagen denaturation in the urethra with a specially designed 4 needle radiofrequency probe. Transurethral treatment changes the collagen at microscopic sites targeted within the bladder neck and areas within the urethral submucosa. The low-level RF energy is believed to strengthen the
sphincter without destroying the tissue, by heating only small areas around the probe tip to a specified
temperature at which collagen begins the denaturation process.

**U.S. Food and Drug Administration (FDA):** Novasys Medical, Inc. received 510(k) approval from the FDA for
the Novasys Transurethral RF System (Renessa System) in July 2005. It is indicated for the transurethral
treatment of stress urinary incontinence due to hypermobility in women who have failed conservative treatment
and who are not candidates for surgical therapy (FDA, 2005). Verathon acquired the Renessa device, and
rebranded it as the Lyrette™ transurethral SUI system.

**Literature Review-Transurethral Radiofrequency Energy**

Kang et al. (2015) reported on a Cochrane review to evaluate the efficacy of transurethral radiofrequency
collagen denaturation, compared with other interventions, in the treatment of women with urinary incontinence
(UI). The analysis included one small sham-controlled randomised trial of 173 women. The authors concluded
that it is not known whether transurethral radiofrequency collagen denaturation, as compared with sham
treatment, improves patient-reported symptoms of UI. Evidence is insufficient to show whether the procedure
improves disease-specific quality of life. In addition, evidence is also insufficient to show whether the procedure
causes serious adverse events or other adverse events in comparison with sham treatment, and no evidence
was found for comparison with any other method of treatment for UI.

Elser et al. (2010) conducted a prospective study including 136 women with stress urinary incontinence caused
by bladder outlet hypermobility who had failed non-surgical treatment and were not considered good surgical
candidates or wished to avoid or postpone surgery. A transurethral collagen denaturation procedure was
performed in a physician’s office or ambulatory treatment center. Patients kept voiding diaries and completed
surveys. At 18 months, 63 women attended the 18-month follow-up visit, with data available for 60 patients.
Intent-to-treat (ITT) analysis was completed on 136 women. At 18 months, 46.7% of patients in the ITT
population and 61.7% of patients evaluated reported a reduction of at least 50% from baseline in leaks due to
activity. This study is limited by the large loss to follow-up (total attrition rate by 18 months in this trial was 48%).
At 36 months, intent-to-treat analysis noted mean I-QOL score improved 17 points from baseline (P = .0004),
while mean UDI-6 score improved (decreased) 19 points (P = .0005) (Elser, et al., 2011). This study is limited by
the large loss to follow-up, and lack of randomization (total attrition rate by 18 months in this trial was 48%).

Lenihan et al. (2005), Appell et al. (2006), and Appell et al. (2007) reported on a randomized controlled trial
(RCT) that included the same 173 patients. Appell et al. (2006) conducted a randomized controlled trial to
demonstrate the safety and efficacy of non-surgical, transurethral radiofrequency (RF) micro-remodeling in the
treatment of female stress urinary incontinence (SUI). A total of 173 women with SUI were enrolled and
randomized to receive RF micro-remodeling (n=110) or sham treatment (brief bladder catheterization) (n=63).
Efficacy was measured using I-QOL and leak point pressure (LPP) testing at 12 months. No serious adverse
events were reported. At 12 months, the evaluable population for the quality of life outcome analysis included
142 women (82% of enrolled), 89 in the treatment (80.1%) and 53 in the sham treatment (84.1%) arm. Ignoring
baseline SUI severity, 48% of all treatment arm and 44% of all sham treatment arm subjects demonstrated ≥10
point I-QOL score improvement at 12 months (p=0.7). Seventy-four percent of women suffering from moderate to
severe SUI experienced ≥10 point I-QOL score improvement at 12 months following RF micro-remodeling versus
50% of women who underwent sham treatment (p=0.03). This was statistically significant. Twenty two percent of
women with mild SUI experienced a ≥10 point I-QOL score improvement at 12 months following micro-
remodeling treatment versus 35% of women who underwent sham treatment (p=0.2). Statistical significance was
not achieved for the entire treatment versus sham treatment population due to the high sham treatment arm
“placebo effect” which was particularly pronounced (relative to treatment arm results) in women with mild
baseline SUI. At 12 months, the evaluable population for the leak point pressure (LPP) analysis included 136
women (78.6% of enrolled), 87 in the treatment (79.1%) and 49 in the sham treatment (77.8%) arm. Women who
underwent RF micro-remodeling demonstrated an increase in mean LPP at 12 months (13.2 ± 39.2 cm H20),
while women who underwent sham treatment demonstrated a reduction in mean LPP at 12 months (-2.0 ± 33.8
cm H20), and the difference in mean LPP change between the two arms was statistically significant (p=0.02). A
limitation of this trial is loss to follow-up of 18%. In 2007, a retrospective three-year evaluation of the 2006 trial
patients was conducted by Appell and colleagues. Of the original 110 women in the treatment group of the
original study, 18 were evaluable (completed three day diaries). Of the 18, 50% of these patients had achieved a
50% or greater reduction in incontinence episode frequency. There were no new reports of serious adverse events.

Sotomayor and Bernal (2003) conducted an initial human study to determine the safety and quality of life impact of transurethral RF micro-remodeling of the proximal urethral and bladder outlet in women suffering from stress urinary incontinence. The data from 37 patients were analyzed and reported. The 37 patients were divided into four different groups dependent on the number of RF lesions administered (Group I, n=8, 24 lesions; Group II, n=9, 36 lesions; Group III, n=11, 48 lesions; Group IV, n=9, 60 lesions). All subjects completed a urinary incontinence quality of life questionnaire (I-QOL) at baseline, one month, three months, and six months. No serious adverse events were noted at any time. At six months, 75–80% of patients in all four groups had demonstrated improvement in quality of life with statistically significant elevations in mean I-QOL score compared to baseline in two groups (Group II p = 0.004; Group IV p = 0.02). The authors also noted that 22–75% of patients in all groups reported being dry (i.e., no incontinence episodes and no pad use in the three months prior to the six month follow-up visit) at six months with a statistically significant decrease in mean incontinence frequency for Group II (p<0.05) and Group IV (p<0.005) and a statistically significant decrease in mean pad use for group IV (p<0.04). In 2005, Sotomayor and Bernal reported on the 12 month follow-up results of the 2003 study. I-QOL scores at 12 months ranged from 75–80% and statistically significant incontinence episode frequency was demonstrated in three of the four treatment groups. There were no serious adverse events reported. The limitations of these studies, including the small sample size, lack of control, long term data, and the lack of urodynamic testing at baseline or follow-up, does not allow for a determination to be made regarding the safety and efficacy of this approach in the treatment of stress incontinence.

Professional Societies/Organizations
American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU): the guideline from these organizations for surgical treatment of female stress urinary incontinence does not include transurethral radiofrequency tissue micro-remodeling (Renessa) (2017).

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services other than CPT® Category III Noncovered Services (L36954). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
A 2006 Horizon Scanning Technology Summary on Renessa® radiofrequency micro-remodelling treatment for female stress urinary incontinence stated that the Renessa system was not currently listed in the Australian Register of Therapeutic Goods and had not yet emerged in Australia. The report further stated that the Renessa RF micro-remodelling system received the Conformité Européene (CE) Mark in April 2003 allowing Novasys Medical Inc. to market the system in European Union countries (HealthPACT, 2006).

References


Transperineal Periurethral Balloon Continence Device (CPT codes 0548T, 0549T, 0550T, 0551T; Codes effective 07/01/2019)
The Adjustable Continence Therapy (ACT®) device (for women) and the ProACT™ device (for men) (Uromedica, Inc., Minnetonka, MN, USA) consists of two silicone balloons placed at either side of the bladder neck. Each balloon is attached to a titanium port, aiming to achieve continence through static extrinsic compression and support of the urethra. The balloons is purported to help protect against accidental leaking of urine by increasing the amount of pressure required to urinate. When the patient needs to urinate, a normal amount of effort is still required to push the urine out. It is proposed the pressure from the balloons will help guard against unintentional urine loss, such as during a sneeze or cough.

U.S. Food and Drug Administration (FDA): The Adjustable Continence Therapy (ACT®) device (for women) (Uromedica, Inc., Minnetonka, MN, USA) is currently in clinical trials and not FDA-approved.

November 2015 the FDA granted premarket approval application (PMA) for the ProACT™ Adjustable Continence Therapy for Men (Uromedica, Inc., Plymouth, MN). This device is indicated for the treatment of adult men who have stress incontinence arising from intrinsic sphincter deficiency of at least twelve months duration following radical prostatectomy or transurethral resection of the prostate (TURP) and who have failed to respond adequately to conservative therapy.
Literature Review-The Adjustable Continence Therapy (ACT®) device (for women): Data supporting the ACT® device for women is lacking. Most studies are small in sample size and lack randomization, a control group or comparator, due to the fact that ACT is used when other treatments have failed.

In a prospective study, Aboseif et al. (2010) performed percutaneous placement of the ACT device in female patients with moderate to severe SUI who failed at least one surgical treatment (sling, Burch, suspension, AUS). A total of 89 patients have undergone implantation with 1–3 years of follow-up. Data are available on 77 patients at one year. Of the patients, 47% were dry at one year and 92% improved after one-year follow-up. Quality of life questionnaire scores improved from 33.9 to 71.6 at one year (p < 0.001). The mean number of adjustment visits prior to one year was 2.03. Explantation was required in 21.7% of patients with 50% of those patients re-implanted before one year, while 28% were awaiting re-implantation and 22% had been explanted permanently. The authors stated "our hypothesis is that in some instances, the balloon is placed closer (in some cases, maybe too close) to the urethra or bladder, and so requires less filling to reach continence but also results in a higher incidence of perioperative perforations and postoperative complications leading to explantations."

Literature Review- ProACT™ Adjustable Continence Therapy for Men:
Larson et al. (2019) conducted a systematic review and meta-analysis to evaluate the efficacy of adjustable balloon devices or adjustable continence therapy (ProACT) in the treatment for male stress urinary incontinence (SUI) and also to investigate the safety profile and rates of adverse events associated with the implantation of adjustable balloon devices. The review included studies with adult male patients with SUI and the outcomes included pads or pad weight per day and quality of life (QOL) questionnaires, as well as safety outcomes. Nineteen studies were included with a total of 1,264 patients and 4,517 patient-years of follow-up data (mean follow-up time 3.6 years). Ten studies were found to be of good quality, seven of fair quality, and two of poor quality. ProACT implantation resulted in an incontinence QOL improvement of 30.8 points from baseline. At baseline, patients on average were using 4.0 pads per day (PPD) (95% confidence interval [CI]: 2.6-5.4), which was reduced to an average of 1.1 PPD (95% CI: 0.5-1.7) after ProACT implantation. The number of patients that were considered "dry" was 60.2% (95% CI: 54.2%-65.9%) and the number of patients who were found to be either "dry" or improved greater than 50% was 81.9% (95% CI: 74%-87.8%). The meta-analysis estimate for intraoperative perforation of the bladder or urethra is 5.3% (95% CI: 3.4%-8%). Estimates for infection and urinary retention were 2.2% (95% CI: 1.1%-4.3%) and 1.5% (95% CI: 0.7%-3.4%), respectively. The estimated overall revision rate for all causes is 22.2% (95% CI: 15.2%-31.2%) with a mean follow-up of 3.6 years (range 12-118 months). Heterogeneity in the studies was a major issue in areas of the median follow-up ranges, the number of patients per study, surgical technique, and management of complications were greatly variable across studies. The review does not include the type of studies or comparators used in studies.

Ronzi et al. (2019) conducted a retrospective cohort study to assess the effectiveness and complications of treatment for neurogenic stress urinary incontinence (nSUI) by Adjustable Continence Therapy (ACT™ and ProACT™) in 102 patients with neurological pathologies. Patients were followed-up for a mean 2.7 years. After implantation, 5.9% of patients were totally continent, 51.2% had an improvement in symptoms of at least 50% and 48.8% had improvements of < 50%, including 7.3% of treatment failures. Complications occurred in 70 patients (120 balloons): 21 balloon infections, 34 migrations, 18 device failures, 28 urethral erosions and 28 cutaneous erosions. The procedure was ineffective for 35 patients. Twenty patients underwent permanent explantation. The authors note that despite the multicenter study and the learning curves for the surgery, they did not find a place for ACT™/ProACT™ in nSUI therapy and the small number of patients and their heterogeneity did not enable subgroup analyses. The study was limited by the retrospective nature and lack of randomization.

Nash et al. (2018) reported on eight month follow-up results for patients enrolled in a pivotal study conducted to support an FDA premarket approval application (PMAA) of the ProACT Adjustable Continence Therapy for the treatment of post-prostatectomy stress urinary incontinence (SUI). One hundred twenty-three patients underwent ProACT implantation, of whom 98 completed 18-month follow-up. The endpoints included 24-h pad weight, Incontinence Quality of Life Questionnaire (I-QOL), UCLA Prostate Cancer Index-Urinary Function (PCI-UF), residual volume, and device or procedure-related adverse events (AEs). Statistically significant improvements during follow-up were observed in 24-h pad weight, for which the cohort mean pre-implant urine loss was 399 g, which was reduced at 18 months to 160 g (P < 0.001). Reductions in pad weight were observed across all levels of pre-implant SUI severity. Improvements were also seen in quality of life as measured by the I-QOL (P < 0.001) as well as measures of urinary function and pad count. A total of 30 subjects (24.2%) underwent device explant

Page 101 of 153
Medical Coverage Policy: 0504
Nash et al. (2019) reported on four year follow-up results for patients enrolled in a pivotal study conducted to support an FDA premarket approval application (PMAA). The study evaluated the safety and efficacy of the ProACT Adjustable Continence Therapy for the treatment of post-prostatectomy stress urinary incontinence (SUI). One hundred twenty-three patients underwent ProACT implantation with baseline and outcomes for 68 patients who completed 4-year follow-up visits reported. Endpoints included 24-h pad weight, Incontinence Quality of Life Questionnaire (I-QOL), UCLA Prostate Cancer Index-Urinary Function (PCI-UF), residual volume, and incidence and severity of device or procedure-related adverse events. Statistically significant improvements during follow-up were observed in 24-h pad weight, for which the mean pre-implant urine loss was 293 g, which was reduced at 4 years to 73 g (P < 0.001). Reductions in pad weight were observed across all levels of pre-implant SUI severity. Significant improvements were also seen in quality of life as measured by the I-QOL (P < 0.001) as well as measures of urinary function and pad use. Of the 68 patients included in this analysis, 19 patients had one explant and re-implant and three patients had two explants and re-implants. Overall, 77.3% of the 22 explanted and re-implanted patients experienced a reduction of greater than 50% from baseline to four years. The time to first explant for this cohort was 16.4 months +/-12.0 SD, a median of 12.7 months, and range of 0.4-45.6 months. There were a total of twelve procedure-related adverse events (AEs) recorded, with the most common being urethral or bladder perforation during implant. There were a total of 39 device-related adverse events recorded, balloon migration being the most common. The majority of device-related adverse events were resolved by explant.

Nestler, et al. (2019 conducted a retrospective study to evaluate the success and revision rates of ProACT over long-term follow-up and if repeat ProACT implantation after failure is a reasonable strategy. The study obtained a recent follow-up of all patients, who underwent an implantation of a ProACT system between 2003 and 2013 by a single surgeon. One hundred thirty four patients were implanted a ProACT system. Median age was 71 years; median follow-up was 118 months. Initially, 112 implantations were successful (82.6%) and the number of pads used decreased significantly (p < 0.005); 63 patients were revised and 49 were successful (77.8%). No differences in success rate, pads used, or filling volume were seen (all p > 0.8). Ten of 59 successfully revised patients (20.4%) underwent a second revision after a median of 39 months (IQR 22–65) due to rupture (n = 6) or dislocation (n = 4) of at least one of the balloons. Eight of ten patients were successfully reimplanted (80%). In the second revision, no differences in success rate or pads used were noted (all p > 0.7). The study is limited by the retrospective design, and lack of randomization.

In a prospective multicenter trial, Lebret et al. (2008) assessed the safety and efficacy of the ProACT system in the treatment of stress urinary incontinence (SUI) after prostate surgery. All 62 patients had failed previous rehabilitation (including pelvic floor training and electrostimulation). Daily pad usage decreased from a mean of 4.6 per day (range, 1 to 10) before surgery to 1.8 per day at 6 months (range, 0 to 10) and 1.06 per day (range 0 to 6) at 1 year after surgery. After 6 months (adjustments completed) 71% of the patients were wearing no pads or 1 pad per day (including security pads). Among the 44 patients who had RP without adjuvant radiotherapy, 89% improved, including 30% of patients becoming pad free. Conversely, for the 12 patients with adjuvant radiotherapy before ProACT implantation the failure rate was 83%. A total of 19 patients required explantation 89% improved, including 30% of patients becoming pad free. Conversely, for the 12 patients with adjuvant radiotherapy before ProACT implantation the failure rate was 83%. A total of 19 patients required explantation.

