Medical Coverage Policy

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Omnibus Codes

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are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses multiple services and procedures.

Coverage Policy

Cardiology

Endovascular repair of iliac artery by deployment of an iliac branched endograft (CPT code 34717)

Unilateral internal iliac stent graft placement (CPT 34717) is considered medically necessary if ALL of the following criteria are met:

- individual is undergoing endovascular abdominal aortic aneurysm (AAA) repair at the same time as the internal iliac artery (IIA) procedure
- the ipsilateral common iliac artery demonstrates an aneurysm that meets criteria for clinical significance (greater than 3.5 cm in diameter)
- documentation of an adequate landing zone for the distal end of the IIA stent graft
- contralateral internal iliac artery occlusion

Endocrinology

Radiofrequency Ablation (RFA) Thyroid Nodules (CPT code 60699)

Radiofrequency ablation (RFA) is considered medically necessary for treatment of ANY of the following:

- differentiated thyroid cancer (i.e., papillary, follicular, and Hürthle cell)
- medullary thyroid cancer
- benign thyroid nodule when BOTH of the following criteria are met:
  - compressive symptoms (e.g., changes of voice, dysphagia, dyspnea, pain)
  - limited to a single RFA treatment in a 12-month period

Gastroenterology

Transanal Endoscopic Microsurgery (TEMS) Approach for Excision of Rectal Tumor (CPT Code 0184T)

Transanal endoscopic microsurgery (TEMS) is considered as medically necessary for EITHER of the following indications:

- Benign adenoma
- T1N0 rectal cancer when ALL of the following criteria are met:

  - tumor has a diameter of < 3cm
  - tumor is located within 8 cm of the anal verge
  - tumor is well to moderately differentiated
  - tumor is limited to < 30% of the rectal circumference
  - lesion is adequately identified in the rectum
  - no signs of systemic or metastatic disease

TEMS for any other indication is not covered or reimbursable.

Other

Bioimpedance Spectroscopy to Measure Extracellular Fluid Differences Between Limbs (CPT Code 93702)

Bioimpedance spectroscopy is considered medically necessary for measurement of extracellular fluid volume in an individual at risk for developing lymphedema (e.g., undergoing breast cancer treatment, lymph node biopsy, regional lymphadenectomy, and/or radiation therapy for other non-breast malignancies).

Frequency of Physical, Occupational, and Chiropractic Services

Under many benefit plans, coverage for physical therapy, occupational therapy and chiropractic care programs provided in the outpatient setting is subject to the terms, conditions and limitations of the applicable benefit plan's Short-Term Rehabilitative Therapy benefit and schedule of copayments.

In addition, coverage for physical therapy, occupational therapy and chiropractic care varies across plans. Refer to the customer's benefit plan document for coverage details.

The following services are each not covered or reimbursable when the treatment visit extends beyond 4 timed unit services, per date of service, per provider type, (equivalent to one hour):

- Physical therapy*
- Occupational therapy*
- Chiropractic care*

***Note: Please reference the following Medical Coverage Policies for additional conditions of coverage: Physical Therapy (CPG 135), Occupational Therapy (CPG 155) or Chiropractic Care (CPG 278).**

Otolaryngology

Tympanostomy (requiring insertion of ventilating tube), using an automated tube delivery system, iontophoresis local anesthesia (CPT® 0583T)

Tympanostomy tube insertion using the Tula® System (CPT® 0583T) is considered medically necessary for an individual six months of age or older when ANY of the following criteria are met:

- chronic (at least three months) otitis media with effusion (OME) in the ear considered for tube insertion, AND documented hearing difficulties
- chronic unilateral or bilateral OME AND symptoms that are likely attributable, all or in part, to OME that include, but are not limited to, ear pain, ear fullness, balance (vestibular) problems, poor school performance, behavioral problems, or reduced quality of life
- recurrent acute otitis media (AOM) AND unilateral or bilateral middle ear effusion (MEE) at the time of assessment for tube candidacy
- children at risk for developmental delays or disorders* AND unilateral or bilateral OME that is likely to persist as reflected by a type B (flat) tympanogram or a documented effusion for three months or longer

  *Sensory, physical, cognitive, or behavioral factors that place children with otitis media with effusion at increased risk for developmental difficulties (delay or disorder) may include:
  - Permanent hearing loss independent of otitis media with effusion
  - Suspected or confirmed speech and language delay or disorder
  - Autism spectrum disorder
  - Syndromes (e.g., Down) or craniofacial disorders that include cognitive, speech, or language delays
  - Blindness or uncorrectable visual impairment
  - Cleft palate, with or without associated syndrome
  - Developmental delay
  - Intellectual disability, learning disorder, or attention-deficit/ hyperactivity disorder

EXPERIMENTAL, INVESTIGATIONAL OR UNPROVEN SERVICES

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

CPT®* Codes	Description	Comment
33289	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	CardioMEMS™ HF System (St. Jude Medical, Inc.)
34718	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	GORE® EXCLUDER® Iliac Branch Endoprosthesis (IBE) (W. L. Gore & Associates, Inc.)

CPT®* Codes	Description	Comment
	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 other than rupture (eg, for aneurysm, pseudoaneurysm, dissection, arteriovenous malformation, penetrating ulcer), unilateral	
46999	Unlisted procedure, anus	When used to report the SECCA procedure (transanal radiofrequency therapy for fecal Incontinence)
53451	Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance	Adjustable Continence Therapy (ACT®) device (for women) and the ProACT™ device (for men) (Uromedica, Inc.)
53452	Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance	Adjustable Continence Therapy (ACT®) device (for women) and the ProACT™ device (for men) (Uromedica, Inc.)
88104	Cytopathology, fluids, washings or brushings, except cervical or vaginal; smears with interpretation	Considered Experimental/Investigational/Unproven when used to report wide-area transepithelial tissue sampling with computer-assisted 3D analysis (WATS3D)
88112	Cytopathology, selective cellular enhancement technique with interpretation (eg, liquid based slide preparation method), except cervical or vaginal	Considered Experimental/Investigational/Unproven when used to report wide-area transepithelial tissue sampling with computer-assisted 3D analysis (WATS3D)
88305	Level IV - Surgical pathology, gross and microscopic examination	Considered Experimental/Investigational/Unproven when used to report wide-area transepithelial tissue sampling with computer-assisted 3D analysis (WATS3D)
88312	Special stain including interpretation and report; Group I for microorganisms (eg, acid fast, methenamine silver)	Considered Experimental/Investigational/Unproven when used to report wide-area transepithelial tissue sampling with computer-assisted 3D analysis (WATS3D)
88361	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu,	Considered Experimental/Investigational/Unproven

CPT®* Codes	Description	Comment
	estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology	when used to report wide-area transepithelial tissue sampling with computer-assisted 3D analysis (WATS3D)
91299	Unlisted diagnostic gastroenterology procedure	When used to report the Vibrant® System (Vibrant Ltd., Philadelphia, PA)
0106U	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	13C-Spirulina Platensis Gastric Emptying Breath Test Gastric Emptying Breath Test (GEBT) (Advanced Breath Diagnostics LLC)
0176U	Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (ie, ELISA)	IBSchek (Commonwealth Diagnostics International Inc.)
95999	Unlisted neurological or neuromuscular diagnostic procedure	When used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
0100T	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intraocular retinal electrode array, with vitrectomy	Argus II Retinal Prosthesis System (Argus II) (Second Sight Medical Products, Inc.)
0408T	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	OPTIMIZER® Smart System (Impulse Dynamics)
0409T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only	OPTIMIZER® Smart System (Impulse Dynamics)
0410T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only	OPTIMIZER® Smart System (Impulse Dynamics)
0411T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only	OPTIMIZER® Smart System (Impulse Dynamics)

CPT®* Codes	Description	Comment
0412T	Removal of permanent cardiac contractility modulation system; pulse generator only	OPTIMIZER® Smart System (Impulse Dynamics)
0413T	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)	OPTIMIZER® Smart System (Impulse Dynamics)
0414T	Removal and replacement of permanent cardiac contractility modulation system pulse generator only	OPTIMIZER® Smart System (Impulse Dynamics)
0415T	Repositioning of previously implanted cardiac contractility modulation transvenous electrode (atrial or ventricular lead)	OPTIMIZER® Smart System (Impulse Dynamics)
0416T	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator	OPTIMIZER® Smart System (Impulse Dynamics)
0417T	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	OPTIMIZER® Smart System (Impulse Dynamics)
0418T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system	OPTIMIZER® Smart System (Impulse Dynamics)
0472T	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	Argus II Retinal Prosthesis System (Argus II) (Second Sight Medical Products, Inc.)
0473T	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	Argus II Retinal Prosthesis System (Argus II) (Second Sight Medical Products, Inc.)
0533T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; includes set-up,	When used to report tremor measurement with accelerometer(s) and/or gyroscope(s)

CPT®* Codes	Description	Comment
	patient training, configuration of monitor, data upload, analysis and initial report configuration, download review, interpretation and report	
0534T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; set-up, patient training, configuration of monitor	When used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
0535T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; data upload, analysis and initial report configuration	When used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
0536T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; download review, interpretation and report	When used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
0715T	Percutaneous transluminal coronary lithotripsy (List separately in addition to code for primary procedure)	Shockwave Intravascular Lithotripsy (IVL) System (Shockwave Medical, Inc.) (Use 0715T in conjunction with 92920, 92924, 92928, 92933, 92937, 92941, 92943, 92975)

HCPCS Codes	Description	Comment
A9999	Miscellaneous DME supply or accessory, not otherwise specified	When used to report the Vibrant® System (Vibrant Ltd., Philadelphia, PA)
C1761	Catheter, transluminal intravascular lithotripsy, coronary	Shockwave Intravascular Lithotripsy (IVL) System (Shockwave Medical, Inc.)
C1824	Generator, cardiac contractility modulation (implantable)	OPTIMIZER® Smart System (Impulse Dynamics)
C2624	Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components	CardioMEMS™ HF System (St. Jude Medical, Inc.)
C9777	Esophageal mucosal integrity testing by electrical impedance, transoral, includes esophagoscopy or esophagogastroduodenoscopy	Mucosal Integrity Conductivity (MI) Test System (Diversatek Healthcare Inc.)
E2120	Pulse generator system for tympanic treatment of inner ear endolymphatic fluid	Meniett™ Device (Medtronic Xomed, Inc.)
G0255	Current perception threshold/sensory nerve conduction test, (sNCT) per limb, any nerve	Examples include: Medi-Dx 7000 (Neuro Diagnostic Associates, Inc.); Neurometer® (Neurotron, Inc.)

HCPCS Codes	Description	Comment
K1030	External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only	OPTIMIZER® Smart System (Impulse Dynamics)
S2103	Adrenal tissue transplant to brain	

NOT COVERED OR REIMBURSABLE

Each of the following services is not covered or reimbursable when used to report the applicable technology for any indication:

CPT®* Codes	Description	Comment
93701	Bioimpedance-derived physiologic cardiovascular analysis	When used to report thoracic electrical bioimpedance (TEB, also known as thoracic bioimpedance, impedance cardiography [ICG], or bioimpedance cardiography) Examples include: BioZ Portable, BioZ.PC, BioZDX (SonoSite); PhysioFlow® Enduro (Vasocom, Inc.); Cheetah Starling™ SV (Cheetah Medical)
99199	Unlisted special service, procedure or report	When used to report near-infrared guidance for vascular access requiring real-time digital visualization of subcutaneous vasculature for evaluation of potential access sites and vessel patency.

General Background

Cardiovascular

Endovascular repair of iliac artery by deployment of an iliac branched endograft (CPT codes 34717, 34718)

Endovascular aneurysm repair (EVAR) is the predominant method for treatment of abdominal aortic aneurysms (AAAs) in contemporary practice, and between 20% and 30% of patients undergoing EVAR are estimated to also have associated iliac artery aneurysms (IAA). The "coil-and-cover" technique with embolization of the internal iliac artery and extension of the stent graft limb into the external iliac artery has routinely been used as an adjunct during EVAR when treating patients with common iliac artery aneurysms (CIAAs) or aortoiliac aneurysms (AIAs) involving the iliac bifurcation. Although enabling successful exclusion of a CIAA during EVAR, internal iliac artery sacrifice may be associated with pelvic ischemic complications such as buttock claudication, erectile dysfunction.

The category III code that has previously described this service (CPT 0254T) has been deleted. CPT codes 34717 and 34718 are used to describe placement of a bifurcated endograft in the common iliac artery with extensions into both the internal and external 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.

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

The Instructions for Use (IFU) (2/23/2022) state that the GORE® EXCLUDER® Iliac Branch Endoprosthesis is to be used with the GORE® EXCLUDER® AAA Endoprosthesis or GORE® EXCLUDER® Conformable Endoprosthesis and is not intended to be used on its own.

Under Implant Procedure, the IFU states that Implantation of both GORE® EXCLUDER® Iliac Branch Endoprosthesis components (Iliac Branch Component and Internal Iliac Component) should be performed prior to implantation of any GORE® EXCLUDER® AAA Endoprosthesis or GORE® EXCLUDER® Conformable Endoprosthesis components (Trunk-Ipsilateral Leg Component and Contralateral Leg Component as bridging component).

The IBE device has to be connected to an aortic bifurcated stent-graft even in cases of isolated CIAAs to improve endograft stability and reduce the risk of device migration and endoleak (Giaquinta, et al., 2018).

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

There is a lack of large, randomized trials comparing the use of GORE® EXCLUDER® Iliac Branch Endoprosthesis (IBE Device) to standard current treatment. No symptomatic (e.g., buttock claudication, erectile dysfunction) or morbidity/mortality advantage has been demonstrated.

Schneider et al. (2017) reported on six-month primary end point results of the pivotal trial for endovascular treatment of aortoiliac aneurysms (AIAs) and common iliac artery (CIA) aneurysms using the GORE EXCLUDER Iliac Branch Endoprosthesis (IBE device). The trial prospectively includes 63 patients with AIA or CIAA who underwent implantation of the IBE device at 28 centers in the United States. All patients underwent placement of a single IBE device. After insertion of the IBE device, the GORE EXCLUDER AAA Endoprosthesis is inserted. Twenty-two patients (34.9%) with bilateral CIAs were enrolled after undergoing staged coil or plug embolization (21 of 22) or surgical revascularization (1 of 22) of the contralateral internal iliac artery. Follow-up at 30 days and six months included clinical assessment and computed tomography angiography evaluation as assessed by an independent core laboratory. The primary effectiveness end point was freedom from IBE limb occlusion and reintervention for type I or III endoleak and ≥60% stenosis at six months, and the secondary effectiveness end point was freedom from new onset of buttock claudication on the IBE side at six months. The mean CIA diameter on the IBE side was 41.0 ± 11.4 mm (range, 25.2-76.3 mm). There were no procedural deaths, and technical success, defined as successful deployment and patency of all IBE components and freedom from type I or III endoleak, was 95.2% (60 of 63). Data for 61 patients were available for primary and secondary effectiveness end point analysis. Internal iliac limb patency was 95.1% (58 of 61), and no new type I or III endoleaks or device migrations were observed at 6 months. The three patients with loss of internal iliac limb patency were asymptomatic, and freedom from new-onset buttock claudication on the IBE side was 100% at 6 months. New-onset buttock claudication occurred on the non-IBE treatment side in six of 21 patients (28.6%) who underwent staged internal iliac artery coil embolization.