In a prospective longitudinal trial, 80 consecutive men who had undergone either ProACT (n = 44) or bone anchored male sling (n = 36) for post-prostatectomy incontinence were followed (Crivellaro, et al., 2008). The two procedures were carried out in two different centers by two different surgeons. All men had significant stress urinary incontinence for at least one year after radical prostatectomy and the incontinence had persisted despite conservative measures (pharmacotherapy or kegel exercises). All patients with urge incontinence or pre-existing voiding dysfunction were excluded from the study. At a mean follow-up of 19 and 33 months respectively, 30/44 (68%) patients treated with ProACT were dry in comparison with 23/36 (64%) patients treated with a sling (p > 0.05). Stratifying the results, ProACT had 33/39 (85%) dry patients in severe (more than three pads/day) preoperative incontinence, in comparison with 21/26 (81%) for the sling (p > 0.05). The authors noted their
results indicate a significant improvement in urinary incontinence and quality of life improvement in patients undergoing these procedures based on pre-operative degree of incontinence. ProACT results seem to be better for moderate to severe incontinence and a bone anchor sling for mild incontinence. The complication rate was higher for ProACT (13% vs. 5%, p > 0.05), primarily reflecting the development and refinement of the new surgical technique and its instrumentation.

Hübner et al. (2007) retrospectively reported on the use of ProACT in 100 men. The authors compared the results of the first 50 men they operated on with the results of the latest group of 50 men they have operated on, noting their “learning curve” and the evolution of the use of the device. All patients in both groups had undergone a radical prostatectomy as their primary operation for prostatic cancer. Observed were changes in pad use and incontinence quality of life (I-QOL) with a mean follow-up of 23 months in group 1 and 20 months in group 2. Complications requiring revision surgery occurred in 29 of 50 patients (58%; total 49 revision surgeries) of group 1 and in 12 patients (24%; total 16 revision surgeries) of group 2. There was a high rate of primary non-response in the first 50 patients (20 of 50, 40%) as the operation and implants evolved. All of these patients proceeded to using an AUS. In group 2 there were four cases (8%) of primary non-response requiring explantation, with two of these proceeding to bulbar urethral slings and two proceeding to implantation with the AUS. Overall, group 2 patients had more consistent outcomes in pad use reduction compared to group 1 (80% vs. 60% dry or >50% improved) and the number of non-responding patients was also dramatically reduced in group 2 compared to group 1 (16% vs. 40%). The authors note that although the “reference standard” for the treatment of severe incontinence remains the AUS, a place exists for a minimally invasive alternative, especially for men who may not have sufficient fine-motor control or the motivation to operate the implanted pump used with the AUS.

The published studies on ProACT consist mainly of retrospective and prospective studies and report high revision rates and explantation rates. Well-designed, comparative trials are needed to demonstrate safety and efficacy of the device as compared to other surgical incontinence treatments such as the artificial urinary sphincter.

**Professional Societies/Organizations**

**American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU):** AUA/SUFU published guidelines for incontinence after prostate treatment (2019). The guideline includes in treatment options:

- Adjustable balloon devices may be offered to patients with mild stress urinary incontinence after prostate treatment. (Moderate Recommendation; Evidence Level: Grade B)

The guidelines note, “While the adjustable balloon devices have been shown to improve incontinence, providers should be aware of an increased incidence of intraoperative complications and need for explanation within the first two years compared to the male sling and artificial urinary sphincter (AUS). Given the limited clinical experience of implanters across the United States, providers should obtain specialty training prior to device implantation.”

Grade B: (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), and is evidence about which the Panel has a moderate level of certainty.

**American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU):** the guideline from these organizations for surgical treatment of female stress urinary incontinence does not include adjustable continence therapy (ACT) (2017).

**International Consultation on Incontinence:** In a systematic review by the International Consultation on Incontinence on Surgical Treatment of Stress Incontinence in Men (Herschorn, et al., 2010), the following conclusions were drawn:

- Adjustable balloons (Adjustable Continence Therapy)

The ProACT balloon technique appears to be a feasible procedure in the short to medium term, with better results occurring with more operator experience. Appropriate candidates are those with mild to moderate leakage and no previous radiation. The benefit of an adjustable system should be weighed against the need for multiple sessions of refilling the balloon, and the reported rate of peri- and post-operative complications. Longer follow-up is needed before definitive comparison to male sling or
artificial urinary sphincter (AUS) can be made. No recommendation is possible due to variable data on complication rates (12–58%).

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Local Coverage Determination (LCD): Category III Codes (L35490). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
European Association of Urology (EAU): EAU published guidelines for urinary incontinence in adults (2018). Regarding ProACT, the guidelines note:
Summary of evidence for compression devices in males:
- Very limited short-term evidence suggests that the non-circumferential compression device (ProACT) is effective for treatment of post-prostatectomy SUI. Level of evidence: 3
- The non-circumferential compression device (ProACT) is associated with a high failure and complication rate leading to frequent explantation. Level of evidence: 3

Recommendations for men with stress urinary incontinence:
- Implantation of AUS or ProACT for men should only be offered in expert centres. Strength rating: Weak
- Warn men receiving AUS or ProACT that, although cure can be achieved, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation. Strength rating: Weak
- Do not offer non-circumferential compression device (ProACT) to men who have had pelvic radiotherapy. Weak

The Australia and New Zealand Horizon Scanning Network’s (ANZHSN) scanning program is a collaborative Commonwealth and State initiative guided by the Health Policy Advisory Committee on Technology (HealthPACT). HealthPACT provides jurisdictions with evidence-based advice on emerging technologies. This information is used to inform jurisdiction financing decisions and to assist in the managed introduction of new technologies. A Horizon Scanning report prepared by the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) on behalf of HealthPACT provided recommendations on ProAcCT device for male stress urinary incontinence. The ProACT Therapy system has already being approved for clinical use in the European market and is distributed throughout Europe, Canada, Brazil, Malaysia and Australasia The ProACT Therapy system is registered in the Australian Register of Therapeutic Goods (ARTG). Stage of development of the technology was determined to be “established” in Australia, with limited use in Europe. According to the HealthPACT recommendation, “higher quality studies, preferably randomized controlled trials are required to better evaluate the safety and efficacy of this implant for male stress urinary incontinence” (HealthPACT, 2006). A 2008 update to the report stated that “long-term comparative evidence is still required for ProACT therapy, but the potential of the device warrants monitoring for a further 12 months” (HealthPACT, 2008).

References
4. Angulo JC, Schönburg S, Giammò A, Abellán FJ, Arance I, Lora D. Systematic review and meta-analysis comparing Adjustable Transobturator Male System (ATOMS) and Adjustable Continence


Coding/Billing Information Urology

Page 105 of 153
Medical Coverage Policy: 0504
Note: 1) This list of codes may not be all-inclusive.
   2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Urology Services Considered Experimental/Investigational/Unproven:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>53860</td>
<td>Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence</td>
</tr>
<tr>
<td>0548T</td>
<td>Transperineal periurethral balloon continence device; bilateral placement, including cystoscopy and fluoroscopy</td>
</tr>
<tr>
<td>0549T</td>
<td>Transperineal periurethral balloon continence device; unilateral placement, including cystoscopy and fluoroscopy</td>
</tr>
<tr>
<td>0550T</td>
<td>Transperineal periurethral balloon continence device; removal, each balloon</td>
</tr>
<tr>
<td>0551T</td>
<td>Transperineal periurethral balloon continence device; adjustment of balloon(s) fluid volume</td>
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</tbody>
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Ophthalmology

Suprachoroidal Injection of a Pharmacologic Agent (does not include supply of medication (CPT code 0465T)
The leading causes of blindness include those affecting the back of the eye: age-related macular degeneration, diabetic retinopathy, and uveitis. Although treatments are available, delivering drugs to the posterior regions of the eye is challenging because of architecture as well as natural barriers (Patel, 2011). Drug delivery techniques include intravitreal injections, periocular injections and intravitreal implants. Suprachoroidal drug delivery has been proposed as an alternative method to access the suprachoroid space (SCS). There have been several techniques described for injections into the SCS (Moisseiev, et al., 2016). The injection can be done using standard small-gauge needles, but this is a delicate procedure with a risk of penetration into the choroid or the vitreous cavity. Surgical cannulation may be used for drug delivery to the posterior pole, however, this is a complicated procedure and cannot be performed in-office. SCS drug delivery using microneedles is also being investigated. The micro-needles are small-gauge needles (30–33 G) and 0.7–1.0 mm in length that are only long enough to penetrate the sclera and reach the SCS. These microneedles have been demonstrated to be safe and effective in several animal studies. SCS™ microinjector (Clearside Biomedical Inc. Alpharetta, GA), is a microneedle being developed for SCS injection in humans. The device is currently undergoing two Phase 2 clinical trials with its proprietary formulation of triamcinolone acetonide (CLSTA) for the treatment of macular edema associated with noninfectious uveitis and along with aflibercept for the treatment of macular edema associated with RVO.

U.S. Food and Drug Administration (FDA)
The iScience Surgical Ophthalmic Microcannula (iScience Surgical Corporation, Redwood City, CA) is a flexible microcannula designed to allow atraumatic cannulation of spaces in the eye such as the anterior chamber and posterior segment (FDA, 2004). It received 510(k) approval on June 22, 2004 for the following indications: fluid infusion and aspiration, as well as illumination, during surgery.

SCS™ microinjector (Clearside Biomedical Inc. Alpharetta, GA) has not yet received FDA approval.

Literature Review
The published studies regarding suprachoroidal injection are limited by uncontrolled design and small populations.

Professional Societies/Organizations
Guidelines from the American Academy of Ophthalmologists for suprachoroidal delivery as a method for delivering drugs to the posterior regions of the eye are lacking.
Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
No relevant information.

References


Conjunctival Incision with Posterior Extrascleral Placement of a Pharmacological Agent (CPT Code 68399)
Neovascular age-related macular degeneration (AMD) is associated with a rapid loss of vision due to an abnormal growth of blood vessels in the macula of the eye, leakage, and scarring (Geltzer, 2007). Treatment options for this disease are limited and there are a variety of therapies currently being investigated for neovascular AMD. Surgical implantation of steroids with antiangiogenic and anti-inflammatory properties has been proposed as a practical method of administering these agents into the eye (Geltzer, 2007). Extrascleral placement of steroids involves an incision into the orbit posterior to the limbus, through the conjunctiva. A cannula is inserted outside the sclera until the tip is near the macula, and the drug is administered. Advantages to this procedure may include a reduced risk for retinal detachment and endophthalmitis (Geltzer, 2007).

Literature Review
Randomized controlled trial (RCT) data are scarce regarding the safety and effectiveness of conjunctival incision with posterior extrascleral placement of pharmacological agents.

Geltzer et al. (2013) reported on a Cochrane review which analyzed outcomes of three RCTs involving the administration of triamcinolone acetonide versus placebo, anecortave acetate versus placebo, and anecortave acetate versus photodynamic therapy for the treatment of age-related macular degeneration. One trial found posterior juxtrascleral depot of anecortave acetate may be effective in preventing severe vision loss. Overall the
assessment noted weak evidence as to the benefits and harms of steroids with antiangiogenic properties for treating neovascular AMD by posterior juxtrascleral placement of drugs.

**Centers for Medicare & Medicaid Services (CMS)**
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCD found.

**Use Outside of the US**
No relevant information.

**References:**

**Automated Evacuation of Meibomian Glands (CPT Code 0207T, 0563T)**
The meibomian glands are located on the eyelids and are responsible for the production of sebum. Sebum prevents the tear film from evaporating too quickly from the eye’s surface. Meibomian gland dysfunction leads to decreased secretion and abnormal composition of the tear film lipid layer, which in turn can lead to blockage of the glands, dry eye, and infection. Conventional treatment includes eyelid washing, use of preservative-free tears, omega-3 dietary supplementation, topical and oral antibiotics, corticosteroids, warm compresses and gentle eyelid massage. The use of an automated heated compression device has been proposed as a treatment of meibomian gland dysfunction.

**U.S. Food and Drug Administration**
The LipiFlow Thermal Pulsation System (TearScience, Morrisville, NC) received FDA 510(k) clearance in July, 2011. This system is intended to be used by a physician in an in-office procedure. The FDA approval indicates “The LipiFlow Thermal Pulsation System is intended for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including meibomian gland dysfunction (MGD) also known as evaporative dry eye or lipid deficiency dry eye.”

**Literature Review**
Ahmed et al. (2019 conducted a study to assess the effect of a intense pulsed light (IPL) therapy on tear proteins and lipids in eyes with Meibomian gland dysfunction (MGD). The study included twenty-four eyes of 12 patients with MGD. Tear samples were evaluated immediately before and 2 weeks after IPL therapy and included measurements of protein concentration, electrophoretic mobility by using sodium dodecyl sulfate-polyacrylamide gel electrophoresis, lipid profile assessments, and thin-layer chromatography (TLC) for phospholipids. Improvements was observed in tear protein concentrations and molecular weight after IPL therapy. The most pronounced effect was in the molecular weight of tear lysozyme, lactoferrin, and albumin. Tear lipids showed an improvement in the concentrations of total lipids, triglycerides, cholesterol, and phospholipids. On TLC, the tears in patients with MGD had significantly lower amounts of anionic
phosphatidylethanolamine, phosphatidylinositol, and phosphatidylserine but amounts zwitterionic neutral phospholipid phosphatidylcholine were normal. These anionic phospholipids showed obvious recovery after IPL therapy. The authors concluded that IPL therapy is effective in eyes with MGD. It improved tear protein and lipid content and composition. The anionic phospholipids were more responsive to IPL therapy than were the other zwitterionic phospholipids. The study was limited with lack of comparator and randomization and the small number of patients.

Choi et al. (2019) conducted a study to investigate the baseline characteristics associated with an improvement in symptoms after Intense Pulsed Light (IPL) treatment; to examine the course of change in inflammatory tear cytokines, meibomian gland function, and tear stability; and to investigate the correlation between cytokines and ocular surface parameters. The study included 30 participants who underwent three sessions of IPL treatment. Tear film lipid layer interferometry, meibography, tear meniscus height measurement, tear sampling, and slit-lamp examination were performed at each treatment, and the Ocular Surface Disease Index (OSDI) questionnaire was administered. Meibum quality, meibum expressibility, lid margin abnormality, tear film breakup time (TBUT), ocular surface staining, and the OSDI improved after treatment. Poor meibum expressibility and short TBUT were associated with greater recovery in the OSDI after IPL. Tear levels of IL-4, IL-6, IL-10, IL-17A, and TNF-α decreased after IPL, and IL-6, and TNF-α were correlated with the improvement in meibum expressibility. The authors note that IPL treatment improved meibomian gland function, stabilized the tear film, and decreased ocular surface inflammation. Patients with obstructive MGD and tear instability were more likely to experience an improvement in ocular discomfort after IPL treatment.

Blackie, et al (2017) conducted a prospective, multicenter, open-label clinical trial that included 200 subjects (400 eyes) who were randomized to a single VTP treatment (treatment group) or twice-daily, 3-month, conventional warm compress and eyelid hygiene therapy (control group). Control group subjects received crossover VTP treatment at 3 months (crossover group). Effectiveness measures of meibomian gland secretion (MGS) and dry eye symptoms were evaluated at baseline and one, three, six, nine and 12 months. Subjects with inadequate symptom relief could receive additional meibomian gland dysfunction therapy after 3 (treatment group) and 6 months (crossover group). At three months, the treatment group had greater mean improvement in MGS (P<0.0001) and dry eye symptoms (P=0.0068), compared to controls. At 12 months, 86% of the treatment group had received only one VTP treatment, and sustained a mean improvement in MGS from 6.4±3.7 (baseline) to 17.3±9.1 (P<0.0001) and dry eye symptoms from 44.1±20.4 to 21.6±21.3 (P<0.0001); 89% of the crossover group had received only one VTP treatment with sustained mean improvement in MGS from 6.3±3.6 to 18.4±11.1 (P<0.0001) and dry eye symptoms from 49.1±21.0 to 24.0±23.2 (P<0.0001). Greater mean improvement in MGS was associated with less severe baseline MGS (P=0.0017) and shorter duration of time between diagnosis and treatment (P=0.0378). The authors concluded that a single VTP treatment can deliver a sustained mean improvement in meibomian gland function and mean reduction in dry eye symptoms, over 12 months.

To compare the effectiveness of a single LipiFlow treatment with combined lid warming and massage in patients with meibomian gland dysfunction (MGD), Finis et al. (2014) published results of a prospective, randomized, crossover, observer-masked clinical trial involving 40 subjects. Subjects were randomized to receive either a single LipiFlow treatment (LipiFlow group) or to perform standardized, twice-daily combined lid warming and massage (lid margin hygiene or control group) for three months. The primary outcome measure was improvement of subjective symptoms, as assessed by the Ocular Surface Disease Index (OSDI) scores. Secondary outcome measures included improvement of TFBUT, decreased tear osmolarity, increased LLT, and increased number of expressible meibomian glands. A total of 31 subjects completed the study. A total of 31 subjects completed the 3-month follow-up. At 1 and 3 months, patients in the LipiFlow treatment group had a significant reduction in Ocular Surface Disease Index (OSDI) scores compared with those in the lid-margin hygiene group (p<0.01). Both treatments produced a significant improvement in expressible meibomian glands compared to the baseline parameters, but no significant difference was noted between the two groups. The other investigated objective parameters did not show a significant difference. The authors note while results of this small study suggest that a single LipiFlow treatment is as least as effective as a 3-month, twice-daily lid margin hygiene regimen for MGD, the study was observer-masked only, and a placebo effect may have confounded any improvements in subjective symptoms and other parameters in both groups. Study limitations include non-blinded design and small study size. Larger, blinded randomized clinical trials are required to determine impact on health outcomes.
Lane et al. (2012) conducted a study examining the safety and effectiveness of the LipiFlow System compared with the iHeat Warm Compress (WC) for adults with meibomian gland dysfunction. This was a prospective open-label, randomized, crossover multicenter clinical trial. One hundred thirty-nine subjects were randomized between LipiFlow (n=69) and WC control (n=70). Subjects in the LipiFlow group received a 12-minute LipiFlow treatment and were reexamined at one day, two weeks and four weeks. Control subjects received a five-minute iHeat treatment with instructions to perform the same treatment daily for two weeks. At two weeks, they crossed over and received the LipiFlow treatment. LipiFlow resulted in significant improvement in meibomian gland secretion at two and four weeks (p < 0.05). There was no change in meibomian gland secretion in the control group. Limitations to the study were the small population size. Results replicated in larger RCTs are required to demonstrate the ability to apply outcomes to the general population.