In 2022, Schneider et al. reported 5 year follow-up. At 5 years, 36/63 patients completed the final study follow up; 35 had clinical examination and 32 had CT imaging (evaluated by an independent core laboratory and adverse events adjudicated by clinical events committee). At 5 years, freedom from all-cause mortality was 85.7% and freedom from aneurysm-related mortality was 100%. The nine deaths that occurred were adjudicated as unrelated to the aneurysm or the procedure. Primary patency of the internal and external iliac artery IBE limbs was 95.1% and 100%, respectively. No patients experienced new onset buttock claudication on the IBE side or self-reported new onset erectile dysfunction (Schneider et al., 2022). Limitations of this study include the lack of randomized comparison and the small study population.

van der Veen et al. (2021) reported 12 month follow-up on 87 patients from the International Multicenter Prospective Cohort Study. Participants will be followed for five years. The Gore Excluder Iliac Branch Endoprosthesis (IBE) device was used. According to the IFU the Gore Excluder IBE should be placed together with the Gore Excluder Endoprosthesis; however, seven were placed in isolation without the main endoprosthesis. The other seven patients were anatomically outside the requirements of the IFU. A total of 100 patients (97% were male, median age 70) with an indication for elective treatment of a common iliac or aorto-iliac aneurysm were included:

- N=92 Gore Excluder IBE in combination with Gore Excluder Endoprosthesis

- N=1 Only Gore Excluder Endoprosthesis (technical failure)
- N=22 Bilateral Gore Excluder IBE in combination with Gore Excluder Endoprosthesis
- N=7 Isolated Gore Excluder IBE

Data of 99, 84, and 87 patients were available for the 30 day, six month, and 12 month analysis. Results demonstrated the primary patency of the internal iliac artery (IIA) 12 months after the procedure was 91.3%. Primary patency for patients treated inside and outside the instructions for use were 91.8% and 85.7%, respectively (p= .059). Freedom from secondary interventions was 98% and 97% at 30 days and 12 months, respectively. CIA and AAA diameters decreased significantly through 12 months. At 30 day follow up, there were no new onset type I or III endoleaks, and a type II endoleak was present in 18 patients. At 12 months, there were no new type I endoleaks. A persistent type II endoleak was present in 15 patients. All patients with a type II endoleak were treated with both a Gore Excluder IBE and Gore Excluder Endoprosthesis. Limitations of this study include the lack of randomized comparison and the small study population at 12 months.

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). Reinterventions 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.

Maldonado et al. (2018) reported a retrospective review of 47/40 patients with bilateral common iliac artery (CIA) aneurysms. Six patients (12.7%) were symptomatic. Imaging was available in 40 of 47 patients (85.1%). Median follow up was 6.5 months. Maldonado et al. (2018) assessed the safety and efficacy of the GORE IBE device in treating bilateral CIA aneurysms. Reported results included 12 type II endoleaks (25.5%) and no type I or type III endoleaks, no sac enlargement, and no device migration. Two of 80 (2.5%) IIA branches imaged were occluded; one was intentionally sacrificed perioperatively. On clinical follow-up, in all 47 patients, there were no aneurysm-related deaths (two nonaneurysm-related deaths from cardiac causes at 1 year). There were no new cases of impotence reported; however, there was one new-onset buttock claudication related to an IIA branch occlusion. There was no significant perioperative morbidity or mortality, however, IIA branch adjunctive stenting was required in four patients (one IIA distal dissection, three kinks).

A Cochrane review evaluated internal iliac artery revascularization versus internal iliac artery occlusion for endovascular treatment of aorto-iliac aneurysms. New endovascular devices and alternative techniques such as iliac branch devices and the sandwich technique have been used to revascularize the internal iliac artery and decrease pelvic ischemic complications in patients not suitable for an adequate seal zone in the common iliac arteries. The authors stated "no evidence-based RCTs have been done to support their use". The authors noted that they acknowledge that designing and conducting an appropriate study for this topic is difficult, given that the overall incidence of aorto-iliac aneurysms with inadequate distal seal zone is low (Sousa, et al., 2020).

Kouvelos et al. (2016) conduct a systematic review of the literature investigating outcomes after interruption or preservation of the internal iliac artery (IIA) during endovascular aneurysm repair (EVAR). The search identified 57 articles: 30 reported on IIA interruption (1468 patients) and 27 on IIA preservation (816 patients). Most patients (87.6%) had an iliac branched device, and technical success was 96.2%. Within 30 days of EVAR, 4.3% of internal iliac branches occluded. In patients treated with an iliac-branched device, 5.2% of internal iliac branches and 1.7% of external iliac arteries occluded. Anatomy of the aorto-iliac aneurysm is important in order to select suitable patients and the proper therapeutic strategy. The existing literature suggests that up to 40% of patients may eventually not be suitable for an IBD use based on anatomical criteria (Cited by ACC).

Bosanquet et al. (2017) conducted a systematic review of literature to determine pooled complication rates of internal iliac artery (IIA) coverage. The authors noted that internal iliac artery (IIA) embolization is frequently required prior to EVAR in order to achieve a suitable landing zone. However, patients can experience considerable morbidity following this, which in part has driven the introduction of iliac branched devices.
The authors concluded that buttock claudication occurs in approximately one third of patients, although this resolves in half of those affected. New onset erectile dysfunction occurs in approximately 10% of males. Major ischemic complications, such as buttock, colonic and spinal ischemia were all very rare, and reporting of such events was much more likely from older publications. In general, all complications were worse after bilateral than unilateral IIA occlusion. The authors stated that historically, external iliac artery (EIA) to IIA bypasses were performed, and, more recently, iliac branched devices (IBDs) allow preservation of hypogastric perfusion. However, there are limited data on which to base current practice, and utilization of IBDs varies considerably. These variations are in part due to limited understanding of the long-term morbidity of IIA exclusion (Cited by ACC).

Professional Societies/Organizations
The 2022 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline for the Diagnosis and Management of Aortic Disease (Isselbacher et al., December 2022) states:

The prevalence of common iliac artery aneurysms in the presence of AAA has been reported to be as high as 20% to 40% in surveillance studies. In patients with both aortic and iliac aneurysms, it is common for an iliac aneurysm to reach a size appropriate for elective repair before the AAA does. Although no randomized studies for iliac aneurysm repair size thresholds exist, in large case series and registry reports, rupture of iliac aneurysms at diameters <4 cm is rare. Thus, a **repair threshold of 3.5 cm** seems reasonable to balance procedural risks with rupture risk. Furthermore, to achieve adequate AAA repair, repair of iliac artery ectasia or aneurysms often may be required. Consideration of pelvic perfusion is of great importance when managing concomitant iliac disease. In such cases, there is a high risk of ischemic complications from exclusion of internal iliac arteries that can lead to buttock claudication, bowel ischemia, and erectile dysfunction. For some patients, adequate treatment of diseased iliac arteries cannot be accomplished without internal iliac artery sacrifice. Thus, individualized treatment plans with shared decision-making are important when treating aorto-iliac aneurysm disease.

6.5.5.5. Recommendations for the Treatment of Concomitant Common Iliac Aneurysms	Class of Recommendation (COR) and Level of Evidence (LOE)*
For patients with asymptomatic small AAA and concomitant common iliac artery aneurysm(s) ≥3.5 cm, elective repair of both abdominal and iliac aneurysms is recommended.	COR:1; LOE: C-LD
When treating common iliac artery aneurysms or ectasia as part of AAA repair, preservation of at least 1 hypogastric artery is recommended, if anatomically feasible, to decrease the risk of pelvic ischemia.	COR:1; LOE: B-NR

*Applying ACC/AHA Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care

The Class (Strength) of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk.

Class I – Strong (is recommended)
Class 2a – Moderate (is reasonable)
Class 2b – Weak (may/might be reasonable)
Class 3 – No benefit (Moderate) (is not recommended)
Class 3 – Harm (Strong) (potentially harmful)

The Level (Quality) of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources.

Level A – High quality evidence from more than one randomized clinical trial, Meta-analyses of high-quality randomized clinical trials, One or more randomized clinical trials corroborated by high-quality registry.
Level B-R – Randomized. Moderate quality evidence from one or more randomized clinical trials, Meta-analyses of moderate-quality randomized clinical trials.
Level B-NR – Non-randomized. Moderate quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies, Meta-analyses of such studies.
Level C-LD – Limited data. Randomized or nonrandomized observational or registry studies with limitations of design or execution, Meta-analyses of such studies, Physiological or mechanistic studies of human subjects.
Level C-EO – Expert Opinion. Consensus expert opinion based on the clinical experience

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

Heart failure (HF) is a complex clinical syndrome identified by presence of current or prior characteristic symptoms, such as dyspnea and fatigue, and evidence of cardiac dysfunction as a cause of these symptoms (e.g., abnormal left ventricular [LV] and/or right ventricular [RV] filling and elevated filling pressures). From a hemodynamic perspective, HF is a disorder in which the heart cannot pump blood to the body at a rate commensurate with its needs, or can do so only at the cost of high filling pressures. Patients with HF may or may not have associated physical signs, such as those related to fluid retention. HF can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The functional status of

patients with HF is often described using the New York Heart Association (NYHA). The NYHA classification, with severity of disability ranging from I to IV is the classification system that is most commonly used to quantify the degree of functional limitation imposed by HF is one first developed by the NYHA. This system assigns patients to one of four functional classes, depending on the degree of effort needed to elicit symptoms:

- Class I – Patients with heart disease without resulting limitation of physical activity. Ordinary physical activity does not cause HF symptoms such as fatigue or dyspnea.
- Class II – Patients with heart disease resulting in slight limitation of physical activity. Symptoms of HF develop with ordinary activity but there are no symptoms at rest.
- Class III – Patients with heart disease resulting in marked limitation of physical activity. Symptoms of HF develop with less than ordinary physical activity but there are no symptoms at rest.
- Class IV – Patients with heart disease resulting in inability to carry on any physical activity without discomfort. Symptoms of HF may occur even at rest.

Blacks have a higher incidence of HF and disproportionately have poor outcomes related to HF compared with whites. These racial differences in HF outcomes are caused, in part, by the higher prevalence of clinical risk factors for HF such as uncontrolled hypertension, endothelial dysfunction, and deleterious genetic polymorphisms among nonwhites. Before 50 years of age, HF is more common among Blacks than whites. This higher risk is considered to be the result of differences in the prevalence of hypertension, diabetes mellitus, and low socioeconomic status (SES). Women with HF report worse health-related quality of life than men with HF. Women differ from men in clinical symptoms and experience more morbidity, particularly decreased functional status and depression. Generally speaking, the treatment guidelines for men and women are the same, although women have been underrepresented in trials evaluating HF therapy (White-Williams, et al., 2020).

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 (Abbotts, formerly 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.

In February 2022, the FDA approved a PMA supplement for the CardioMEMs HF System (St. Jude Medical [Abbott]) for expanding the indications to include NYHA Class II patients (P100045/S056). The Feb 18, 2022 approval letter states: "The CardioMEMS HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides. The hemodynamic data are used by physicians for heart failure management with the goal of controlling pulmonary artery pressures and reducing heart failure hospitalizations."

Literature Review

Brugts et al. (2023) conducted an open-label, randomized trial, done in 25 centers in the Netherlands. A total of 348 patients with chronic heart failure of New York Heart Association class III and a previous heart failure hospitalization were randomly assigned to:

1. CardioMEMS-HF group (n=176) (heart failure management with guideline-directed medical therapy [GDMT] and diuretics with the addition of hemodynamic monitoring by a pulmonary artery pressure sensor); or
2. standard care group (n=172) (heart failure management with GDMT and diuretics).

CardioMEMS-HF participants:

- Of the 176, 168 received treatment (8 did not receive intervention because 5 withdrew informed consent, 1 met exclusion criteria, 2 died before implantation).
- Of the 168, 49 discontinued treatment (7 withdrew informed consent, 40 died, and 2 stopped active monitoring [1 non-compliance, 1 sensor failure]).
- 176 included in intention-to-treat (ITT) analysis

Standard care participants:

- 172 received treatment
- 50 discontinued treatment (5 withdrew informed consent, and 45 died)
- 172 included in intention-to-treat (ITT) analysis

The primary endpoint was the mean difference in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at 12 months. The mean follow-up time was 1.8 years.

- The mean change in KCCQ overall summary scores between baseline and 12 months among patients in the CardioMEMS-HF group was +7.05 (p=0.0014), compared with -0.08 points among those in the standard care group (p=0.97).
- The total number of heart failure hospitalizations was 117 in the CardioMEMS-HF group and 212 in the control group.
- The median NT-proBNP was significantly reduced from 2377 pg/mL at baseline to 1708 pg/mL (p=0.013) at 12 months in the CardioMEMS-HF group. In the standard care group, there was non-significant difference in NT-proBNP (1907 pg/mL to 1607 pg/mL, p=0.81) at 12 months.

There was no difference on CV/all-cause mortality in patients with CardioMEMS or standard of care. The authors summarized that this MONITOR-HF study showed that hemodynamic monitoring and subsequent individualized adjustment of diuretics and GDMT significantly improved QOL and reduced the number of heart failure hospitalizations. The authors noted a study limitation is the open-label design, as well as the absence of a device (or sham) in controls, which can be prone to bias in the QOL endpoint by unmasking. Another study limitation is the large percentage of treatments that were discontinued, in both groups, for various reasons including death.

The hemodynamic-GUIDEed management of Heart Failure (GUIDE-HF) trial included a randomized arm (n=1000, completed) and a single-arm, observational study (n=2600, ongoing). The single arm of the trial is an observational arm in which NYHA class III patients (n = 2,600) with either a previous heart failure hospitalization (HFH) or elevated natriuretic peptides (but no recent HFH) will be implanted with a PA pressure sensor and observed for occurrence of the primary composite end point of cumulative HF events and mortality at 12 months.

The randomized arm was a multicenter, single-blind study at 118 centers in the USA and Canada. The study enrolled 1022 patients with NYHA functional class II–IV heart failure, regardless of left ventricular ejection fraction, with a heart failure hospitalization within the 12 months before study consent or elevated natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]) within 30 days before study consent. A total of 22 patients had unsuccessful implants. This left 1000 participants receiving an implantable PA pressure sensor (CardioMEMS HF System) who were then randomly assigned (1:1) to either hemodynamic-guided heart failure management based on pulmonary artery pressure (n=497) or a usual care (control) group (n=503). Patients were masked to their study group assignment. Investigators were aware of treatment assignment but did not have access to pulmonary artery pressure data for control patients. The primary study end point is the composite of cumulative HF events and all-cause mortality at 12 months. Secondary end points include quality-of-life and functional assessments. A total of 25 treatment group patients and 44 control group patients withdrew from the study before 12 months.

The authors reported that hemodynamic-guided management did not reduce the combined endpoint of all-cause mortality, heart failure hospitalizations, and urgent heart failure hospital visits despite significant reductions in pulmonary artery pressure during study follow-up compared with the control group. They found no significant between-group differences in the prespecified secondary endpoints of total heart failure events, health related quality of life (KCCQ-12 and EQ-5D-5L), or functional capacity (6MHW). The authors stated that the COVID-19 pandemic had an important effect on the trial. A pre-COVID-19 impact analysis indicated a possible benefit of hemodynamic-guided management on the primary outcome in the pre-COVID-19 period, primarily driven by a lower heart failure hospitalization rate compared with the control group (Lindenfeld, et al., 2019; Lindenfeld, et al., 2021).