Mitra et al. (2005) reported results of a prospective, controlled, observer masked, single intervention trial in which 24 normal subjects were randomized into three groups: Group 1: 10 minutes with the activated device, Group II: 10 minutes with the inactivated device, Group III: no intervention. The lipid layer thickness of each subject was measured prior and subsequent to the 10-minute period. A statistically significant increase in lipid layer thickness was seen in 87% of subjects in Group I (p<0.001, left eye, p<0.003, right eye.). Seventy-five percent of subjects experienced subjective improvement in ocular comfort. The authors note that meibomian therapy using this novel device results in increased lipid layer thickness. A limitation of this study was the small study population.

Korb et al. (2011) reported on a study attempting to determine the pressure required to express the first non-liquid material from nonfunctional lower lid meibomian glands, the pressure required to evacuate all of the expressible material from the glands, and the level of pain associated with these actions. Custom instrumentation was applied to the lower lid, exerting pressures from 1.0 to 150.0 pounds per square inch (psi). Pressure was monitored throughout the procedure as was pain level. The pressure required to obtain the first non-liquid material ranged between 5-40 pounds per square inch. Pain was the limiting factor for this treatment. Only 7% of the patients could tolerate the pressure necessary to administer complete expression of the non-liquid material.

Professional Societies/Organizations
American Academy of Ophthalmology (AAO) (2018): The AAO preferred practice patterns for dry eye syndrome include as a recommendation when the first step options are inadequate: “In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow, or intense pulse light treatment”).

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
National Institute for Health and Care Excellence (NICE): Nice published a Medtech innovation briefing for LipiFlow thermal pulsation treatment for dry eyes caused by blocked meibomian glands (2015). The report notes that, “The LipiFlow system is not currently being offered within the NHS, although it is available for purchase in the UK. The LipiFlow system is currently only available in private clinics. If adopted within the NHS, the LipiFlow system would be used to treat people who have not responded to currently available treatments. These people are likely to be referred from their optician or GP to ophthalmologists for treatment with the LipiFlow system.”

References


**Insertion of Ocular Telescope Prosthesis Including Crystalline Lens (CPT Codes 0308T, HCPCS Code C1840)**

The prosthetic intraocular telescope system is intended for the treatment of central vision loss (bilateral central scotomas) due to age-related macular degeneration (AMD). The device projects an image onto the part of the retina which is still healthy and can still see images. The device not intended to cure AMD, however it has the potential to improve quality of life and daily functioning for patients with end-stage AMD. The implantation inside the eye allows the patient to use natural eye movements to see, rather than head movements, which are required when using external magnification devices for AMD-related low vision.

**U.S. Food and Drug Administration (FDA):** The Implantable Miniature Telescope™ (VisionCare Ophthalmic Technologies, Saratoga, CA) received FDA premarket approval in July 2010. According to the FDA, this device is an implantable device which, when combined with the optics of the cornea, constitutes a telephoto system for improvement of visual acuity in patients with severe to profound vision impairment due to bilateral, end-stage, age-related macular degeneration(AMD). The implantable miniature telescope (IMT) is surgically implanted in the capsular bag and is held in position by haptic loops. The intraocular telescope is available in two models: Wide Angle (WA) 2.2X and Wide Angle (WA) 2.7X. Both models are indicated for monocular implant. The implanted eye provides central vision, while the fellow eye continues to be used for peripheral vision.
The initial FDA approval noted the device is intended to improve vision in patients 75 years of age or older with stable, severe to profound vision impairment caused by end-stage age-related macular degeneration. The device is indicated for (FDA, 2010):

- monocular implantation to improve vision in patients greater than or equal to 75 years of age with stable, severe to profound vision impairment (best corrected distance visual acuity 20/160 to 20/800) caused by bilateral central scotomas associated with endstage age-related macular degeneration.
- Patients must:
  - have retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography;
  - have evidence of visually significant cataract (> grade 2);
  - agree to undergo presurgery training and assessment (typically 2 to 4 sessions) with low vision specialists (optometrist or occupational therapist) in the use of an external telescope sufficient for patient assessment and for the patient to make an informed decision;
  - achieve at least a 5-letter improvement on the ETDRS chart with an external telescope;
  - have adequate peripheral vision in the eye not scheduled for surgery; and
  - agree to participate in postoperative visual training with a low vision specialist.

In October 2014, the FDA expanded the age limit for Implantable Miniature Telescope (IMT) to 65 years of age or older. The supplement also included revisions to the professional and patient labeling with updated data based on the results out to eight years post IMT implantation; to revise the acceptance of risk and informed decision agreement; and to the professional and patient labeling to emphasize that the longer the IMT is in the eye, the greater the potential risk of developing vision-impairing corneal edema which may lead to the need for corneal transplant and possible telescope removal.

As part of the initial approval, there was a requirement for extended follow-up of the premarket cohort population. According to the FDA, this continued follow-up of individuals in the long-term follow-up cohort (5 years postoperatively) will be conducted to provide additional long-term (up to eight years) safety data. The FDA also requires a multicenter, prospective, open label, single group assignment cohort study for safety. The study is required to consecutively enroll 770 presurgical subjects aged 75 years and older with severe to profound vision impairment caused by end-stage age-related macular degeneration and a cataract. The subjects enrolled and undergoing implantation of the IMT will be followed for a total of five years with approximately six follow-up visits during the first year followed by annual visits thereafter for the next four years (FDA, 2010).

According to the FDA Summary Of Safety And Effectiveness implantation of the device is contraindicated in patients (FDA, 2010):

- Stargardt's macular dystrophy
- central anterior chamber depth (ACD) <3.0 mm; measurement of the ACD should be taken from the posterior surface of the cornea (endothelium) to the anterior surface of the crystalline lens
- presence of corneal guttata
- minimum age and endothelial cell density requirements are not met
- with cognitive impairment that would interfere with the ability to understand and complete the Acceptance of Risk and Informed Decision Agreement or prevent proper visual training/rehabilitation with the device
- who have evidence of active choroidal neovascularization (CNV) on fluorescein angiography or treatment for CNV within the past six months
- with any ophthalmic pathology that compromises the patient's peripheral vision in the fellow eye
- with previous intraocular or cornea surgery of any kind in the operative eye, including any type of surgery for either refractive or therapeutic purposes
- who have prior or expected ophthalmic related surgery within 30 days preceding intraocular telescope implantation
- with a history of steroid-responsive rise in intraocular pressure (IOP), uncontrolled glaucoma, or preoperative IOP >22 mm Hg, while on maximum medication
- with known sensitivity to post-operative medications
• who have a history of eye rubbing or an ocular condition that predisposes them to eye rubbing
• in whom the planned operative eye has:
  ➢ myopia > 6.0 D
  ➢ hyperopia > 4.0 D
  ➢ axial length < 21 mm
  ➢ a narrow angle, i.e., < Schaffer grade 2
  ➢ cornea stromal or endothelial dystrophies, including guttata
  ➢ inflammatory ocular disease
  ➢ zonular stromal or endothelial dystrophies, including pseudoexfoliation
  ➢ diabetic retinopathy
  ➢ untreated retinal tears
  ➢ retinal vascular disease
  ➢ optic nerve disease
  ➢ a history of retinal detachment
  ➢ intraocular tumor
  ➢ retinitis pigmentosa.
• in eyes in which both haptics cannot be placed within the capsular bag during surgery, the intraocular telescope should be removed and replaced with a conventional intraocular lens (IOL); sulcus fixation of either one or both haptics increases the risk of severe endothelial cell loss and corneal transplant

Literature Review
Hudson et al. (2006) reported on a prospective, open-label, multicenter clinical trial (IMT-002 clinical trial) with fellow eye controls. The trial included 217 patients with AMD and moderate to profound bilateral central visual acuity loss (20/80-20/800) resulting from bilateral untreatable geographic atrophy, disciform scars. A visual prosthetic device (implantable telescope), designed to enlarge retinal images of the central visual field, was implanted monocularly in the capsular bag after lens extraction. Fellow eyes were not implanted to provide peripheral vision and served as controls. Study patients participated in six visual rehabilitation visits after surgery. At one year, 67% of implanted eyes achieved a 3-line or more improvement in best-corrected distance visual acuity (BCDVA) versus 13% of fellow eye controls (P<0.0001). Fifty-three percent of implanted eyes achieved a 3-line or more improvement in both BCDVA and BCNVA versus 10% of fellow eyes (P<0.0001). Mean BCDVA and best-corrected near visual acuity (BCNVA) improved 3.5 lines and 3.2 lines, respectively, in implanted eyes versus 0.8 lines and 1.8 lines, respectively, in fellow eyes (P<0.0001). Eleven eyes did not receive the device because of an aborted procedure. Endothelial cell density was reduced by 20% at three months and 25% at one year. The decrease in Endothelial cell density (ECD) was correlated with postsurgical edema (P<0.0001) with no evidence that endothelial cell loss is accelerated by ongoing endothelial trauma after implantation, the authors concluded that the device can improve visual acuity and quality of life in patients with moderate to profound visual impairment caused by bilateral, end-stage AMD.

Hudson et al. (2008) reported on two year results of the above study. The main outcome measures included BCVA change from baseline, endothelial cell density (ECD) and morphometry, and incidence of complications. At two years, data from 174 (92.6%) of 188 available patients were analyzed with findings that overall, 103 (59.5%) of 173 telescope-implanted eyes gained three lines or more (doubling of visual angle) of BCVA compared with 18 (10.3%) of 174 fellow control eyes (P < .0001). Mean BCVA improved 3.6 lines (standard deviation [SD], 1.9 lines) and 2.8 lines (SD, 2.3 lines) from baseline in eyes with the 3X and 2.2X device models, respectively. Mean ECD stabilized through two years, with 2.4% mean cell loss occurring from one to two years. There was no significant change in coefficient of variation or percentage of hexagonal endothelial cells from within six months to two years after surgery. The most common complication found to be inflammatory deposits. The authors concluded that the device can improve visual acuity and quality of life in patients with moderate to profound visual impairment caused by bilateral, end-stage AMD.

Boyer et al. (2015) reported on the long-term results (60 months) of implantable miniature telescope (IMT) in patients with bilateral, end-stage, age-related macular degeneration (AMD) (studies above Hudson, et al., 2006; Hudson et al., 2008). A subgroup analysis was performed with stratification for age (patient age 65 to <75 years [group 1; n=70] and patient age ≥75 years [group 2; n=127]), with a comparative evaluation of change in best-
corrected distance visual acuity (BCDVA), quality of life, ocular complications from surgery, adverse events, and endothelial cell density (ECD). The mean BCDVA improvement from baseline to 60 months was 2.41±2.69 lines in all patients (n=76), with 2.64± 2.55 lines in group 1 and 2.09±2.88 lines in group 2. The quality of life scores were significantly higher in group 1. The most common significant surgery-related ocular complications in group 1 were iritis >30 days after surgery (7/70; 10%) and persistent corneal edema (3/70; 4.3%); and in group 2 were a decrease in BCDVA in the implanted eye or IMT removal (10/127 each; 7.9%), corneal edema >30 days after surgery (9/127; 7.1%), and persistent corneal edema (6/127; 4.7%). The significant adverse events included four corneal transplants, comprising two (2.9%) in group 1 and two (1.6%) in group 2. At 60 months, one patient in group 1 (3.2%) and three patients in group 2 (9.4%) had lost ≥2 lines of vision. The IMT was removed in one (1.4%) and ten (7.9%) patients in group 1 and group 2, respectively. Mean ECD loss was 20% at 3 months. Chronic loss was 3% per year. ECD loss was less in group 1 than in group 2 (35% versus 40%, respectively) at 60 months. These long-term results indicate substantial retention of improvement in BCDVA. The chronic ECD loss appears consistent with that reported for conventional intraocular lenses. The results indicate that younger patients retained more vision than their older counterparts with fewer adverse events.

Gupta et al. (2018) reported on a Cochrane review to assess the effectiveness and safety of the implantable miniature telescope (IMT) in improving visual acuity and quality of life in people with late or advanced AMD. The selection criteria included randomized controlled trials (RCTs) and quasi-randomized trials that compared the IMT versus no IMT. The review included four studies; three were non-randomized studies and there was one ongoing RCT that compared the OriLens intraocular telescope with standard low vision training in eyes with end-stage AMD with results for this study expected in 2020. The authors found no RCT or quasi-RCT and noted that they can draw no conclusion about the effectiveness and safety of the IMT in improving visual acuity in individuals with late or advanced AMD. The authors noted that since the IMT is typically implanted monocularly based upon which eye has better best-corrected distance visual acuity, randomization between eyes within an individual may not be acceptable and studies are needed that compare outcomes between individuals randomized to the device versus individuals not implanted.

Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCD): No NCD found

Use Outside of the US

National Institute for Health and Care Excellence (NICE) published guidelines for miniature lens system implantation for advanced age-related macular degeneration. The guidelines note (NICE, 2016) that, “Evidence on the efficacy of miniature lens system implantation for advanced age-related macular degeneration (AMD) shows that the procedure can improve both vision and quality of life in the short term. Data on short-term safety are available for limited numbers of patients. There is currently insufficient long-term evidence on both efficacy and safety. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.”

References

Quantitative Pupillometry (CPT Codes 92499, 0341T) (Code 0341T deleted 12/31/2019, Add CPT code 92499 as replacement)
Pupil reactivity and sensitivity may indicate neurological issues or worsening of neurological status. Current practice is to use a penlight to observe the pupillary light reflex which is a subjective measurement. Several quantitative pupillometer devices are available, although their use is primarily restricted to the research setting (Couret, et al., 2016). The stimulation and subsequent measurement of pupil reactivity by a hand held infrared camera and use of a digital device and data processor to calculate measurements has been proposed for a number of indications including the evaluation of autonomic function, response to pain, drug metabolism, sleep disorders, and various psychological indications and has been use in the research setting. A pupillometer is made of three components: the light source to stimulate the pupil, an image capturing device capable of taking measurements of the pupil in real-time, and a data processor that performs the calculations using the measurements. The device is held in the patient’s visual field, the data is interpreted, and a report is generated.

Literature Review
High level, randomized and controlled data are lacking regarding the effectiveness of this device in the published, peer viewed scientific literature.

Jahns et al. (2018) conducted a study using automated infrared pupillometry to examine the relationship between the Neurological Pupil index (NPI) and invasive ICP in patients with severe TBI. This was observational cohort of 54 consecutive subjects with severe TBI (Glasgow Coma Scale [GCS] < 9 with abnormal lesions on head CT) who underwent parenchymal ICP monitoring and repeated NPI assessment with the NPI-200® pupillometer. NPI trends over time (four consecutive measurements over intervals of 6 h) prior to sustained elevated ICP > 20 mmHg were examined. Further analysis of the relationship of cumulative abnormal NPI burden (%NPI values < 3 during total ICP monitoring time) with intracranial hypertension (ICHT)—categorized as refractory (ICHT-r; requiring surgical decompression) vs. non-refractory (ICHT-nr; responsive to medical therapy)—and with the 6-month Glasgow Outcome Score (GOS). Among subjects with ICHT, episodes of sustained elevated ICP (n = 43, 172 matched ICP-NPI samples; baseline ICP [T− 6 h] 14 ± 5 mmHg vs. ICPmax [T0 h] 30 ± 9 mmHg) were associated with a concomitant decrease of the NPI (baseline 4.2 ± 0.5 vs. 2.8 ± 1.6, p < 0.0001 ANOVA for repeated measures). Abnormal NPI values were more frequent in patients with ICHT-r (n = 17; 38 [3–96]% of monitored time vs. 1 [0–9]% in patients with ICHT-nr [n = 15] and 0.5 [0–10]% in those without ICHT [n = 22]; p = 0.007) and were associated with an unfavorable 6-month outcome (15 [1–80]% in GOS 1–3 vs. 0 [0–7]% in GOS 4–5 patients; p = 0.002). The authors concluded that in a selected cohort of severe TBI patients with abnormal head CT lesions and predominantly focal cerebral injury, elevated ICP episodes correlated with a concomitant decrease of NPI and sustained abnormal NPI was in turn associated with a more complicated ICP course and worse outcome. The authors notes that additional studies also may help to better
refine the role of the NPI as a monitoring tool, its place in ICP management algorithms, and potential role in future guidelines for TBI care.