Shavelle et al. (2020) conducted a multi-center, prospective, open-label, observational, single-arm trial to assess the efficacy and safety of PA pressure-guided therapy in routine clinical practice with special focus on subgroups defined by sex, race, and ejection fraction (one-year outcomes from the CardioMEMS Post-Approval Study [PAS]). The study included 1,200 patients with New York Heart Association class III heart failure (HF) and a prior heart failure hospitalization (HFH) within 12 months and evaluated patients undergoing PA pressure sensor implantation between September 1, 2014, and October 11, 2017. The primary efficacy outcome was the difference between rates of adjudicated HFH one year after compared with the one year before sensor implantation. Safety end points were freedom from device- or system-related complications at two years and freedom from pressure sensor failure at two years. The mean age was 69 years, 37.7% were women, 17.2% were non-White, and 46.8% had preserved ejection fraction (37.7% women; Black 14.3%; Asian 1%; Other 1.5%). For the duration of year after sensor implantation, the mean rate of daily pressure transmission was 76±24% and PA pressures declined significantly. The rate of HFH was significantly lower at one year compared with the year before implantation ($P<0.0001$). The rate of all-cause hospitalization was also lower following sensor implantation ($P<0.0001$). Results were consistent across subgroups defined by ejection fraction, sex, race, cause of cardiomyopathy, presence/absence of implantable cardiac defibrillator or cardiac resynchronization therapy and ejection fraction. Freedom from device- or system-related complications was 99.6%, and freedom from pressure sensor failure was 99.9% at 1 year. The authors found that both HF hospitalizations and all-cause hospitalizations were significantly lower in the year following implantation of a PA pressure sensor to guide HF management. The magnitude of decrease in PA pressures was related to baseline PA pressures, with greatest

reductions in those with the highest pressures at baseline. Reductions in HF hospitalization were consistent across sex and race, across all EF ranges and in addition to best medical and rhythm device therapy.

DeFilippis et al. (2021) reported on a cohort of the above CardioMEMS Post-Approval Study (PAS) study (Shavelle, et al., 2020) to examine sex differences in response to ambulatory hemodynamic monitoring in clinical practice. Four hundred fifty-two women (38% of total) enrolled in the PAS were less likely to be White (78% versus 86%) and more likely to have non-ischemic cardiomyopathy (44% versus 34%) and had significantly higher systolic blood pressure (132 versus 124 mm Hg), mean ejection fraction (44% versus 36%), and pulmonary vascular resistance (3.2 versus 2.6 WU) than men (P<0.001 for all). Both sexes experienced significant decreases in heart failure hospitalizations (HFH) over 12 months. In adjusted models, there were no significant differences in change in HFH between men and women (interaction P=0.13) or all-cause mortality at one year.

Angermann et al. (2020) reported on a prospective, non-randomized, multicenter study (CardioMEMS European Monitoring Study for Heart Failure [MEMS-HF]) to evaluate the safety, feasibility, and performance of CardioMEMS™ HF system in Germany, The Netherlands, and Ireland. The study noted that previously, the findings have not been replicated in health systems outside the United States. The study included 234 NYHA class III patients (68 ± 11 years, 22% female, ≥1 HFH in the preceding year) from 31 centers that were implanted with a CardioMEMS sensor and underwent pulmonary artery pressure (PAP)-guided heart failure (HF) management. The co-primary outcomes were one-year rates of freedom from device- or system-related complications and from sensor failure and the results were 98.3% [95% confidence interval (CI) 95.8-100.0] and 99.6% (95% CI 97.6-100.0), respectively. Survival rate was 86.2%. The secondary endpoints was annualized HFH rate during 12 months after vs.12 months before implant and additional endpoints included: 12-month all-cause death rate; PAP change from baseline; changes in the KCCQ clinical and overall summary scores (CSS, OSS), 20 PHQ-9 sum score, 21 and EQ-VAS score 22 at six and 12 months; changes in HF medications and NYHA class at six and 12months; patient compliance with taking PAP readings, and healthcare provider compliance for weekly PAP readings. For the 12 months post- vs. pre-implant, HF hospitalizations (HFH) decreased by 62% (0.60 vs. 1.55 events/patient-year; hazard ratio 0.38, 95% CI 0.31-0.48; P < 0.0001). After 12 months, mean PAP decreased by 5.1 ± 7.4 mmHg, Kansas City Cardiomyopathy Questionnaire (KCCQ) overall/clinical summary scores increased (P < 0.0001), and the 9-item Patient Health Questionnaire sum score improved (P < 0.0001). The study is limited by the lack of randomization, and a control group, and use of within-patient comparisons.

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 short-term 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.

Abraham et al. (2016) examined the results of the above CHAMPION study (Abraham, et al., 2011) over 18 months of randomized follow-up and the clinical effect of open access to pressure information for an additional 13 months in patients formerly in the control group. The primary outcome was the rate of hospital admissions between the treatment group and control group in both the randomized access and open access periods. Analyses were by intention to treat. The study included 550 patients that were randomly assigned to either the treatment group (n=270) or to the control group (n=280). 347 patients (177 in the former treatment group and 170 in the former control group) completed the randomized access period, and transitioned to the open access period. Over the randomized access period, rates of admissions to hospital for heart failure were reduced in the treatment group by 33% (hazard ratio [HR] 0·67 [95% CI 0·55-0·80]; p<0·0001) compared with the control group. After pulmonary artery pressure information became available to guide therapy during open access (mean 13 months), rates of admissions to hospital for heart failure in the former control group were reduced by 48% (HR 0·52 [95% CI 0·40-0·69]; p<0·0001) compared with rates of admissions in the control group during randomized access. Eight (1%) device-related or system related complications and seven (1%) procedure-related adverse events were reported. The reduction in the need for admission to hospital, both all-cause and heart failure
related, seen during the first six months was maintained during longer randomized access follow-up and subsequently during open access in which adjustment of therapy was no longer monitored by study staff protocol.

Assad et al. (2019) conducted a retrospective chart review of patients with recurrent admissions for heart failure implanted with the wireless pressure monitoring system (CardioMEMS) at one institution. The study examined the total number of all-cause hospital admissions as well as heart failure-related admissions pre- and post-implantation. The study included 27 patients followed for 6-18 months. The total number of all-cause hospital admissions prior to device implantation was 61 admissions for all study patients, while the total number for the post-implantation period was 19, correlating with 2.26 + 1.06 admissions/person-year prior to device implantation versus 0.70 + 0.95 admissions/person-year post-implantation (p-value < 0.001). For heart failure-related admissions, the total number prior to device implantation was 46 compared to 9 admissions post device implantations, correlating with 1.70 + 1.07 admissions/person-years pre-implantation versus 0.33 + 0.62 admissions/person-years post-implantation (p-value < 0.001). This translates to 80.4% and 68.9% reduction in heart failure and all-cause admissions, respectively. The study is limited by the retrospective nature and the lack of randomization.

Tran et al. (2019) conducted a single center, retrospective study to assess how input from multiple independent elements and the CardioMEMs system and how this affects heart failure hospitalization (HFH). The primary outcome was the number of HFH days patients (n=78) experienced in the first year following CardioMEMS sensor implant. The primary independent

variables were the average number of days between patient transmissions of data and the average number of days between health care provider reviews of those data. Covariates included patient demographics, medical comorbidities, history of HFHs, and initial pressure response to hemodynamic-guided therapy at 28 days after implant. Data were fit to a zero-inflated negative binomial regression. The mean age was 64 ± 15 years, 52 (67%) were male, and 58 (76%) had heart failure with reduced ejection fraction. During the study period, there were 538 cumulative HFH patient-days. Based on the regression model, there was an exponential relationship between HFH days and the mean number of days between patient transmissions (p=0.019). There was also an exponential relationship between HFH days and the mean number of days between health care provider reviews (p=0.013). The authors concluded that the study suggests that more frequent patient transmissions and health care provider reviews of the CardioMEMS system are associated with a decreased number of HFH days, but larger multicenter studies are required.

Heywood et al. (2017) reported on a retrospective observational study that examined pulmonary artery (PA) pressure changes in the first 2000 US patients implanted in general practice use with at least 6 months of follow-up. Changes in PA pressures were evaluated with an area under the curve methodology to estimate the total sum increase or decrease in pressures (mm Hg-day) during the follow-up period relative to the baseline pressure. As a reference, the PA pressure trends were compared with the CHAMPION clinical trial (Abraham, et al. (2011/2016). The area under the curve results are presented as mean±2 SE, and P values comparing the area under the curve of the general-use cohort with outcomes in the CHAMPION trial were computed by the t test with equal variance. Patients were on average 70±12 years old; 60% were male; 34% had preserved ejection fraction; and patients were followed up for an average of 333±125 days. At implantation, the mean PA pressure for the general use patients was 34.9±10.2 mm Hg compared with 31.3±10.9 mm Hg for CHAMPION treatment and 32.0±10.5 mm Hg for CHAMPION control groups. The general-use patients had an area under the curve of −32.8 mm Hg-day at the 1-month time mark, −156.2 mm Hg-day at the 3-month time mark, and −434.0 mm Hg-day after 6 months of hemodynamic guided care, which was significantly lower than the treatment group in the CHAMPION trial. Patients consistently transmitted pressure information with a median of 1.27 days between transmissions after 6 months. The authors concluded that the first 2,000 general-use patients managed with hemodynamic-guided heart failure care had higher PA pressures at baseline and experienced greater reduction in PA pressure over time compared with the pivotal CHAMPION clinical trial.

In a subgroup analysis of the CHAMPION trial, Krahnke et al. (2015) compared HF and respiratory hospitalization rates in the entire CHAMPION cohort with the rates observed within the COPD and non-COPD subgroups. A total of 187 subjects met criteria for classification into the COPD subgroup. In the entire cohort, the treatment group had a 37% reduction in HF hospitalization rates (P<.0001) and a 49% reduction in respiratory hospitalization rates (P=.0061). In the COPD subgroup, the treatment group had a 41% reduction in HF hospitalization rates (P=.0009) and a 62% reduction in respiratory hospitalization rates (P=.0023). The rate of respiratory hospitalizations in subjects without COPD was not statistically different (P=.76). The authors stated that HF management incorporating hemodynamic information from an implantable PA pressure monitor significantly reduces HF and respiratory hospitalizations in HF subjects with comorbid COPD compared with standard care. The authors noted a limitation of this study was that pulmonary function test data were not available in this study and were not part of the COPD classification criteria.

Professional Societies/Organizations
The ACC/AHA/Heart Failure Society of America (HFSA) 2022 Guideline for the Management of Heart Failure Section 4.6. Wearables and Remote Monitoring (Including Telemonitoring and Device Monitoring), notes the following:

- In selected adult patients with NYHA class III HF and history of a HF hospitalization in the past year or elevated natriuretic peptide levels, on maximally tolerated stable doses of GDMT with optimal device therapy, the usefulness of wireless monitoring of PA pressure by an implanted hemodynamic monitor to reduce the risk of subsequent HF hospitalizations is uncertain (2b B-R).

- In patients with NYHA class III HF with a HF hospitalization within the previous year, wireless monitoring of the PA pressure by an implanted hemodynamic monitor provides uncertain value. (Value Statement: Uncertain Value, B-NR) (Heidenreich, et al., 2022).

  Class (Strength) of Recommendation:
  Class 1 (Strong) (is recommended)
  Class 2a (Moderate) (is reasonable)
  Class 2b (Weak) (may/might be reasonable)
  Class 3 No Benefit (Moderate) (is not recommended)
  Class 3 Harm (Strong) (potentially harmful)

  Level (Quality) of Evidence:
  Level A: High-quality evidence from more than one randomized clinical trial, Meta-analyses of high-quality randomized clinical trials, One or more randomized clinical trials corroborated by high-quality registry.
  Level B-R (Randomized): Moderate quality evidence from one or more randomized clinical trials, Meta-analyses of moderate-quality randomized clinical trials.
  Level B-NR (Nonrandomized); Moderate-quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies, Meta-analyses of such studies.
  Level C-LD (Limited Data); Randomized or nonrandomized observational or registry studies with limitations of design or execution, Meta-analyses of such studies, Physiological or mechanistic studies of human subjects.
  Level C-EO (Expert Opinion): Consensus expert opinion based on the clinical experience.

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Near-Infrared Guidance for Vascular Access Requiring Real-Time Digital Visualization for Evaluation of Potential Access Sites and Vessel Patency (CPT Code 99199)

A peripheral venous catheter is most commonly used for venous access. Traditional techniques for determining the location of a peripheral vein includes palpating 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. Also referred to as Veinsite, 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.

Hellovein website states Hellovein vein finder machine is a FDA Class I approved device.

There are numerous non-contact infrared devices developed to aid in the visualization of superficial vasculature. NextVein (NextVein LLC) website states that the "NextVein V800NV Project Vein Finder, as is true for most non-contact projection vein visualization systems, is a Class 1 510(k) exempt device in the US. As such, it does not require FDA approval". The website also states that the "NextVein device carries the same FDA registrations as the AccuVein AV500. (NextVein is not affiliated with AccuVein)".

Others NOT reflecting FDA-approval include but are not limited to:

- AccuVein® AV500 Vein Viewing System
- Aimvein™ (AimVein Pro, AimVein Go)
- VascuLuminator Vision®
- Vein Finder VF30
- Veinlite®
- VeinSight™ vein finder VS400
- VeinViewer® (VeinViewer® Vision2, VeinViewer® Flex)

Literature Review
The majority of published studies show success at the first IV attempt was not significantly different with the use of infrared devices.

Yalçınlı et al. (2022) conducted a RCT in a tertiary care hospital in Turkey. Emergency department patients who describe difficult vascular access (DVA) history, have no visible or palpable veins, and were assessed by the nurse to have a difficult peripheral intravenous catheter (PIVC) were included to study. The PIVC procedure was performed on patients by standard (n=90), ultrasonography (USG) (n=90), or near-infrared light (NIR) (n=90) device techniques. For all approaches, the success of the first attempt was the primary aim. This study evaluated 270 patients. The first attempt success rates for USG, standard, and NIR methods were 78.9%,

62.2%, and 58.9%, respectively. More attempts were performed in the infrared device group than in the ultrasound group. The authors concluded that USG increases the success of the first attempt compared with the standard method and NIR in patients with DVA.

Kleidon et al. (2021) conducted a meta-analysis on technologies proposed to improve peripheral intravenous catheterization (PIVC) outcomes in pediatric patients (first-time insertion success, overall insertion success, time to insertion, dwell time, failure, and complications). Twenty-one studies (3237 children; 3098 PIVCs) were included. Conventionally, PIVC insertion involved physical assessment through palpation and visualization (landmark approach). Difficult intravenous access (DIVA), were defined by study authors as age (0-3 years; >3 years up to 18 years); hospital setting during PIVC insertion (awake clinical environment vs awake emergency department vs asleep operating room setting); and by operator (bedside nurse, anesthesiologist).Results reported include that there was no evidence of an effect of near-infrared (compared with landmark) on first-time insertion success or number of attempts; however, it significantly reduced PIVC insertion time and increased first-time insertion success in subgroup analysis of patients with difficult intravenous access. First-time insertion success significantly increased with ultrasound guidance.

Inal et al. (2021) randomly studied 54 children aged 0 to 3 years who were inpatient and required peripheral intravenous catheterization (PIVC). The Study group (n=27) had AccuVeinAV400 Vein Visualization Device-supported PIVC. The Control group include 27 also. Reported results included the first attempt success rate in the study group (74.1%) was higher than in the control group (40.7%; P = 0.028).

Çağlar et al. (2019) randomly evaluated the AccuVein AV400 vein visualization device in 30 preterm infants. Inclusion criteria included: (a) were of 32 to 37 gestational weeks, (b) were not taking analgesic medications, and (c) had no previous peripheral intravenous catheterization [PIVC] placement. The transilluminator group (n = 30) used Wee-Sight Transilluminator vein visualization device (LED light). Control group also included 30 infants. Results reported include success of the first attempt was significantly higher in the infrared and transilluminator groups than in the control group (P ≤ .05).