Najjar et al. (2018) conducted a cross-sectional study to evaluate the ability of chromatic pupillometry to reveal abnormal pupillary responses to light in patients with early-stage primary open-angle glaucoma (POAG) and to test whether the degree of pupillometric impairment correlates with structural hallmarks of optic nerve damage in the disease. The study included 46 patients with early-stage POAG and 90 age-matched healthy controls. The participants underwent a monocular 2-minute exposure to blue light (462 nm) followed by another 2-minute exposure to red light (638 nm). The light stimuli intensity was increased logarithmically to evaluate the combined extrinsic and intrinsic response of intrinsically photosensitive retinal ganglion cells (ipRGCs). Light-induced changes in horizontal pupil diameter were assessed monocularly using infrared pupillography. Light-induced pupillary constriction was reduced in patients with early-stage POAG compared with controls at moderate to high irradiances and red light. Maximal pupillary constriction amplitude was correlated with retinal nerve fiber layer thickness (RNFL) thickness in patients with POAG but not in controls. Conversely, pupillometric parameters were not correlated with visual field scores in patients with early-stage POAG. The limitations of the study include the lack of randomization and small number of subjects.

Couret et al. (2016) reported on a study that compared automated quantitative pupillometry with the standard clinical pupillary examination currently used for brain-injured patients. Repetitive measurements were made in 200 healthy volunteers providing a total of 400 paired (alternative right eye, left eye) measurements under a wide variety of ambient light conditions with the NeuroLight Algiscan pupillometer and then a prospective, observational, double-blinded study was conducted in two neurocritical care units. In 200 healthy volunteers, intra-class correlation coefficient for maximum resting pupil size was 0.95 (IC: 0.93-0.97) and for minimum pupil size after light stimulation 0.87 (0.83–0.89). It was found 3-pupil asymmetry (≥1 mm) in these volunteers (1.5% of the population) with a clear pupil asymmetry during clinical inspection. The mean pupil light reactivity was 40 ± 7%. In 59 patients, 406 pupillary measurements were prospectively performed. Concordance between measurements for pupil size collected using the pupillometer, versus subjective assessment, was poor (Spearman's rho = 0.75, IC: 0.70-0.79; P < 0.001). A global rate of discordance of 18% (72/406) was found between the two techniques when assessing the pupillary light reflex. For measurements with small pupils (diameters <2 mm) the error rate was 39% (24/61). The results demonstrated that pupillary evaluations obtained subjectively at the patient's bedside were inaccurate compared with those obtained with an automatic quantitative pupillometer device. The authors concluded that the standard practice in pupillary monitoring yields inaccurate data, that automated quantitative pupillometry is a appears to be a more reliable method with which to collect pupillary measurements at the bedside; however, the impact of a pupillometer use on patients' outcome has to be demonstrated in further prospective studies.

In a cross-sectional cohort study Kantor et al. (2014) assessed the association between postoperative pain (NRS) and pupillary diameter or pupillary light reflex amplitude (PLRA) in 145 Post Anesthesia Care Unit (PACU) patients after routine anesthetic care. Sedation, hemodynamic, pupillary and pain assessments were performed in each patient after their arrival in the PACU or before morphine titration. In patients receiving morphine titration, a second assessment was performed after titration. Sedation was assessed using the modified Observer's Assessment of Alertness/Sedation (OAAS) scale. Hemodynamic assessment consisted of non-invasive systolic and diastolic blood pressure and heart rate. Pupillary assessment was performed with an infrared portable dynamic videopupillometer. Mean numerical rating score (NRS) for pain as assessed by study participants was 4.7, and was more than four in 79 patients (55%). No statistically significant association was observed between NRS and pupillary diameters (p=0.54). Twenty-seven patients (19%) received morphine titration with significant decreases in NRS, pupillary diameter and PLRA afterwards. No association was observed between NRS changes and pupillary diameter or PLRA changes. The authors concluded acute postoperative pain is not associated with pupillary diameter or PLRA. Further high quality randomized clinical trial data is required to demonstrate the impact of pupillometry as a means to assess pain in the PACU.

Bremner et al. (2006) reported results of a prospective study of involving the use of light reflex pupillography in 150 consecutive patients with symptomatic generalized autonomic failure. Inclusion criteria was heterogeneous with a variety of indications represented including amyloidosis, multiple system atrophy, pure autonomic failure, diabetes mellitus, hereditary neuropathies, and paraneoplastic syndromes. Infra-red video pupillography was used to measure resting pupil diameters in light and dark, the light reflex response, the miosis associated with an
accommodative effort, and responses to topical administration of various pharmacological agents. No significant correlation between the type of pupil abnormality and the predominant type of systemic autonomic deficit was seen in most conditions. The authors note “Although there does appear to be some weak correspondence between our pupillographic findings and the results of autonomic function tests, a x2 test suggests that this association could have arisen by chance (p=0.072).”

Professional Societies/Organizations

Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L37777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
No relevant information

References

Visual Field Assessment with Concurrent Real Time Data Analysis (CPT Codes 0378T, 0379T)
Visual field assessment is reported for up to 30 days. The patient transmits daily test-data to monitoring center (IDTF) for input into secured database. The technician with physician analyzes the data and prepares report and the results are then interpreted by a physician.

Literature Review
There is insufficient evidence in the published, peer-reviewed scientific literature to establish improved health outcomes with this testing. At this time the role of this service has not been established.
Professional Societies/Organizations
Professional society guidelines are lacking regarding visual field assessment with concurrent real time data analysis.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
No relevant information

References

Computer-Aided Animation and Analysis of Time Series Retinal Images for the Monitoring of Disease Progression (CPT Codes 92499, 0380T) (Code 0380T deleted 12/31/2019, Add CPT code 92499 as replacement)
MatchedFlicker® (EyeIC Inc., Wayne, PA) is a device that is purported to enable fast and accurate comparison of digital fundus images to aid clinicians in diagnosis. According to the vendor’s website, MatchedFlicker automatically combines time-series images selected from a patient record to create an animation wherein images are aligned, superimposed and alternated back and forth.

There is insufficient evidence in the published, peer-reviewed scientific literature to establish improved health outcomes using this technology. At this time the role of computer-aided animation and analysis of time series retinal images to monitor disease progression has not been established.

U.S. Food and Drug Administration (FDA): The MatchedFlicker received 510(K) premarket approval (PMA) in 2009 for the intended for use by health care professionals to collect, store, and spatially calibrate (i.e. register and align) images of the posterior segment of the human eye.

Literature Review
There is insufficient evidence in the published, peer-reviewed scientific literature to establish improved health outcomes with this testing. At this time the role of this service has not been established.

Professional Societies/Organizations
Professional society guidelines are lacking regarding computer-aided animation and analysis of time series retinal images for the monitoring of disease progression.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
No relevant information

References


Retinal prosthesis system (Device evaluation, interrogation, and initial programming of intra-ocular retinal electrode array) (CPT codes 0100T, 0472T, 0473T, C1841, C1842, L8608)

Retinitis pigmentosa (RP) comprises a complex group of inherited dystrophies characterized by progressive degeneration and dysfunction of the retina, primarily affecting photoreceptor and pigment epithelial function. The clinical manifestations of RP include night blindness, loss of peripheral vision from progressive loss of photoreceptors, and variably loss of central vision due to cataracts and macular edema (Garg [UpToDate], 2017). The Argus II Retinal Prosthesis System (Argus II) (Second Sight Medical Products, Inc. Sylmar, CA) is intended to provide electrical stimulation of the retina to elicit visual perception in blind individuals with severe to profound retinitis pigmentosa. The implant is an epiretinal prosthesis that is surgically implanted in and on the eye that includes an antenna, an electronics case, and an electrode array. The external equipment includes glasses, a video processing unit (VPU) and a cable.

U.S. Food and Drug Administration (FDA): The Argus II Retinal Prosthesis System received a Humanitarian Device Exemption (HDE) from the FDA in February 2013. This device is indicated for use in patients with severe to profound retinitis pigmentosa who meet the following criteria:

- Adults, age 25 years or older.
- Bare light or no light perception in both eyes. (If the patient has no residual light perception, then evidence of intact inner layer retina function must be confirmed.)
- Previous history of useful form vision.
- Aphakic or pseudophakic. (If the patient is phakic prior to implant, the natural lens will be removed during the implant procedure.)
- Patients who are willing and able to receive the recommended post-implant clinical follow-up, device fitting, and visual rehabilitation.

Literature Review

Agency for Healthcare Research and Quality (AHRQ) published a technology assessment for retinal prostheses systems (RPS) in the Medicare population (Fontanarosa, et al., 2016). The review included 30 publications of 11 RPS studies. The report notes that, “Although some patients clearly experienced improved visual acuity, visual field, and visual function, the percentages varied greatly among studies of Moderate to High risk of bias. Thus, evidence is insufficient to estimate the proportion of patients who will benefit from an RPS.” The report concluded that some patients clearly benefit from implantation with an RPS, but determining who those patients are is still a challenge. Future studies of retinal prostheses devices should make an effort to report valid and reliable measures of important outcomes, especially day-to-day function and quality of life (QoL).

Dagnelie et al. (2017) conducted a study with the objective to test 28 Argus II subjects, all profoundly blind on three real-world functional vision tasks. Subjects were tested on the three real-world functional vision tasks: Sock Sorting, Sidewalk Tracking and Walking Direction Discrimination task. The mean percentage correct OFF versus ON for the Sock Sorting task was found to be significantly different for both testing conditions (t-test, P<0.01). On the Sidewalk Tracking task, subjects performed significantly better with the system ON than they did with the system OFF (t-test, P<0.05). Eighteen (18) of 27 subjects (67%) performed above chance with the system ON, and 6 (22%) did so with system OFF on the Walking Direction Discrimination task. The authors concluded that Argus II subjects performed better on all three tasks with their systems ON than they did with their systems OFF. The study is limited by the small number of subjects and needs to be confirmed in a larger study.
Da Cruz conducted a prospective, multicenter, single-arm, clinical trial of 30 subjects in 10 centers in US and Europe to study the long-term safety and efficacy of the Argus II System in patients with bare or no light perception due to end-stage RP. Within-patient controls included the non-implanted fellow eye and patients' native residual vision compared to their vision when using the System. The primary outcome measures were safety (the number, seriousness, and relatedness of adverse events) and visual function, as measured by three computer-based, objective tests. Secondary measures included functional vision performance on objectively-scored real-world tasks. Twenty-four out of 30 patients remained implanted with functioning Argus II Systems at 5 years post-implant. Only one additional serious adverse event was experienced since the three-year time point. Patients performed better with the System ON than OFF on all visual function tests and functional vision tasks. The authors concluded that the five-year results of the Argus II trial support the long-term safety profile and benefit of the Argus II System for patients blind from RP.

Schaffrath et al. (2019) reported on collection of post-approval safety and visual function data for the Argus II in a multicenter, postapproval clinical trial conducted at 9 sites in Germany and Italy including 47 patients. Patients were followed-up for 12 months or longer. Patients were 25 years or older with severe to profound outer retinal degeneration, some residual light perception or the ability of the retina to respond to electrical stimulation, and a history of useful form vision and were already planning to undergo Argus II implantation. The primary end point of this study was the nature and rate of adverse events and secondary end points included 3 visual function tests: square localization (SL), direction of motion, and grating visual acuity (GVA). Mean (SD) age was 56 (12) years, 37 (79%) had retinitis pigmentosa, and 27 (57%) were male. Through the first 12 months postimplantation, 23 patients (49%) experienced 51 nonserious adverse events and 12 (26%) experienced 13 serious adverse events (SAEs), nine of which were judged to be related to the Argus II, and four of which were judged to be related to the procedure. The most common SAE was conjunctival erosion, reported in four patients. When averaged across the group, patients’ accuracy on the SL test, but not on the direction-of-motion test, appeared better when the Argus II was on than when it was switched off. For GVA, more patients at each point in time achieved the 2.9 GVA cutoff in the implanted eye when the Argus II was on compared with it switched off. The authors concluded that safety and visual function outcomes in this clinical practice setting cohort of patients with Argus II implants were consistent with previously reported results and that longer follow-up of these patients and data from additional patients are required to better outline the risks and benefits of this approach to addressing blindness secondary to severe-to-profound outer retinal degeneration.

Professional Societies/Organizations
Professional society guidelines are lacking regarding intra-ocular retinal electrode array for treatment of retinitis pigmentosa.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Non-Covered Services (L35008) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
Health Quality Ontario: this organization published a health technology assessment for retinal prosthesis system for advanced retinitis pigmentosa (2017). The recommendation of the assessment notes, “The Ontario Health Technology Advisory Committee recommends publicly funding the Argus II retinal prosthesis system for advanced retinitis pigmentosa.” The committee determined that the Argus II system has demonstrated clinical effectiveness in restoring partial functional vision for patients with advanced retinitis pigmentosa. The Ontario Health Technology Advisory Committee took into account value for money, as well as the lived experience of people with retinitis pigmentosa and noted that the Argus II system offers the possibility of quality-of-life improvements in a population for whom there is no other treatment option.

National Institute for Health and Care Excellence (NICE): NICE published interventional procedure guidance for insertion of epiretinal prosthesis and insertion of a subretinal prosthesis system for retinitis pigmentosa (NICE, 2015). The guidance includes these recommendations:

Subretinal prosthesis system:
Current evidence on the safety and efficacy of insertion of a subretinal prosthesis system for retinitis pigmentosa is limited in quality and quantity. Therefore, this procedure should only be used in the context of research.

NICE encourages further research on this procedure. Outcomes should include the impact on quality of life and activities of day-to-day living, and durability of implants.

Epiretinal prosthesis:

Current evidence on the safety and efficacy of insertion of epiretinal prosthesis for retinitis pigmentosa is limited in quality and quantity. Therefore, this procedure should only be used in the context of research.

NICE encourages further research on this technology. Outcomes should include the impact on quality of life and activities of day-to-day living, and durability of implants.

References

13. PubMed Central PMCID: PMC6547244.
Macular pigment optical density measurement by heterochromatic flicker photometry (CPT code 0506T)

In order to explore methods of preventing, delaying the onset, or retarding the progression of age-related macular degeneration (AMD) attention has been directed toward the possible protective role of macular pigment, a yellow-colored pigment that accumulates within the inner retinal layers at the macula and is optically undetectable beyond 7° eccentricity. Macular pigment is composed of three carotenoids, lutein, zeaxanthin, and meso-zeaxanthin. Macular pigment has generated interest in recently due to its possible protective role for AMD, putatively attributable to its antioxidant properties and/or its prereceptoral filtration of damaging (short-wavelength) blue light, given that (photo-) oxidative retinal injury is known to be important in the pathogenesis of this condition (Sabour-Pickett, et al., 2014).

The measurement of macular pigment optical density can be divided into two categories: subjective psychophysical techniques and objective optical techniques. Objective techniques include fundus reflectance and autoreflectance. Subjective techniques are psychophysical in nature and include heterochromatic flicker photometry. Heterochromatic flicker photometry involves the calculation of macular pigment optical density based on the luminance ratio of short wavelength blue light presented in the central retina (where it is assumed to be partly absorbed by the macular pigment) compared to that presented at a more peripheral retinal point (where macular pigment levels are assumed to be minimal). When the short wavelength light is alternated at an appropriate frequency with a wavelength that is not absorbed by macular pigment and luminance of the two wavelengths is not perceived to be equal, the combined stimulus will appear to flicker (Barlett, et al., 2010).

Literature Review

Akuffo et al. (2015) conducted a study to compare macular pigment (MP) measurements using customized heterochromatic flicker photometry (Macular Metrics Densitometer) and dual-wavelength fundus autofluorescence (Heidelberg Spectralis HRA ÷ OCT MultiColor) in subjects with early age-related macular degeneration (AMD). Macular pigment (MP) was measured in 117 subjects with early AMD using the Densitometer and Spectralis. Baseline and 6-month study visits data were used for the analyses. Agreement was investigated at four different retinal eccentricities, graphically and using indices of agreement, including Pearson correlation coefficient (precision), accuracy coefficient, and concordance correlation coefficient (ccc). Agreement was poor between the Densitometer and Spectralis at all eccentricities, at baseline and at six months. Agreement between the two devices was significantly greater for males at 0.58 and 1.08 of eccentricity. At all eccentricities, agreement was unaffected by cataract grade. In subjects with early AMD, MP measurements obtained using the Densitometer and Spectralis are not statistically comparable and should not be used interchangeably in either clinical or research settings. The authors noted that despite the lack of agreement, statistically significant increases in MP, following six months of supplementation with macular carotenoids, were detected with each device, indicating confirming that these devices are capable of measuring change in MP within subjects over time.

Tsika et al. (2010) conducted a study to compare the macular pigment optical density (MPOD) of patients with unilateral wet age-related macular degeneration (AMD) with the MPOD of bilateral dry AMD patients and healthy elderly individuals. The MPOD of 34 patients with unilateral wet AMD was measured in their fellow eye that had the dry form of the disease (study group). The MPOD of the group was compared with the MPOD of 33 patients with bilateral dry AMD (patients' control group) and 35 subjects without signs of retinal disease (control group). The MPOD was measured with Heterochromatic Flicker Photometry. The overall mean MPOD was 0.52 (SD 0.15). Patients with unilateral wet AMD have significantly higher levels of MPOD in their fellow eye compared with patients with bilateral dry AMD (0.58 versus 0.48, p = 0.026). Mean MPOD of patients with bilateral dry AMD does not differ significantly from that of healthy elderly subjects (0.48 versus 0.50, p = 0.865). In this population sample, no correlation with age was observed, while women have slightly but significantly higher levels of MPOD (0.55 versus 0.49, p = 0.029). The authors concluded that the mean MPOD at the fellow eye of patients with unilateral wet AMD was found to be significantly higher than that of patients with bilateral dry AMD, while no other significant difference emerged between groups and that further investigation is needed to clarify the role of macular pigment in AMD progression.