Curtis et al. (2015) conducted a RCT on pediatric children, comparing standard approach, US-assisted and infrared-assisted vein location. The VeinViewer GS (Luminetx Corp.) was used for the near-infrared vascular imaging. A total of 418 children were stratified by age (≤ 3 yr and > 3 yr). Results showed that the rate of successful first attempts did not differ significantly between either of the 2 intervention groups and the standard approach. Among children 3 years and younger, the difference in success rates relative to standard care was significantly worse for near-infrared imaging. The authors stated their findings do not support investment in these technologies for routine peripheral intravenous catheterization in children.

de Graaff et al. (2013) conducted a RCT of three devices in 1913 children 0-18 years of age. Randomization included: Control group (n = 444); VeinViewer (n = 357); AccuVein (n = 292); VascuLuminator (n = 290). The authors concluded success at the first attempt was not significantly different among groups, ranging from 73.1% to 75.3% (p = 0.93) and stated that that although vein visibility is enhanced, near-infrared devices do not improve cannulation.

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)]. 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 in the intervention group and 1 min in the control group ($p< 0.01$). Median number of attempts was higher in the intervention group than in the control group ($p < 0.01$). The rate of cannulations successful at first attempt was 0.45 (51 of 114) in the intervention group and 0.73 (90 of 124) 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 retrospective design.

Van der Woude et al. (2013) reported results of a RCT 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. The authors stated that success at first attempt was not significant between the two groups ($p=0.27$).

Kim et al. (2012) evaluated a group of 111 children who were randomized into one of the two groups (VeinViewer, n=54) or control (n=57). There was no significant difference in the overall first attempt success rate using the VeinViewer compared with control ($p=0.526$).

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 ($p=0.55$).

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 (n=163) or PIV cannulation with the VeinViewer (Christie Medical Holdings) (n=160). No differences in time to PIV placement, number of PIV attempts or pain scores was noted for the overall study group.

Perry et al. (2011) conducted a prospective RCT to determine whether the use of a near-infrared light venipuncture aid (VeinViewer, Christie Medical Holdings) 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). There was no significant difference in first-attempt success rate between the standard and device groups.

Professional Societies/Organizations
No applicable guidelines found.

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Permanent Cardiac Contractility Modulation System (CPT Codes 0408T, 0409T, 0410T, 0411T, 0412T, 0413T, 0414T, 0415T, 0416T, 0417T, 0418T, HCPCS code C1824, K1030)

CCM® is the brand name for cardiac contractility modulation (CCM), the non-excitatory electrical pulses delivered by the implantable Optimzer device 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 comprised 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.

CCM® is the brand name for cardiac contractility modulation, the non-excitatory electrical pulses delivered by the implantable Optimzer device. Unlike a pacemaker or a defibrillator, the OPTIMIZER system is designed to control the strength of contraction of the heart muscle rather than the rhythm.

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%. On 07/30/2021, the FDA gave approval for commercial distribution of the OPTIMIZER SMART Mini System (P180036/S007).

On October 6, 2021, the FDA approved a modification of labeling for the Optimizer Smart medical device, giving approval for removing the Indications for Use requirement for patients to be in normal sinus rhythm (P180036/S008).

Literature Review

Long-term RCT data are lacking to demonstrate the impact of using the Optimizer Smart System on morbidity/mortality. Studies fail to demonstrate if cardiac contractility modulation-guided therapy impacts long-term outcomes/survival.

The 1500 patient AIM HIGHer trial (NCT05064709) is recruiting. The AIM HIGHer trial will assess the safety and efficacy of CCM therapy in patients with HFrEF and also in patients with HF with higher LVEFs (40%-60%).

Linde et al. (2022) conducted a prospective, multicenter, single-arm pilot study to evaluate the efficacy and safety of CCM (Optimizer device) in heart failure patients with preserved ejection fraction (HFpEF). Some of the inclusion criteria included:

- Baseline ejection fraction ≥50% (echocardiogram, as assessed by the site within 30 days of enrolment and confirmed by the core lab).
- NYHA class II or III symptoms despite receiving stable optimal medical therapya for at least 30 days based on patient's medical records (chronic stable, not transient or crescendo HF or angina pectoris).
- Stable optimal medical therapy for HF for 3 months.

There were 47 individuals who met all the eligibility criteria and were implanted at 17 sites in Europe and Australia and completed the 24-week follow-up study. No patient was lost to follow-up. Reported results include a significant improvement in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score from baseline to 24 weeks (18.0±16.6 points, $p<0.001$) (represents a 37% improvement from baseline). There were three procedure-related complications reported in three patients: two lead dislodgements and one worsening tricuspid regurgitation. The authors stated, "The current results are subject to the customary limitations of a pilot study: small sample size, single-arm design with no control group, and hence a potential role of placebo effect for the primary endpoint".

Akhtar et al. (2022) conducted a meta-analysis to review the effect of heart failure therapies on improvement in 6-minute walk distance (6MWD), which was analyzed across randomized controlled trials (RCTs) of drug-based therapy, device-based therapy, autonomic modulation, and exercise in patients with heart failure with reduced ejection fraction (HFrEF). The primary outcome was improvement in 6-minute walk distance (6MWD) at follow-up. A total of 4 studies with 847 patients with device-based intervention were identified. Included studies compared cardiac resynchronization therapy (CRT) and cardiac contractility modulation (CCM) with the control. Follow-up duration was six months, and the studies reported change in 6MWD. Overall results showed that device-based therapy (cardiac resynchronization therapy and cardiac contractility modulation), autonomic modulation, and exercise training programs are associated with improvement in 6MWD in patients with HFrEF.

Linde et al. (2022) conducted a prospective, multicenter study to assess the potential benefits of CCM in 47 patients with HF with preserved left ventricular (LV) EF (HFpEF). After CCM device implantation, patients were followed for 24 weeks. The primary efficacy endpoint, mean change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score, improved by 18.0 ± 16.6 points ($p<0.001$). This study is limited by small sample size and lack of comparison.

Fastner et al. (2021) published a retrospective analysis on 174 consecutive patients with chronic heart failure and CCM device implantation between 2002 and 2019, to compare the long-term therapeutic effects of CCM therapy in patients with ischemic (ICM) versus non-ischemic cardiomyopathy (NICM). Authors used data from the MAnnheim cardIac coNtracTility modulAtIoN obsErvational study (MAINTAINED) study in order to test for such differences in patients with ICM versus NICM. MAINTAINED is a single-center, observational study that retrospectively enrolled all patients with CCM device implantation. Before 2016, 3-lead Optimizer® II, III, or IVs systems were implanted; at later dates, 2-lead Optimizer® Smart devices were implanted. Baseline

characteristics: 170 (61%) had ICM whereas 67 patients (39%) had NICM. Patients generally had advanced symptoms, with 77% having NYHA class III, 13% having NYHA class IV and 11% having NYHA class II (p = 0.45 between groups).
There was loss to follow-up: 129 patients were available at 3 years and 84 patients available at 5 years.
LVEF improved significantly in both groups (each p < 0.01), while the comparison of changes yielded no statistically significant difference (p = 0.83). There was a mortality rate of 28 (NYHA II group) vs. 35% (NYHA III/IV group) in the overall follow-up period (p = 0.54).
Reported results include that LVEF was significantly higher in NICM patients after 3 years of CCM therapy (p = 0.0211), and after 5 years, also tricuspid annular plane systolic excursion (TAPSE) of NICM patients was significantly higher (p = 0.0437). There were no differences in other effectiveness parameters. Over the entire follow-up period, 35% of all patients died (p = 0.81); only in ICM patients, mortality was lower than predicted at 3 years (35 vs. 43%, p = 0.0395). The authors concluded that NICM patients can expect greater functional improvement in response to CCM therapy than ICM patients. Study limitations include retrospective design, change in number of leads, small sample size, with loss to follow-up.