Professional Societies/Organizations

Professional society guidelines are lacking regarding macular pigment optical density measurement by heterochromatic flicker photometry in the diagnosis or management of age-related macular degeneration.
Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCD found.

Use Outside of the US
National Institute for Health and Clinical Excellence (NICE) guidelines for age-related macular degeneration do not include the use of macular pigment optical density measurement by heterochromatic flicker photometry for diagnosis or management of age-related macular degeneration.

References

Near-infrared dual imaging (simultaneous reflective and trans-illuminated light) of meibomian glands (CPT code 0507T)
Blepharitis is a clinical diagnosis based on characteristic findings of redness and irritation of the eyelid margin associated with crusting or flakes on the lashes or lid margins. Slit lamp allows for more detailed examination of the meibomian glands, which can help distinguish between posterior and anterior blepharitis; however, it is generally not necessary to make the diagnosis (Shtein, 2018).

According to the TearScience website, the LipiScan Dynamic Meibomian Imager provides rapid high-definition meibomian imaging. LipiScan offers a fast and intuitive gland imaging option allowing physician assessment of meibomian gland structure during routine workups in any practice setting. Dynamic Meibomian Imager (DMI) renders a multidimensional view of meibomian gland structure with simultaneous integration of dynamic surface illumination and adaptive transillumination technologies. Dynamic surface illumination originates from multiple light sources to minimize reflection. The adaptive transillumination technology changes light intensity across the surface of the illuminator compensates for the lid thickness variations between patients. The dual-mode DMI consists of a combination of dynamic illumination and adaptive transillumination offering an enhanced view of the meibomian gland structure.

Literature review
There is a lack of evidence regarding the effectiveness of near-infrared dual imaging in the diagnosis and management of patients with Meibomian gland dysfunction or blepharitis.

Professional Societies/Organizations
Professional society guidelines are lacking regarding near-infrared dual imaging of meibomian glands.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCD found.

Use Outside of the US
No relevant information

References

Coding/Billing Information Ophthalmology
Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Insertion of Ocular Telescope Prosthesis Including Crystalline Lens

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>03081</td>
<td>Insertion of ocular telescope prosthesis including removal of crystalline lens or intraocular lens prosthesis</td>
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</tbody>
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<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>C1840</td>
<td>Lens, intraocular (telescopic)</td>
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## Ophthalmology Services Considered Experimental/Investigational/Unproven:

<table>
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<th>CPT® Codes</th>
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<tr>
<td>68399</td>
<td>Unlisted procedure, conjunctiva</td>
<td>Considered Experimental/Investigational/Unproven when used to report conjunctival incision with posterior extrascleral placement of a pharmacologic agent</td>
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<tr>
<td>92499</td>
<td>Unlisted ophthalmological service or procedure</td>
<td>Considered Experimental/Investigational/Unproven when used to report computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report</td>
</tr>
<tr>
<td>0100T</td>
<td>Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy</td>
<td></td>
</tr>
<tr>
<td>0207T</td>
<td>Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral</td>
<td></td>
</tr>
<tr>
<td>0341T</td>
<td>Quantitative pupillometry with interpretation and report, unilateral or bilateral</td>
<td>(Code deleted 12/31/2019)</td>
</tr>
<tr>
<td>0378T</td>
<td>Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; review and interpretation with report by a physician or other qualified health care professional</td>
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</tr>
<tr>
<td>0379T</td>
<td>Visual field assessment, with concurrent real time data analysis and accessible data storage with patient initiated data transmitted to a remote surveillance center for up to 30 days; technical support and patient instructions, surveillance, analysis, and transmission of daily and emergent data reports as prescribed by a physician or other qualified health care professional</td>
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<td>0380T</td>
<td>Computer-aided animation and analysis of time series retinal images for the monitoring of disease progression, unilateral or bilateral, with interpretation and report</td>
<td>(Code deleted 12/31/2019)</td>
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<td>0465T</td>
<td>Suprachoroidal injection of a pharmacologic agent (does not include supply of medication)</td>
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<tr>
<td>0472T</td>
<td>Device evaluation, interrogation, and initial programming of intraocular retinal electrode array (eg, retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed</td>
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values with analysis, including visual training, with review and report by a qualified health care professional

<table>
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<td>0473T</td>
<td>Device evaluation and interrogation of intraocular retinal electrode array (eg, retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional</td>
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<tr>
<td>0506T</td>
<td>Macular pigment optical density measurement by heterochromatic flicker photometry, unilateral or bilateral, with interpretation and report</td>
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<tr>
<td>0507T</td>
<td>Near-infrared dual imaging (ie, simultaneous reflective and transilluminated light) of meibomian glands, unilateral or bilateral, with interpretation and report</td>
</tr>
<tr>
<td>0563T</td>
<td>Evacuation of meibomian glands, using heat delivered through wearable, open-eye eyelid treatment devices and manual gland expression, bilateral</td>
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<th>Description</th>
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<tr>
<td>C1841</td>
<td>Retinal prosthesis, includes all internal and external components</td>
</tr>
<tr>
<td>C1842</td>
<td>Retinal prosthesis, includes all internal and external components; add-on to C1841</td>
</tr>
<tr>
<td>L8608</td>
<td>Miscellaneous external component, supply or accessory for use with the argus ii retinal prosthesis system</td>
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</table>


**Oncology**

Tumor Treatment Fields Therapy (e.g., Optune™) (HCPCS Codes A4555, E0766)
Electric tumor treatment fields (TTF) therapy, also known as alternating electric field therapy, has been proposed for the treatment of recurrent glioblastoma multiforme (GBM). Inferred mechanism of action is disruption of the rapid cell division exhibited by cancer cells by alternating electrical currents applied to the brain through electrically insulated surface transducer arrays which are placed on the patient’s shaved scalp. The fields alter the tumor cell polarity at an intermediate frequency. The frequency used for a particular treatment is specific to the cell type being treated (NovoCure, 2014).

At this time, Optune™ (formerly the NovoTTF-100A System) (Novocure, Portsmouth, NH) is the only TTF device that has received FDA approval electric tumor fields therapy. This system is a wearable, non-invasive, portable battery or power-supply operated device designed for continuous use throughout the day or night. It produces continuous TTF treatment at 100-200kHz. TTF are applied to two pairs of insulated electrode arrays in an alternating fashion. The electrodes are placed on the scalp over a layer of adhesive hydrogel which is held in place by adhesive strips. The scalp must be re-shaved to maintain optimal contact between the electrode and the skin. Gel under the electrodes requires replacement every three-four days. The treatment period is for a minimum of four weeks.

**U.S. Food and Drug Administration (FDA)**
The NovoTTF-100A System (Portsmouth, NH) was granted premarket approval (PMA) by the FDA in April, 2011. This device is indicated for treatment of adult patients who are 22 years of age or older who have histologically-confirmed glioblastoma multiforme (GBM), following histologically-or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted. The pre-market approval requires a post market nonrandomized, unblended,
concurrent control study to be undertaken using the NovoTTF-100A system in patients with recurrent GBM (FDA, 2011).

In October 2015, the FDA approved an expanded indication for the Optune device to treat patients with newly-diagnosed glioblastoma multiforme (GBM), an aggressive form of brain cancer. It is given along with the chemotherapy drug temozolomide (TMZ) following standard treatments that include surgery, and radiation therapy and chemotherapy used together.

**Literature Review**

Stupp et al. (2015) reported on an interim analysis of a multicenter, open-label, randomized phase 3 trial designed to test the efficacy and safety of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. The study included 210 patients randomized to TTFields plus temozolomide and 105 patients randomized to temozolomide alone, and conducted at a median follow-up of 38 months. Results included that median progression-free survival in the intent-to-treat population was 7.1 months (95%CI, 5.9-8.2 months) in the TTFields plus temozolomide group and 4.0 months (95%CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7%CI, 0.43-0.89]; P=.001). Median overall survival in the per-protocol population was 20.5 months (95%CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n=196) and 15.6 months (95%CI, 13.3-19.1 months) in the temozolomide alone group (n=84) (HR, 0.64 [99.4%CI, 0.42-0.98]; P=.004). The authors concluded that in this analysis of patients with glioblastoma who had completed standard chemoradiation therapy, the addition of TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

Stupp et al. (2017) reported on the final analysis randomized, trial noted above (Stupp, et al., 2015) of all 695 patients with median follow-up of 40 months and minimum follow-up of 24 months. Patients were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy (n = 466) or temozolomide alone (n = 229). The TTFields, consisting of low-intensity, 200 kHz frequency, alternating electric fields, was delivered (≥ 18 hours/d) via 4 transducer arrays on the shaved scalp and connected to a portable device. Temozolomide was administered to both groups for 5 days per 28-day cycle (6-12 cycles). Progression-free survival (tested at α = .046). The secondary end point was overall survival (tested hierarchically at α = .048). Analyses were performed for the intent-to-treat population. Of the 695 patients 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76; P < .001). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; P < .001). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide compared to none in patients who received temozolomide alone.

Hayes published a directory report regarding Tumor Treating Fields (TTF) (Hayes, March 2016; 2018). The review concluded that although clinical trials have shown that Novocure is at least comparable with chemotherapy, the body of literature is small and individual studies are subject to serious limitations, including lack of a control or comparator group, high loss to follow-up, and lack of statistical comparisons. Additional evidence including randomized, controlled trials and cohort studies of sufficient size and design are needed to further investigate the safety and efficacy of Novocure in patients with recurrent and newly diagnosed glioblastoma and other cancers.

Data regarding the safety and effectiveness for TTF are limited in the published, peer-reviewed scientific literature and consist of several prospective studies and a randomized clinical trial (RCT) involving a total of 273 patients (Stupp, 2012; Kirson, 2009; Salzberg, 2008; Kirson, 2007). In the prospective phase III RCT, Stupp et al. (2012) reported results of 237 individuals with recurrent GBM. Participants were randomized to TTF (n=120) versus physician’s choice of chemotherapy (n=117). The study failed to reach its primary end-point of improved survival compared to active chemotherapy. Neither overall survival nor progression-free survival were significantly improved at six months in the group randomized to TTF versus chemotherapy (p=0.23 and 0.13, respectively). The authors noted that responses were more frequent in the group treated with TTF but this was not significant (p=0.19). Quality of life measurement favored TTF over chemotherapy for emotional and cognitive functioning; no significant difference was noted for global health and social functioning. Physical functioning
favored the chemotherapy arm. TTF-related adverse events were mild (14%) to moderate (2%), usually involving skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% (p = 0.022) of patients treated with TTF and chemotherapy, respectively. Results do not demonstrate improved OS or PFS with TTF compared to active chemotherapy.

NovoTAL™ (CPT code 64999)
NovoTAL (Novocure, Portsmouth, NH) is software that may be used for treatment planning before the Optune treatment. According to vendor’s website, NovoTAL is optional software that a physician can purchase and create individualized treatment maps for patients starting Optune. It is performed in-office. The physicians are required to complete training and certification in order to use the NovoTAL System. The Optune device is available preset from Novocure. The device is preset to deliver TTFields at a frequency of 200 kHz and is operated by the patient independently. It is monitored periodically by device specialists, who are available 24/7 to provide technical support to the patient, their family and physician (Trusheim, et al., 2017). The published literature does not indicate that the use of the software for treatment planning with Novotal is superior to using Optune with preset settings or that it improves clinical outcomes.

Literature Review—NovoTAL
Wenger et al. (2016) reported on a study with a human head model generated from MRI images of a healthy subject to investigate tumors of different size, shape, and location and the effect of varying transducer layouts on Tumor Treating Fields (TTF) distribution in an anisotropic model. Four different virtual tumors were placed at separate locations. The transducer arrays were modeled to mimic the TTF-delivering commercial device. For each tumor location, varying array layouts were tested. The finite element method was used to calculate the electric field distribution, taking into account tissue heterogeneity and anisotropy. In all tumors, the average electric field induced by either of the two perpendicular array layouts exceeded the 1-V/cm therapeutic threshold value for TTF effectiveness. Field strength within a tumor did not correlate with its size and shape but was higher in more superficial tumors. Additionally, it always increased when the array was adapted to the tumor’s location. Compared with a default layout, the largest increase in field strength was 184%, and the highest average field strength induced in a tumor was 2.21 V/cm. The authors concluded that the result adapting transducer array layouts to specific tumor locations was highly beneficial, because it led to substantial increases in the induced field strength within the tumor and better TTF coverage in the affected areas.

Connelly et al. (2016 reported on a case series of eight patients where treating physician has utilized non-contrast enhancement and advanced imaging to inform tumor treatment fields (TTF) treatment planning based on a clinical evaluation of where a patient is believed to have active tumor. All patients presented with gliomas (grades 2–4). Each patient had previously received standard therapy including surgery, radiation therapy and/or chemotherapy prior to initiation of TTF and the majority had progressed on prior therapy. A standard pre- and postcontrast MRI scan was acquired and used for TTF treatment planning. The authors concluded that the case series details important approaches for integrating clinical considerations, nonmeasurable disease and advanced imaging into the treatment planning workflow for TTF. The author noted that as TTF become integrated into standard care pathways for glioblastoma, the case series demonstrates that treatment planning beyond the extent of contrast enhancement is clinically feasible and should be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

Chaudry et al. (2015) reported on a study that evaluated performance of 14 physicians in conducting transducer array layout mapping using the NovoTAL System compared with mapping performed by the Novocure in-house clinical team. The physicians evaluated five blinded cases of recurrent glioblastoma and performed head size and tumor location measurements using a standard Digital Imaging and Communications in Medicine reader. Concordance with Novocure measurement and intra- and inter-rater reliability were assessed using relevant correlation coefficients. The study criterion for success was a concordance correlation coefficient (CCC) >0.80. CCC for each physician versus Novocure on 20 MRI measurements was 0.96 (standard deviation, SD ± 0.03, range 0.90–1.00). Intra- and inter-rater reliability correlation coefficients were similarly high: 0.83 (SD ±0.15, range 0.54–1.00) and 0.80 (SD ±0.18, range 0.48–1.00), respectively. This user study has a low number of participants and while it appears that there is a high agreement between the two groups, it does not indicate that NovoTAL provides improved health outcomes compared to mapping provided by Novocure.

Professional Societies/Organizations
National Comprehensive Cancer Network™ (NCCN™): NCCN guideline for cancer of the central nervous system includes in the recommendation for treatment of recurrent disease, the option to consider alternating electric field therapy for recurrent disease for anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic astrocytoma, and glioblastoma. Category 2B*

The 2018 update of the NCCN guidelines includes in the recommendation for treatment of glioblastoma (with supratentorial disease), adjuvant treatment, the option of using adjuvant temozolomide and alternating electric field therapy. Category 1*

*NCCN Categories of Evidence and Consensus:
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate (NCCNa, 2018).

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Tumor Treatment Field Therapy (TTFT) (L34823) (2017). Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
National Institute for Health and Clinical Excellence (NICE): NICE published guideline for brain tumours (primary) and brain metastases in adults (2018). Regarding TTF the guidelines note: “Based on the available evidence, the committee recommended that certain treatments should not be offered. This included tumour treating fields (TTF) based on published health economic evidence that they are not an efficient use of NHS resources.”.

References


Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed (CPT code 55874)

SpaceOAR (Augmenix, Inc, Waltham, MA), an absorbable perirectal spacer (APS), is a polyethylene glycol hydrogel that is injected under anesthesia with transrectal ultrasound guidance into a space between the prostate and rectum. The APS is injected via dual syringes attached to a Y connector to allow for the 2 precursor agents to mix while being injected. The APS polymerizes into a solid spacer within 10 seconds following injection and is said to maintain its structure for 3 months before it starts to slowly hydrolyze and is cleared from the body.
via the kidneys, with only traces remaining by 6 months (Hayes, 2018). The use of the APS is to prevent rectal toxicity in patients undergoing radiation therapy (RT) for prostate cancer (PCa).

**U.S. Food and Drug Administration (FDA)**
The SpaceOAR system was cleared by the FDA through the 513(a) (1) (de novo) process April 2015 as an absorbable perirectal spacer. The intended use of the SpaceOAR System is:
SpaceOAR System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of SpaceOAR System to reduce the radiation dose delivered to the anterior rectum. The SpaceOAR System is composed of biodegradable material and maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient’s body over time.

**Literature Review**
Hayes (2018) published a health technology assessment focused on the use of an absorbable perirectal spacer (APS) (SpaceOAR; Augmenix Inc.) to prevent rectal toxicity in patients undergoing radiation therapy (RT) for prostate cancer (PCa). The review included eight clinical studies that met the inclusion criteria and evaluated the efficacy and safety of the APS when used with RT for patients with PCa. English-language comparative studies with ≥ 20 patients that evaluated ≥ 1 clinically relevant outcome were eligible for review. The patient populations included in the eligible studies had T1- T3 grade low-, intermediate-, and high-risk clinically localized PCa. The radiation technologies included IMRT, volumetric-modulated arc therapy, 3-dimensional CRT (3DCRT), and low-dose-rate (LDR) brachytherapy. The review noted that published evidence suggests potential benefit with the use of the APS for the prevention of rectal toxicity in patients undergoing EBRT for the treatment of PCa. However, it was noted that there was substantial uncertainty, chiefly due to conflicting results. Rectal dose volumes were all statistically significantly less with the APS compared with no spacer but not when compared with a rectal balloon. There may be a benefit with the APS in prevention of gastrointestinal (GI) toxicity, but results are conflicting. In addition, bowel quality-of-life (QOL) results were mixed. Only 1 study reported results for the surrogate disease outcome of prostate-specific antigen (PSA) level and no study evaluated local control; thus, the role of the APS in control of PCa is unclear. The overall low-quality body of evidence consisted of seven fair- to very-poor-quality studies with 2 to 63 months of follow-up. The report also noted that there is insufficient published evidence to assess the safety and efficacy of the APS in patients with PCa treated with LDR brachytherapy with or without EBRT.

Mariados et al. (2015) conducted a prospective randomized controlled pivotal trial to assess outcomes following absorbable spacer (SpaceOAR system) implantation. The study included 222 patients with clinical stage T1 or T2 prostate cancer who underwent computed tomography (CT) and magnetic resonance imaging (MRI) scans for treatment planning, followed with fiducial marker placement, and were randomized to receive spacer injection or no injection (control). The patients received post-procedure CT and MRI planning scans and underwent image guided intensity modulated radiation therapy. Spacer safety and impact on rectal irradiation, toxicity, and quality of life were assessed throughout 15 months. Spacer application was rated as “easy” or “very easy” 98.7% of the time, with a 99% hydrogel placement success rate. There were no device-related adverse events, rectal perforations, serious bleeding, or infections within either group. Pre-to post-spacer plans had a significant reduction in mean rectal V70 (12.4% to 3.3%, P<.0001). Overall acute rectal adverse event rates were similar between groups, with fewer spacer patients experiencing rectal pain (P=.02). A significant reduction in late (3-15 months) rectal toxicity severity in the spacer group was observed (P=.04), with a 2.0% and 7.0% late rectal toxicity incidence in the spacer and control groups, respectively. There was no late rectal toxicity greater than grade 1 in the spacer group. At 15 months 11.6% and 21.4% of spacer and control patients, respectively, experienced 10-point declines in bowel quality of life. MRI scans at 12 months verified spacer absorption. The authors concluded that spacer application was well tolerated and that increased perirectal space reduced rectal irradiation, reduces rectal toxicity severity and decreased rates of experiences in decline of bowel quality of life.

Hamstra reported on three year results of the Mariados et al. (2015) study above. The study reviewed the cumulative (Common Terminology Criteria for Adverse Events, version 4.0) toxicity which was evaluated using the log-rank test. Quality of life (QOL) was examined using the Expanded Prostate Cancer Index Composite (EPIC), and the mean changes from baseline in the EPIC domains were tested using repeated measures.
The proportions of men with minimally important differences (MIDs) in each domain were tested using repeated measures logistic models with prespecified thresholds. The three-year incidence of grade ≥1 (9.2% vs 2.0%; P=.028) and grade ≥2 (6.7% vs 0%; P=.012) rectal toxicity was improved in the spacer arm. Grade ≥1 urinary incontinence was lower in the spacer arm (15% vs 4%; P=.046), with no difference in grade ≥2 urinary toxicity (7% vs 7%; P=0.7). From six months onward, bowel QOL consistently favored the spacer group (P=.002), with the difference at 3 years (5.8 points; P<.05) meeting the threshold for a MID. The control group had a 3.9-point greater decline in urinary QOL compared with the spacer group at three years (P<.05), but the difference did not meet the MID threshold. At three years, more men in the control group than in the spacer group had experienced a MID decline in bowel QOL (41% vs 14%; P=.002) and urinary QOL (30% vs 17%; P=.04). Furthermore, the control group were also more likely to have experienced large declines (twice the MID) in bowel QOL (21% vs 5%; P=.02) and urinary QOL (23% vs 8%; P=.02). The authors concluded that the benefit of a hydrogel spacer in reducing the rectal dose, toxicity, and QOL declines after image guided intensity modulated radiation therapy for prostate cancer was maintained or increased with a longer follow-up period.

Chao et al. (2018) conducted a study to determine whether the degree of prostate to rectal separation using a hydrogel spacer (HS) and its effect on decreasing rectal dose can be reproduced in the community setting. The study included 31 patients with cT1-3aN0M0 prostate adenocarcinoma receiving radical radiotherapy to 78 Gy. The primary endpoint was the proportion of patients achieving at least 25% reduction in volume of rectum receiving 70 Gy (rV70). Other endpoints included degree of prostate to rectum separation, HS insertion-related adverse events and the proportion of patients with grade 1 or worse acute or late gastrointestinal (GI) and genitourinary (GU) toxicity. All patients had successful insertion of their HS with no peri-operative toxicity. The mean prostate-rectal separation achieved was 10.5 mm. Twenty nine (93.5%) patients achieved a reduction in rV70 of at least 25%. Acute grade 1 GI toxicity was reported in 3 patients. All symptoms had resolved by three months post RT. Late grade 1 GI toxicity was reported in one patient (3.2%) with bowel frequency occurring at 6 months and resolving by 12 months post RT. There was no grade 2 or 3 acute or late GI toxicity seen. The study was limited by the small number of patients and lack of comparator.

Wilton et al. (2017) conducted a retrospective study to investigate any dosimetric difference between two methods of rectal displacement (Rectafix and SpaceOAR) for prostate stereotactic body radiation therapy (SBRT). Rectal dosimetry of 45 men who received SBRT within the PROMETHEUS trial were retrospectively examined, across two radiation therapy centers using the two rectal displacement device (RDD). In comparison (1) Rectafix demonstrated lower mean doses at 9 out of 11 measured intervals (P = 0.0012). Comparison (2) demonstrated a moderate difference with center 2 plans producing slightly lower rectal doses (P = 0.013). Comparison (3) further demonstrated that Rectafix returned lower mean doses than SpaceOAR (P < 0.001). Although all dose levels were in favor of Rectafix, in absolute terms differences were small (2.6-9.0%). The authors concluded that in well-selected prostate SBRT patients, Rectafix and SpaceOAR RDD's provide approximately equivalent rectal sparing.

Professional Societies/Organizations

National Comprehensive Cancer Network® (NCCN): The 2018 NCCN clinical practice guidelines for Prostate Cancer note, "Ideally, the accuracy of treatment should be verified by daily prostate localization with any of the following: techniques of IGRT using CT, ultrasound, implanted fiducials, or electromagnetic targeting/tracking. Endorectal balloons may be used to improve prostate immobilization. Perirectal spacer materials may be employed when the previously mentioned techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient related factors, such as medication usage and or comorbid conditions. Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation." Category level 2A

*NCCN Categories of Evidence and Consensus:
Category 2A: based on lower-level evidence there is uniform NCCN consensus that the intervention is appropriate

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Prostate Rectal Spacers (L37485) (2018). Refer to the CMS LCD table of contents link in the reference section.
**Use Outside of the US**

National Institute for Health and Clinical Excellence (NICE): NICE guidelines for biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer (NICE, 2017) include the recommendation:

Current evidence on the safety and efficacy of insertion of a biodegradable spacer to reduce rectal toxicity during radiotherapy for prostate cancer is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit.

**References**

2. Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer

Coding/Billing Information Oncology

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Tumor Treatment Fields (TTF) Therapy (i.e., Optune™)

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>A4555</td>
<td>Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only</td>
</tr>
<tr>
<td>E0766</td>
<td>Electrical stimulation device used for cancer treatment, includes all accessories, any type</td>
</tr>
</tbody>
</table>

Considered Experimental/Investigational/Unproven when used to report treatment planning software (i.e., NovoTAL) for use with tumor treatment fields:

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<th>CPT® Codes</th>
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<tbody>
<tr>
<td>64999</td>
<td>Unlisted procedure, nervous system</td>
<td>Considered Experimental/Investigational/Unproven when used to report treatment planning software (i.e., NovoTAL) for use with tumor treatment fields</td>
</tr>
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</table>

Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed (i.e., SpaceOAR)

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>55874</td>
<td>Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed</td>
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Otolaryngology

Automated Audiometry Devices (CPT Codes 0208T, 0209T, 0210T, 0211T, 0212T)

Audiometers measure and characterize hearing loss by determining an individual’s hearing threshold. Conventional tests utilized for assessment include the behavioral pure-tone audiogram (hearing sensitivity of single-frequency signals) and speech recognition (hearing sensitivity for spoken material). These tests require interaction between the trained technician or audiologist and the patient. Convention audiometry tests are performed manually and interpretation of the raw data is performed by the audiologist.

The use of automated audiometry devices has been proposed as an alternative to manually operated devices. Automated units use conventional technology; however, the equipment is fully automated. Results are displayed as pass or fail/refer and do not require further interpretation by a technician or audiologist. A failure score may result in further referral to a health care professional.
U.S. Food and Drug Administration (FDA)
Several automated audiometric devices have received FDA 510 (k) approval. The Otogram™ Hearing Diagnostic System (Ototronix Diagnostics, Houston, TX, formerly marketed by Tympany, Inc., Salt Lake City, UT) received FDA 510(k) approval as an equivalent device in March 2007. The device is indicated for use by trained healthcare professionals on both adults and pediatric subjects for measurement of audiometric parameters to identify and supply to help diagnose hearing loss and ear disorders.

Literature Review
Although there are a number of cohort and case series reported in the published peer-reviewed scientific literature, randomized controlled trial, meta-analysis and systematic review data are lacking. Brennan-Jones conducted a study to compare remote interpretation of manual and automated audiometry. Five audiologists each interpreted manual and automated audiograms obtained from 42 patients. The main outcome variable was the audiologist's recommendation for patient management between the manual and automated audiometry test. Cohen's Kappa and Krippendorff's Alpha were used to calculate and quantify the intra- and inter-observer agreement, respectively, and McNemar's test was used to assess the audiologist-rated accuracy of audiograms. Audiograms were randomised and audiologists were blinded as to whether they were interpreting a manual or automated audiogram. The intra-observer agreement was substantial for management outcomes when comparing interpretations for manual and automated audiograms. Inter-observer agreement was moderate between clinicians for determining management decisions when interpreting both manual and automated audiograms. Audiologists were 2.8 times more likely to question the accuracy of an automated audiogram compared to a manual audiogram. The authors noted that there is a lack of agreement between audiologists when interpreting audiograms, whether recorded with automated or manual audiometry.

In a nonrandomized comparison study by Lancaster et al. (2008) involving screening results of 32 children using on-site and tele-health screening methods the authors report identical otoscopic and immittance results. Pure-tone results were different between on-site and telehealth screening methods for five of 32 students. Using the on-site pure-tone screening protocol as the ‘gold standard’ the authors report that the tele-health pure-tone screening protocol yielded four false positive responses and one false negative response. This study was limited by uncontrolled study design and small study numbers.

Professional Societies/Organizations
American Academy of Pediatrics (AAP): The AAP (Harlor, et al., 2009) published recommendations for hearing assessment in infants and children. These recommendations include discussion of automated auditory brainstem response (ABR) test as an objective physiologic means of hearing screening. The guideline does not mention the automation of other tests.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Non-covered Services (L33777). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
No relevant information.

References

Transtympanic Micropressure Device for Ménière’s Disease (e.g., Meniett™ Device) (HCPCS Code E2120)
Ménière’s disease (also called idiopathic endolymphatic hydrops) is a disorder of the inner ear. Although the cause is unknown, the disorder probably results from an abnormally large amount of fluid (called endolymph) collecting in the inner ear. The symptoms of Ménière’s disease include episodic vertigo (i.e., a sensation of dizziness or spinning), hearing loss, tinnitus (i.e., ringing in the ears), and a sensation of fullness in the affected ear.

The use of a transtympanic micropressure device/low-pressure pulse generator (i.e., Meniett™) (Medtronic Xomed, Jacksonville, FL) has been proposed as an alternative to surgery. The device is prescribed by a physician and delivers low-frequency, low-amplitude pressure pulses within the range of 0–20 centimeter (cm) H2O to the middle ear via a close-fitting ear cuff and tympanostomy tube. Its mode of action is thought to be transmission of the pulses to the inner ear, promoting the flow of endolymph out of the cochlea, alleviating the hydrops and relieving symptoms. The tympanostomy tube is inserted under local anesthetic in the office setting. The patient then uses the device at home three times per day for approximately three minutes per session. The patient discontinues use when symptoms remit.

U.S. Food and Drug Administration (FDA)
In December 1999, Pascal Medical AB (Sweden) received 510(k) approval from the FDA for the Meniett Low-Pressure Pulse Generator. In 2001, Medtronic Xomed, Inc. (Jacksonville, FL) purchased the device from Pascal Medical. The Meniett Low-Pressure Pulse Generator is classified as a Class II device and is indicated for the symptomatic treatment of Ménière’s disease.

Literature Review
Wang et al. (2019) reported on a systematic review that assess the clinical benefit of device therapy on controlling the symptoms of Meniere's disease (MD). The study included 16 studies with 395 patients. The studies with six studies randomized controlled trials, two studies cross-sectional studies, and eight studies were before-after studies. Vertigo, which was described as the frequency of vertigo days by month, the number of vertigo episodes by month (weighted mean difference [WMD], visual analog score (VAS) of vertigo, and the overall completed vertigo control, was considered as the primary outcome. The secondary outcomes were defined as hearing changes, the number of sick days by month, ECoG recording, and functional level. The Meniett device was used in 385 patients (15 studies) and one study used the TinniTool device. The use of device therapy resulted in improved vertigo control, with: 3.15, 95% confidence interval [CI]: 2.00-4.31), in the number of vertigo episodes by month (WMD: 7.37, 95% CI: 2.40-12.35), and in the vertigo visual analog score (WMD: 41.51, 95% CI: 34.68-48.34). The overall complete vertigo control rate was 50% (95% CI: 37%-64%). The device therapy also reduced the number of sick days by month (WMD: 4.56, 95% CI: 2.15-6.97), and the functional level improved (WMD: 2.66, 95% CI: 2.15-3.17). The device therapy proved beneficial for hearing changes (WMD: 3.19, 95% CI: 0.66-5.71). Limitations included the small number of patients, lack of comparison in some of the studies. The authors noted that additional long-term follow-up studies are needed in this area to explore the benefit of device treatment with MD.

Russo et al. (2017) conducted a randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy of portable Meniett low-pressure pulse generator in Meniere disease. The trial included 129 adults presenting Meniere disease not controlled by conventional medical treatment. The protocol included three phases: 1) placement of a transtympanic tube and evaluation of its effect (with patient was excluded if there was resolution of symptoms); 2) randomization: six-week treatment with Meniett or placebo device; 3) removal of the
device and six-week follow-up period. The evaluation criteria were the number of vertigo episodes (at least 20 minutes with a 12-hour free interval) and the impact on daily life as assessed by self-questionnaires. Ninety-seven patients passed to the second phase of the study: 49 and 48 patients received the Meniett or placebo device, respectively. In the placebo group, the number of vertigo episodes decreased from 4.3 ± 0.6 (mean ± standard error of the mean) during the first phase to 2.6 ± 0.5 after 6 weeks of treatment, and to 1.8 ± 0.8 after the removal of the device. Similar results were observed in the Meniett device group: 3.2 ± 0.4 episodes during the first phase, 2.5 ± after 6 weeks of Meniett device treatment, and 1.5 ± 0.2 after the third phase. The authors concluded that an improvement of symptoms was evidenced in all patients, with no difference between the Meniett and the placebo device groups.

Van Sonsbeek et al. (2015) reported on a Cochrane review to assess the effects of positive pressure therapy (e.g., the Meniett device) on the symptoms of Ménière’s disease or syndrome. The review included five randomized, clinical trials with 265 participants. Regarding primary outcome, control of vertigo, it was not possible to pool data due to heterogeneity in the measurement of the outcome measures. In most studies, no significant difference was found between the positive pressure therapy group and the placebo group in vertigo scores or vertigo days; one study, at low risk of bias, showed a significant difference in one measure of vertigo control in favor of positive pressure therapy. For the secondary outcomes, statistically significant results for loss or gain of hearing were found. Hearing was 7.38 decibels better in the placebo group compared to the positive pressure therapy group mean difference (MD) (95% CI 2.51 to 12.25; two studies, 123 participants). The severity of tinnitus and perception of aural fullness were either not measured or inadequate data were provided in the included studies. For the secondary outcome functional level, it was not possible to perform a pooled analysis with one study showing less functional impairment in the positive pressure group than the placebo group; another study did not show any significant results. The authors concluded that there is no evidence, from five included studies, to show that positive pressure therapy is effective for the symptoms of Ménière’s disease.

The Meniett device has been evaluated in several small clinical trials (Ahsan et al., 2015; Shojaku, et al., 2011; Dornhoffer, et al., 2008; Mattox, et al., 2008; Gates, et al., 2006; Stokroos, et al., 2006; Boudewyns, et al., 2005; Thomsen, et al., 2005; Gates, et al., 2004; Odkvist, et al., 2000) with the number of study participants ranging from 12-62 persons. Ahsan et al. (2014) reported results of a systematic literature review (eight studies) and meta-analysis (18 studies). Eight studies reported hearing evaluation and improvement in in pure tone average after Meniett treatment (p=.0085). Data could not be combined for American Academy of Otolaryngology–Head and Neck Surgery functional score due to heterogeneity. Of six studies reporting frequency of vertigo, Meniett treatment significantly reduced frequency of vertigo (p<.0001). Limitations of the study include data derived from uncontrolled and retrospective studies, short follow-up of five months, and small numbers of study participants.

Limitations which limit the ability to translate outcomes to routine use of this device include small study populations, lack of blinding and randomization in the majority of studies, and improvement in outcomes in individuals who were treated with the Meniett device as well as other interventions. Further large, randomized controlled trials are necessary to determine the effectiveness of this device to improve health outcomes.

Professional Societies/Organizations
The Equilibrium Committee of the American Academy of Otolaryngology-Head and Neck Surgery published a Policy Statement on Micropressure Therapy for Ménière's disease (AAO-HNS 2008, updated 2016) noted that there is some medical evidence to support the use of micropressure therapy (such as the Meniett device) in certain cases of Meniere’s disease. The therapy can be used as a second level therapy when medical treatment has failed and the device represents a largely non-surgical therapy that should be available as one of the many treatments for Meniere’s disease.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCD found

Use Outside of the US
No relevant information.

References

Coding/Billing Information Otolaryngology

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Otolaryngology Considered Experimental/Investigational/Unproven:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>0208T</td>
<td>Pure tone audiometry (threshold), automated; air only</td>
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</tbody>
</table>

Page 138 of 153
Medical Coverage Policy: 0504
**HCPCS Codes**

| Description | Pulse generator system for tympanic treatment of inner ear endolymphatic fluid |


**Other**

**Holotranscobalamin Testing (CPT Code 84999)**

Vitamin B12, also known as cobalamin, is a water-soluble vitamin important in normal neurologic functioning and the formation of red blood cells. Measurement of total serum cobalamin may be used to detect a deficiency state (i.e., <200pg/mL). Sensitivity and specificity of this test is poor in part because serum levels do not always correlate with body stores. Only a portion of cobalamin is metabolically active (i.e., transcobalamin). Transcobalamin-cobalamin complex (i.e., holotranscobalamin or holo-TC) testing has been proposed as an alternative measurement of vitamin B12 deficiency. Testing may be by radio- or enzyme immunoassay. Measurement of holotranscobalamin is not clinically validated nor available for widespread use and is currently an emerging method of detecting deficiency (Langan, et al., 2017).

**U.S. Food and Drug Administration (FDA)**

In January 2004, the HoloTC RIA device (Axis-Shield Biochemicals, ASA, San Diego, CA) was determined by the FDA to be substantially equivalent as an in-vitro diagnostic assay for quantitative measurement of cobalamin (vitamin B12) bound to the carrier protein transcobalamin in human serum or blood.

**Literature Review**

Randomized controlled trial (RCT) data are scarce in the published peer-reviewed scientific literature regarding the effectiveness of holotranscobalamin testing for the diagnosis of vitamin B12 deficiency or for use in monitoring response to therapy. Hoey et al (2009) reported results of a systematic review which assessed the effectiveness of biomarkers: vitamin B12, methylmalonic acid and total homocysteine in determining vitamin B12 status in eight RCTs. All studies measured serum and plasma total vitamin B12. All biomarkers were found to be effective measures of altered vitamin B-12 intake in populations with low and borderline baseline vitamin B-12 status (p<, 0.00001); however, in the case of total vitamin B-12, substantial heterogeneity that could not be fully explained by subgroup analysis was observed. Insufficient data were available to determine the effectiveness of plasma holotranscobalamin, which was measured in only one RCT.

**Centers for Medicare & Medicaid Services (CMS)**

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCD found

**Professional Societies/Organizations**

Professional society guidelines in support of holotranscobalamin testing are lacking.

**Use Outside of the US**

**British Committee for Standards in Haematology ([BCSH]):** The BCSH (Devalia, et al., 2014) published recommendations for the diagnosis and treatment of cobalamin and folate disorders. Regarding holotranscobalamin testing, the Committee notes that serum holotranscobalamin has the potential as a first-line test, but an indeterminate grey area may still exist.
References


Multivariate Analysis of Patient Specific Findings with Quantifiable Computer Probability Assessment (CPT Code 99199)

Quantitative pretest probability assessment or attribute matching matches an explicit clinical profile of a patient to a reference database to estimate the numeric value for the pretest probability of disease. It has been proposed that this assessment, which is available at the bedside, may aid the health care professional in making the decision to perform certain diagnostic tests.

According to Kline et al. (2010) attribute matching works by a selection process whereby a computer algorithm compares the results of a selected number of predictor variables obtained from the patient being evaluated to a library of research patients previously evaluated for a specific indication compiled from multiple hospitals. The algorithm returns from the library only the “matched” patients who share the same profile of predictor variables as the patient under consideration and reports the proportion of patients with disease in this matched sample.

The PREtestConsult ACS and PREtestConsult PE modules (BreathQuant Medical Systems, Inc., Charlotte, NC) are a software application that estimates the probability of acute coronary syndrome or pulmonary embolism in adult patients. According to information on the PREtestConsult website, clinical data are entered into the modules by means of a personal data assistant or computer.

Literature Review

Randomized controlled clinical data that evaluate the effectiveness and clinical utility of quantifiable computerized probability assessment are limited. Kline et al. (2009) reported the results of a randomized clinical trial involving 400 adult patients (control group, n=185; intervention group, n=184) who were evaluated for chest pain in a single medical center emergency department. Patients had neither obvious evidence for acute coronary syndrome nor other obvious reasons for admission. After an electrocardiogram was performed clinicians were asked to give their estimate of the percentage probability that the patient would have an acute coronary syndrome-defining event in the subsequent 45 days. Randomization was performed by way of a sealed, sequentially numbered envelope that contained assignment to either the control or intervention group. A member of the research team followed the patient to determine physical disposition status from the emergency department. Patients were contacted by telephone at seven and 45 days after enrollment by a research coordinator who was unaware of group assignment. The mean of the pretest probability estimates from the clinicians was 4 (5%) compared with 4 (6%) for the computerized device estimate. Safety and efficacy endpoints for controls versus intervention patients, respectively, were as follows: (1) delayed or missed diagnosis of acute coronary syndrome: 1 of 185 versus 0 of 184, (2) hospital admission with no significant cardiovascular diagnosis: 11% versus 5%, (3) thoracic imaging imparting greater than 5 mSv radiation with a negative result: 20% versus 9%, (4) median length of stay: 11.4 hours versus 9.2 hours, (5) reported feeling “very satisfied” with clinician explanation of problem on follow-up survey: 38% versus 49%, and (6) readmitted within 7 days: 11% versus 4%. Data suggest that use of a quantitative estimate of the pretest probability of acute coronary syndrome was associated with reduced resource use.

Professional Societies/Organizations

Professional society guidelines in support of multivariate analysis of patient specific findings with quantifiable computer probability assessment are lacking.
Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCD found

Use Outside of the US
No relevant information.

References

Bioimpedance Spectroscopy to Measure Extracellular Fluid Differences Between Limbs (CPT Code 93702)
Bioelectrical impedance analysis is a noninvasive technique measures the body’s response to electrical current. Current flows along the path of least resistance through the body and thus follows tissues with the highest water content, allowing measurement of edema (AHRQ, 2010). Bioimpedance spectroscopy has been proposed as a tool to detect early stage lymphedema.

Lymphedema is a pathological condition resulting from an accumulation of protein-rich fluid in the interstitial space because of congenital or acquired damage to the lymphatic system. Acquired or secondary lymphedema may be caused by disease, trauma, or an iatrogenic process such as surgery or radiation (Agency for Healthcare Research and Quality [AHRQ], 2010). Lymphedema is generally staged by observation of the individual’s physical condition (i.e., stage 0-3) and is typically diagnosed by clinical history and physical examination. AHRQ notes that it is difficult to detect stage 0 or subclinical lymphedema with current methods. According to a technology assessment by AHRQ (2010) serial measurement of limb volume and or circumference are de facto gold standards for diagnosing secondary edema; however, no single method of assessment has emerged as the standard comparator for randomized clinical trials (AHRQ, 2010).

U.S. Food and Drug Administration (FDA)
Impedimed L-Dex U400 ExtraCellular Fluid analyzer received FDA 510(k) approval on October 3, 2008 with approval of an expansion of indications on November 4, 2011. According to the approval summary it is “indicated for use on adult human patients, utilizing impedance ratios that are displayed as an L-Dex ratio that supports the measurement of extracellular fluid volume between the limbs and is presented to the clinician as an aid to their clinical assessment of unilateral lymphedema of the arm and leg in woman and the leg in men. The device is only indicated for patients who will have or who have had lymph nodes from the axillary and pelvic regions either removed, damaged or irradiated. The device is not intended to diagnose or predict lymphedema of the extremity.”

Literature Review
Ridner et al. (2019 reported on interim results of a randomized, controlled trial that is comparing lymphedema progression rates using volume measurements calculated from the circumference using a tape measure (TM) or bioimpedance spectroscopy (BIS). Patients were randomized to either TM or BIS surveillance. The primary endpoint of the trial was the rate of progression to clinical lymphedema requiring complex decongestive physiotherapy (CDP), with progression defined as a TM volume change in the at-risk arm ≥ 10% above the presurgical baseline. This prespecified interim analysis was performed when at least 500 trial participants had ≥ 12 months of follow-up. A total of 508 patients were included in this analysis, with 109 (21.9%) patients triggering prethreshold interventions. Compared with TM, BIS had a lower rate of trigger (15.8%
vs. 28.5%, p < 0.001) and longer times to trigger (9.5 vs. 2.8 months, p = 0.002). Twelve triggering patients progressed to complex decongestive physiotherapy (CDP) (10 in the TM group [14.7%] and two in the BIS group [4.9%]), representing a 67% relative reduction and a 9.8% absolute reduction (p = 0.130). The author concluded that interim results demonstrated that post-treatment surveillance with BIS reduced the absolute rates of progression of breast cancer-related lymphedema (BCRL) requiring CDP by approximately 10%. These are preliminary results and further analysis of this group will be performed.

Asklöf et al. (2018) conducted a systematic review to summarize the current knowledge of non-invasive bioelectrical impedance analysis (BIA) used with gynecological surgical patients in regard to postoperative development of lymphedema and determination of perioperative fluid balance, and as a prognostic factor in cancer mortality and a predictor of postoperative complications. Two of the articles were retrospective; five had a cross-sectional, and nine were prospective. Three different methods of BIA were used: single frequency-BIA, multifrequency-BIA and bioimpedance spectroscopy. BIA was found to detect lymphedema with a sensitivity of 73% and a specificity of 84%. Studies indicated that BIA was able to detect lower limb lymphedema at an early stage even before it became clinically detectable. The authors note that so far, all studies have set up cut-off limits within the study population, and reference values for a general population need to be defined and there are few studies on a gynecological study population. The authors note that there is a need for further studies within gynecological surgery focusing on early detection of lower limb lymphedema, perioperative fluid balance, and postoperative complications in order to establish the value of BIA in clinical praxis.

Hidding et al. (2016) reported on a systematic review with the purpose to provide best evidence regarding which measurement instruments are most appropriate in measuring lymphedema in its different stages. Inclusion criteria included prognostic, cross-sectional, and case-control studies assessing measurement properties of clinical measurement instruments for lymphedema with at least two repeated measurements with one instrument and studies describing comparisons between two or more measurement instruments were included and the review included 30 studies. Measurement instruments that were described in the studies included: water volumeter, tape measure, perometer, bioimpedance spectroscrope (BIS), MoistureMeter, and tonometer. The authors noted limitations of the study included: no uniform definition of lymphedema was available, and a gold standard as a reference test was lacking. The items concerning risk of bias included study design, patient selection, description of lymphedema, blinding of test outcomes, and number of included participants. The authors found that measurement instruments with evidence for good reliability and validity were BIS, water volumetry, tape measurement, and perometry, where BIS can detect alterations in extracellular fluid in stage 1 lymphedema and the other measurement instruments can detect alterations in volume starting from stage 2.

Erdogan et al. (2015) reported on a study of 37 patients with breast cancer who underwent bioimpedance spectroscopy to assess lymphedema. During a one-year follow-up period where investigators used bioimpedance measures, a statistically significant relationship was apparent between the incidence of lymphedema and disease characteristics, including the total number of lymph nodes and the region of radiotherapy. The authors concluded that preliminary results indicate that bioimpedance may be a reasonable method regular monitoring to detect lymphedema. The study was limited by the small subject number and the lack of randomization.

Barrio et al. (2015) reported on a prospective study that compared bioimpedance (L-Dex) and volume displacement (VD) measurements in a prospective cohort of 186 breast cancer patients at risk for lymphedema. Patients received baseline VD and L-Dex; with follow-up measurements performed at three-six months intervals for three years. At each visit, patients fitted into one of three categories: normal (normal VD and L-Dex); abnormal L-Dex (L-Dex > 10 or increase in 10 from baseline and normal VD); or lymphedema (relative arm volume difference of >10 % by VD ± abnormal L-Dex). Change in L-Dex was plotted against change in VD; correlation was assessed using the Pearson correlation. At a median follow-up of 18.2 months, 152 patients were normal, 25 had an abnormal L-Dex, and 9 developed lymphedema without a prior L-Dex abnormality. Of the 25 abnormal L-Dex patients, four progressed to lymphedema, for a total of 13 patients with lymphedema. Evaluating all time points, 186 patients had 829 follow-up measurements. Sensitivity and specificity of L-Dex compared with VD were 75 and 93 %, respectively. There was no correlation found between change in VD and change in L-Dex at 3 months (r = 0.31) or 6 months (r = 0.21). The authors concluded that VD and bioimpedance demonstrated poor correlation with inconsistent overlap of measurements considered abnormal. It was found that of patients with an abnormal L-Dex, few progressed to lymphedema; with
most patients with lymphedema not having a prior L-Dex abnormality. The authors noted that further studies are needed to understand the clinical significance of bioimpedance.

Hayes published a technology directory report regarding bioelectrical impedance (bioimpedance) analysis for assessment of lymphedema (Hayes, 2015; 2019). The review included 25 comparative studies, including two randomized controlled trials (RCTs) that assessed the use of bioelectrical impedance analysis (BIA) for detection of lymphedema (LE), with sample sizes of 20 to 295 patients known to have LE or at risk for developing LE. The findings of the report noted that there is insufficient evidence to make conclusive statements regarding the impact of BIA on the detection or assessment of LE. Individual studies or single groups of authors with multiple studies have found moderate to high correlation between BIA, circumferential measurements, and perometry; however, accuracy of BIA varied widely depending on reference standards. It was noted that there was only very limited evidence on clinical utility or the impact of BIA on patient management or outcomes.

Controlled clinical trial data are lacking. Published studies are primarily limited to case series and validation studies. A technology review by AHRQ (2010) notes there is consistent evidence to indicate that lymphedema can be reliably measured using circumferential measurements or volume displacement. Additionally the assessment noted that there is insufficient evidence to draw conclusions about the reliability of other measures including tonometry, ultrasound, lymphoscintigraphy, or bioimpedance. The authors reviewed 41 studies related to diagnosis of lymphedema. In one study included in the technology assessment the test of interest involved differences in the sum of arm circumference between treated and untreated arms in persons with breast cancer. Circumferential differences to diagnose lymphedema were established at ≥5cm and ≥10cm. For differences of ≥5cm versus bioimpedance, sensitivity was 35% and specificity was 89%. For a difference of ≥10cm versus bioimpedance, sensitivity was 5% and specificity was 100%. For self-report compared to bioimpedance, sensitivity was 65%, specificity was 77%. In another included study bioimpedance was used diagnostically in 102 persons with breast cancer. The sensitivity of bioimpedance compared to limb volume was 10% and specificity was 98%. Two included studies involved bioimpedance alone. The first study found that mean and median bioimpedance measures were greater in the arms of women with lymphedema who survived breast cancer. In the other study single-frequency bioimpedance was highly correlated to bioimpedance spectroscopy (r=.99). The authors noted the tests did not drive the choice of treatment or outcome.

Professional Societies/Organizations
Professional society guidelines in support of bioimpedance spectroscopy to detect early stage lymphedema are lacking.

Centers for Medicare & Medicaid Services (CMS)
• National Coverage Determinations (NCD): No NCD found
• Local Coverage Determinations (LCDs): Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US
National Institute for Health and Clinical Excellence (NICE): NICE published a medtech innovation briefing (2017) regarding L-Dex U400 for lymphedema after breast cancer treatment. The report notes:
• The main points from the evidence summarized in this briefing are from three studies in the UK and the US using prospective observational data, as well as a budget impact analysis, in a total of 978 patients (female adults) in secondary care. They show that the L-Dex U400 is less effective than comparators in diagnosing lymphedema, but potentially helps detect subclinical lymphedema, in people who have had treatment for breast cancer.
• Key uncertainties around the evidence and technology are that the evidence base is still developing. So far, it shows that the L-Dex U400 is not as effective as current tests for diagnosing lymphedema.

References


Near-Infrared Spectroscopy Studies of Lower Extremity Wounds (CPT Code 0493T)

A standard method for determining the effectiveness of various treatment methods for quantifying wound healing has not been established. Measurements vary from observer to observer and rely on changes in length, width, and depth (Weingarten, et al., 2010). Treatments can include moist wound healing protocols, offloading to reduce the pressure on the wound, active wound healing agents, and/or active therapies such as hyperbaric oxygen and/or negative pressure therapy. Near-infrared spectroscopy has been proposed as a noninvasive method of measuring the optical properties of tissue oxyhemoglobin content of lower extremity wounds beneath the skin surface to guide treatment.

Diffuse photon density wave (DPDW) methodology of near infrared spectroscopy (NIRS) can be used to measure the absolute concentrations of oxyhemoglobin and deoxyhemoglobin in tissue at depths of up to several centimeters. NIRS utilizes a detector and a dispersive element to allow the intensity at different wavelengths to be recorded. More data are needed to determine the threshold value that will distinguish healing from nonhealing wounds (Niedrauer, 2010).

In this procedure the wound is interrogated using a near-infrared spectroscopy device in up to 10 different locations. Data outputs are in the form of concentrations of oxygenated hemoglobin and total hemoglobin in the blood vessels in the wound. Comparing results on a weekly or biweekly basis, the clinician assesses wound healing progression to determine the need for changes in clinical approach.

Literature Review

Randomized controlled clinical trial data are lacking in the published peer-reviewed scientific literature regarding the safety and effectiveness of near-infrared spectroscopy for the measurement of lower extremity wound healing, including its use for the transcutaneous measurement of oxyhemoglobin. Reisman et al. (2016) reported on a cohort study that examined the use of near-infrared spectroscopy (NIRS) to detect sustained hyperemia following lower extremity trauma. The study examined if NIRS may be a useful monitoring tool for acute compartment syndrome (ACS). Expected normal values for this measurement have yet to be established. The study included 25 cases with acute unilateral lower extremity fractures. NIRS measurements for hemoglobin saturated with oxygen (rSO2) were taken approximately 48 hours after surgical stabilization for each compartment bilaterally, using the contralateral (uninjured) leg as an internal control. Mean rSO2 values taken 48 hours from surgical stabilization from each compartment of the patients’ injured legs were significantly higher than the mean values of the contralateral legs (injured = 70, 68, 72, 70; contralateral = 55, 54, 57, 56 for anterior, lateral, deep posterior, and superficial posterior compartments, respectively; p < 0.0001 for all compartments). The study was limited by the lack of randomization and small subject number.

Professional Societies/Organizations

Professional society guidelines in support of near-infrared spectroscopy studies of lower extremity wound healing are lacking.

Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

Use Outside of the US

No relevant information.
Radiofrequency spectroscopy, real time, intraoperative margin assessment, at the time of partial mastectomy, with report (MarginProbe®) (CPT code 0546T)

The MarginProbe System technology is based on the principle of radiofrequency (RF) spectroscopy. The technology relies on subjecting tissue to an electric field, and then measuring the tissue response to that field, yielding an electromagnetic signature. According to the manufacturer, the surgeon applies external fields to suspect tissue and captures minute differences in electromagnetic properties. The system compares those responses to an internal database of known signatures in healthy and cancerous tissues (Dune Medical).

U. S. Food and Drug Administration

In December 27, 2012, MarginProbe® (Dune Medical Devices Inc., Paoli, PA, formerly Farmington, MA) received PMA approval from the Food and Drug Administration (FDA). The Dune MarginProbe System is an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤ 1mm) of the main ex-vivo lumpectomy specimen following primary excision and is indicated for intraoperative use in conjunction with standard methods (such as intraoperative imaging and palpation) for patients undergoing lumpectomy for previously diagnosed breast cancer.

Literature Review

Hayes published a health technology brief regarding the MarginProbe System (Dune Medical Devices) (Hayes, 2018). The review included seven studies (n=42 to 596) that evaluated the clinical validity, utility, and safety of MarginProbe for intraoperative assessment of surgical margins in patients with breast cancer. Two studies were randomized controlled trials (RCTs), 3 were nonrandomized cohort studies with historical controls, and 2 were prospective cohort studies. One study was determined to be fair quality; four poor quality; and, two of very poor quality. Across studies, the rates of re-excision were statistically significantly lower in patients managed using MarginProbe plus standard of care (SOC) methods when compared with SOC methods alone.

While most studies focused on rates of re-excision in patients with positive tumor margins, a critical endpoint—local tumor recurrence—was not evaluated in any study, which precludes any conclusions regarding the impact of the device on clinical oncologic outcomes. Moderate margin-level sensitivity (range, 70% to 75.2%) and low-to-moderate specificity (range, 46.4% to 70%) implies that positive margins could be missed by the device or that healthy tissue could be unnecessarily resected. The review noted study limitations included: use of historical controls; short duration of follow-up; failure to standardize methods used preoperatively to locate nonpalpable lesions; failure to standardize surgical methods and SOC methods to assess specimen margins across study arms; and failure to assess clinically relevant oncologic outcomes such as local recurrence or cancer-free survival rates. Additional studies are needed to determine whether MarginProbe is a useful adjunct to SOC methods for intraoperative margin assessment of breast tumors.
Sebastian et al. (2015) reported on a retrospective, observational study that provided compilation of data from routine use of the device, to assess the impact of device utilization on re-excision rates on groups of consecutive patients, before and after the implementation of intraoperative use of the device during lumpectomy procedures. Historical re-excision rates for each surgeon (four surgeons in three centers) were established based on a consecutive set of patients from a time period proximal to initiation of use of the device. In total, 165 cases lumpectomy cases were performed. Positive margins resulted in additional re-excision procedures in 9.7% (16/165) of the cases. The corresponding historical set from 2012 and 2013 consisted of 186 lumpectomy cases, in which additional re-excision procedures were performed in 25.8% (48/186) of the cases. The reduction in the rate of re-excision procedures was significant 62% (P < 0.0001). This study is limited by the retrospective nature of the study and small sample size.

Schnabel et al. (2014) published results of a randomized prospective clinical trial evaluating lumpectomy margin assessment with the use of MarginProbe in addition to standard methods in 596 patients with nonpalpable breast malignancies. In the device arm, MarginProbe was used to examine the main lumpectomy specimens and direct additional excision of positive margins. Intraoperative imaging was used in both arms; no intraoperative pathology assessment was permitted. False-negative rates were 24.8 and 66.1 % and false-positive rates were 53.6 and 16.6 % in the device and control arms, respectively. In similar proportions of patients in both arms, the main lumpectomy specimen contained at least one positive margin. In patients with positive margins on initial lumpectomy specimens, an average of two margins was involved, with no difference between the two arms. Surgeons correctly identified all positive margins on the main specimen and removed additional tissue from those involved margins in 33 of 147 cases (22 %) in the control arm, versus 101 of 163 (62 %) cases in the device arm (p<0.0001). 19.8 % of patients in the device arm underwent second procedures for reexcision of lumpectomy margins compared with 25.8 % of patients in the control arm, representing a 6 % absolute (23 % relative) reduction associated with MarginProbe use. With regard to reexcision procedures that were required because of positive margins originating from the main lumpectomy specimens the control arm rate was 20.8 % compared with 10.0 % in the device arm (p = 0.002).Study limitations included that this study did not test whether the device would allow for less surgery to be performed if the specimens were carefully examined intraoperatively by pathologists, with or without the selective use of frozen section. Although results are promising, additional large randomized trials and consensus support by way of published society/professional organization are necessary before this device can be considered standard of care.

Thill et al. (2014) assessed the benefit of MarginProbe in intraoperative margin assessment during breast conservation surgery (BCS) of ductal carcinoma in situ, the associated reduction of re-excisions and the cosmetic outcome in 42 patients. The study was a multi-center, single arm, post market study enrolling 55 patients and was conducted at three sites in Germany. During the study MarginProbe was used as an adjunctive tool to standard of care. Results were compared to a historical re-excision rate, defined as the number of re-excisions (26/67 patients, 39%) that had been performed on DCIS patients from the general screening. The device use was associated with a reduction in re-excision rates by 56%, from 39% to 17% (p=0.018). In 21% (9/42) of the cases use of the device led to a direct conversion to mastectomy due to extensive disease identified, sparing an additional re-excision BCS. Study limitations include small number of participants and uncontrolled study design.

Allweis et al. (2008) reported results of a randomized clinical trial in 300 patients (device: n=149, control: n=151) assessing a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. In the device group, the probe was applied to the lumpectomy specimen and additional tissue was excised according to device readings. Study arms were compared by reoperation rates and by correct surgical reaction confirmed by histology. In both arms surgeons were allowed to use any standard of care (SOC) intraoperative methods to evaluate margin status such as palpation, specimen imaging, and intraoperative gross and/or microscopic pathology assessment. Pathology data were collected for the primary lumpectomy and all repeat ipsilateral surgical procedures within 6 months. The device was only applied to the main lumpectomy specimen and was not used in reoperations. Reoperation rate between the two groups was not statically significant (p=0.98). The proportion of patients with long-term “excellent” or “good” cosmetic evaluation was similar in both arms (71% and 69% for the two groups, respectively (p=0.71). Data do not suggest improved reoperation rates compared to control.

Professional Societies/Organizations
Professional society guidelines in support of the MarginProbe System for margin assessment are lacking.

**American Society of Breast Surgeons Consensus Conference:** Published a toolbox to reduce lumpectomy reoperations and improve cosmetic outcome in breast cancer patients. Regarding MarginProbe it is noted that, “Intraoperative devices to assess margin status were discussed as potential tools to decrease reoperation. A recent, randomized trial concluded that the MarginProbe device was associated with fewer reoperations. The conference majority vote was to omit these devices from the toolbox until further investigation.”

**Centers for Medicare & Medicaid Services (CMS)**
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): No LCD found.

**Use Outside of the US**
No relevant information.

**References**

**Optical Coherence Tomography of Breast or Axillary Lymph Node (CPT Codes 0351T, 0352T, 0353T, 0354T)**

Optical coherence tomography (OCT) is a high-resolution, near-infrared light imaging modality that has been proposed as a non-surgical method of assessing breast and axillary lymph node margins.

**Literature Review**

Randomized clinical trial data are lacking in the published, peer-reviewed scientific literature. Butler-Henderson et al. (2014) published a systematic review of 27 studies examining current intraoperative methods for assessing margin status. The final pathology status, statistical measures including accuracy of tumor margin assessment, average time impact on the procedure and second operation rate, were used as criteria for comparison between studies. One third (9/27) of the studies recruited subjects prospectively but did not act on results from intraoperative methods of assessment (IMA), (i.e. prospective observational). About 40% (11/27) of studies also recruited prospectively and acted on IMA results, (i.e. prospective experimental), whereas the remaining (7/27) studies were retrospective chart reviews. Overall, accuracy of IMA was well reported. Accuracy rates for ultrasound, frozen section and optical coherence tomography were 99.6%, 98.02% and 90%, respectively. Imprint cytology had a sensitivity of 80-85% and specificity of 85-100%. Optical coherence tomography reported a sensitivity of 100% and specificity of 82%, but average operation time was unavailable. Only one study examined the use of optical coherence tomography in breast cancer surgery. Additional operation time and second operation rate were not investigated. The authors note that caution is necessary before making any recommendation concerning its use in breast surgery.

Nguyen et al. (2009) reported results of a prospective, observational study. OCT demonstrated a sensitivity of 100% and specificity of 82% for OCT as a real-time method for margin assessment during breast-conserving surgery involving a total of 37 patients. OCT images were acquired from surgical margins of lumpectomy samples. Histologic findings identified nine true positives, nine true negatives, two false positives and no false negatives. The authors concluded that OCT shows potential as a real-time method for intraoperative margin assessment in breast-conserving surgeries. Study limitations include nonrandomized design and small sample size.

**Centers for Medicare & Medicaid Services (CMS)**

- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Noncovered Services (L33777) (2019). The LCD is broader in scope than the Coverage Policy. Refer to the CMS LCD table of contents link in the reference section.

**Professional Societies/Organizations**

Professional society guidelines in support of optical coherence tomography as a non-surgical method of assessing breast and axillary lymph node margins are lacking.

**Use Outside of the US**

No relevant information

**References**


**Donor-Derived Cell-Free DNA (AlloSure®) (CPT code 81479)**

Organ transplant recipients are at risk for allograft rejection, even with modern immunosuppressive therapies. Traditionally, diagnosis of allograft rejection has relied on nonspecific biochemical markers and histologic examination of the grafted tissue. Since this requires an invasive tissue biopsy, there is great interest among those in the field of transplantation medicine to develop a noninvasive method of detecting organ transplant rejection (Verhoeven, et al., 2018). Allosure® (CareDx, Brisbane, CA) is a targeted next-generation sequencing test that evaluates 266 single nucleotide polymorphisms in cell-free DNA samples. It is hypothesized that transplant patients experiencing organ injury associated with acute rejection will have higher levels of donor-derived cell free DNA (dd-cfDNA) which is thought to be due to cell-free DNA being an indicator of dying cells.

In recent years, dd-cfDNA tests have become clinically available to quantify the amount of dd-cfDNA in transplant recipients.

These tests are intended to assess the probability of allograft rejection in a particular patient. The technology does not rely on previous genotyping of either the patient or the donor, which is a benefit over previous methods that have been used to measure dd-cfDNA. Additionally, these tests do not require invasive tissue biopsy, which is necessary for the standard methods of histopathological interpretation that are used to diagnose allograft rejection. However, biopsy is still necessary to confirm and establish the type of active rejection in affected patients (Jordan et al., 2018). It has been proposed that these tests be used for serial monitoring in order to detect new onset injury or rejection prior to clinical symptoms, however the optimal time interval has yet to be established (Bloom et al., 2017). The use of dd-cfDNA to evaluate transplant rejection is a new development in the field of transplant medicine, however the clinical utility of this technology has yet to be established.

**Literature Review**

Bloom et al. (2017) conducted a prospective observational study (DART study). Blood specimens were collected from 102 patients at scheduled intervals and at the time of clinically indicated biopsies. Plasma levels of donor-derived cell-free DNA (dd-cfDNA) were measured and correlated with allograft rejection status ascertained by histology in 107 biopsy specimens. The dd-cfDNA level discriminated between biopsy specimens showing any rejection (T cell-mediated rejection or antibody-mediated rejection [ABMR]) and controls (no rejection histologically), P<0.001 (receiver operating characteristic area under the curve [AUC], 0.74; 95% confidence interval [95% CI], 0.61 to 0.86). Positive and negative predictive values for active rejection at a cutoff of 1.0% dd-cfDNA were 61% and 84%, respectively. The AUC for discriminating ABMR from samples without ABMR was 0.87 (95% CI, 0.75 to 0.97). Positive and negative predictive values for ABMR at a cutoff of 1.0% dd-cfDNA were 44% and 96%, respectively. Median dd-cfDNA was 2.9% (ABMR), 1.2% (T cell-mediated type ≥IB), 0.2% (T cell-mediated type IA), and 0.3% in controls (P=0.05 for T cell-mediated rejection types ≥IB versus controls).

Jordan et al. (2018) conducted a study with a cohort from above DART study to assess the combined use of donor-derived cell-free DNA (dd-cfDNA) and Donor-specific antibodies (DSA) testing to diagnose active antibody-mediated rejection (ABMR). Donor-derived cell-free DNA was assayed in 90 blood samples with paired DSA and clinically indicated biopsies from 87 kidney transplant patients. Sixteen cases met criteria for active ABMR. Performance characteristics of dd-cfDNA for diagnosis of active ABMR were determined for samples with prior or current positive DSA (DSA+, n = 33). The median level of dd-cfDNA (2.9%) in DSA+ patients with active ABMR was significantly higher than the median level (0.34%) in DSA+ patients without ABMR (P<0.001). The median level of dd-cfDNA in DSA- patients was 0.29%. The positive predictive value of dd-cfDNA (at 1%) to detect active ABMR in DSA+ patients was 81%, whereas the negative predictive value was 83%. The positive predictive value for DSA+ alone was 48%.
Broomberg et al. (2017) conducted an observational study of a cohort of the above DART study to establish biological variation and clinical reference intervals of dd-cfDNA in renal transplant recipients by using an analytically validated assay that has a CV of 6.8%. Venous blood was sampled at patient surveillance visits (typically at posttransplant months 1–4, 6, 9, and 12). Patients with stable renal allograft function spanning ≥3 serial visits were selected. AlloSure was used to measure dd-cfDNA in the plasma and computed the intraindividual CV (CVI) and interindividual CV (CVG), the index of individuality (II), and reference change value (RCV). The study included 93 patients with 61% men, 56% Caucasian, mean ages 49 years, and 63% were deceased donor kidney recipients. Of the 380 blood samples, the dd-cfDNA median value was 0.21% (interquartile range 0.12%–0.39%) and the 97.5th percentile was 1.20%. In 18 patients with an average of 4.1 tests, the CVI was 21%, CVG was 37%, II was 0.57, and RCV was 61%. The authors concluded that in a renal transplant recipient, a dd-cfDNA level above 1.2% is out of range and potentially abnormal. A serial increase of up to 61% in level of dd-cfDNA in a patient may be attributable to biological variation.

Centers for Medicare & Medicaid Services (CMS)
- National Coverage Determinations (NCD): No NCD found
- Local Coverage Determinations (LCDs): Multiple LCDs found. Refer to the LCD table of contents link in the reference section.

Professional Societies/Organizations
The evaluation of donor-derived cell free DNA has not yet been addressed by professional societies such as the American Society of Transplantation, European Society for Organ Transplantation, or the British Transplantation Society.

Use Outside of the US
No relevant information

References


**Coding/Billing Information Other**

**Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Considered Experimental/Investigational/Unproven when used to report multivariate analysis of patient specific findings with quantifiable computer probability assessment:**

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**Other Services Considered Experimental/Investigational/Unproven:**

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