Giallauria et al. (2020) performed an individual patient data meta-analysis of prospective trials of CCM that have measured functional capacity and/or quality of life questionnaires in patients with HF. Primary outcomes of interest were peak oxygen consumption (peak VO2), 6 min walk test distance, and quality of life (from established survey). Five trials were identified, four randomized studies enrolling 801 participants for all endpoints of interest, and for peak VO_2 alone (n = 60), there was an additional single arm non-randomized trial (FIX-HF-5C2) with a prospective comparison of its 24 week peak VO_2 data compared with the control group of the FIX-HF-5C control patients. Pooled analysis showed that, compared with control, CCM significantly improved peak VO_2 (P < 0.00001), 6 min walk test distance (P = 0.005), and quality of life measured by MLWHFQ (P < 0.00001). The authors noted study limitations include that the studies analyzed differed in study design limiting our ability to define representative results across different patient subgroups. They also noted that study cohorts are relatively young and predominantly male; therefore, future data would be needed in older individuals and in more women.

Kuschyk et al. (2020) a prospective registry study to assess long-term effects of cardiac contractility modulation delivered by the Optimizer Smart system on quality of life, left ventricular ejection fraction (LVEF), mortality and heart failure and cardiovascular hospitalizations. The study included 503 patients. Effects were evaluated in three terciles of LVEF (≤25%, 26–34% and ≥35%) and in patients with atrial fibrillation (AF) and normal sinus rhythm (NSR). Hospitalization rates were compared using a chi-square test. Changes in functional parameters of New York Heart Association (NYHA) class, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and LVEF were assessed with Wilcoxon signed-rank test, and event-free survival by Kaplan–Meier analysis. For the entire cohort and each subgroup, NYHA class and MLWHFQ improved at 6, 12, 18 and 24 months (P < 0.0001). At 24 months, NYHA class, MLWHFQ and LVEF showed an average improvement of 0.6 ± 0.7, 10 ± 21 and 5.6 ± 8.4%, respectively (all P < 0.001). LVEF improved in the entire cohort and in the LVEF ≤25% subgroup with AF and NSR. In the overall cohort, heart failure hospitalizations decreased from 0.74 [95% confidence interval (CI) 0.66–0.82] prior to enrolment to 0.25 (95% CI 0.21–0.28) events per patient-year during 2-year follow-up (P < 0.0001). Cardiovascular hospitalizations decreased from 1.04 (95% CI 0.95–1.13) events per patient-year prior to enrolment to 0.39 (95% CI 0.35–0.44) events per patient-year during 2-year follow-up (P < 0.0001). Similar reductions of hospitalization rates were observed in the LVEF, AF and NSR subgroups. Estimated survival was significantly better than predicted by the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score which predicted mortality at one and three years in the entire cohort and in the LVEF 26–34% and ≥35% subgroups. The study is limited by the lack of randomization and a control group.

Wiegn et al. (2020) conducted a prospective, multicenter, single-arm study (FIX-HF-5C2 study) to test the performance, safety, and clinical effects of the 2-lead Optimizer Smart System. A total of 60 patients were enrolled. Major criteria included:

- adult subjects with LVEF ≥25% and ≤45% by echocardiography (assessed by core laboratory);
- NYHA III or ambulatory IV symptoms despite 90 days of guideline-directed heart failure medical therapy (including implantable cardioverter defibrillator when indicated) that was stable for 30 days before enrollment;
- and, not indicated for cardiac resynchronization therapy.

Subjects were evaluated at baseline and again at 12 and 24 weeks after implant. The primary effectiveness end point was an assessment of exercise tolerance measured by peak volume rate of oxygen (VO_2) obtained on cardiopulmonary stress testing (CPX). Changes in peak VO2 from baseline to 24-week follow-up in subjects implanted with the 2-lead system were compared to the changes observed in control group subjects of the prior FIX-HF-5C study (Abraham, et al., 2018). A total of 55 subjects (91.7%) completed the 24-week CPX test. In addition, four 24-week CPX tests were deemed inadequate by the core laboratory for which the patients declined requests to repeat testing, resulting in 52 tests for the primary end point analysis. However, to ensure robustness of findings, an additional analysis was performed that included these inadequate tests. Report results included that baseline characteristics were similar between FIX-HF-5C and FIX-HF-5C2 subjects except that 15% of FIX-HF-5C2 subjects had permanent atrial fibrillation versus 0% in FIX-HF-5C. CCM delivery did not differ significantly between 2- and 3-lead systems. The change of peak VO2 from baseline to 24 weeks was 1.72 mL/kg per minute greater in the 2 lead device group versus controls. 83.1% of 2-lead subjects compared with 42.7% of controls experienced ≥1 class New York Heart Association improvement (P<0.001). There were decreased Optimizer-related adverse events with the 2-lead system compared with the 3-lead system (0% versus 8%; P=0.03).
Study limitations include small sample size, loss to follow-up, lack of randomization, and use of a historical control group.

Mando et al. (2019) performed a meta-analysis of the randomized clinical trials (RCTs) to assess the efficacy and safety of CCM therapy. Outcomes of interest were peak oxygen consumption (peak VO2), 6-Minute Walk Distance (6MWD), Minnesota Living with Heart Failure Questionnaire (MLHFQ), HF hospitalizations, cardiac arrhythmias, pacemaker/ICD malfunctioning, all-cause hospitalizations, and mortality. Data were expressed as standardized mean difference (SMD) or odds ratio (OR). Four RCTs including 801 patients (CCM n = 394) were available for analysis. The mean age was 59.63 ± 0.84 years, mean ejection fraction was 29.14 ± 1.22%, and mean QRS duration was 106.23 ± 1.65 msec. Mean follow-up duration was six months. CCM was associated with improved MLWHFQ (p = 0.0008). There were no differences in HF hospitalizations (p = 0.12), 6MWD (p = 0.10), arrhythmias (p = 0.14), pacemaker/ICD malfunction/sensing defect (p = 0.06), all-cause hospitalizations (p = 0.33), or all-cause mortality (p = 0.92) between the CCM and non-CCM groups. The authors concluded that short-term treatment with CCM may improve MLFHQ without significant difference in 6MWD, arrhythmic events, HF hospitalizations, all-cause hospitalizations, and all-cause mortality and that there is a trend towards increased pacemaker/ICD device malfunction. They noted that larger RCTs may be needed to determine if the CCM therapy will be beneficial with longer follow-up.

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% ≤ left ventricular ejection fraction (LVEF) ≤ 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% ≤ LVEF ≤ 45% (CCM-REG35-45) and 25% ≤ 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 (the FIX-HF-5C 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 ≥25% and ≤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 Vo_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. The difference in peak Vo_2 between groups was 0.84 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 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 ≥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 ≥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.

Röger et al. (2017) conducted a prospective blinded randomized trial including 48 patients to compare the efficacy and safety of CCM when the signal is delivered through one vs. two ventricular leads. Patients had symptomatic heart failure (NYHA Classes II–III) and reduced left ventricular ejection fraction. All patients received a CCM system with two ventricular leads and were randomized to CCM active through both or just one ventricular lead; 25 patients were randomized to receive signal delivery through two leads (Group A) and 23 patients to signal delivery through one lead (Group B). The study compared the mean changes from baseline to 6 months follow-up in peakVO_2, NYHA classification, and quality of life (by MLWHFQ). The efficacy and safety of CCM in this study were similar when the signal was delivered through either one or

two ventricular leads. The authors noted their results support the potential use of a single ventricular lead for delivery of CCM.

Kadish et al. (2011) conducted a randomized controlled trial (FIX-HF-5 trial) to test the longer-term safety and efficacy of CCM treatment. The study tested CCM in 428 New York Heart Association class III or IV, narrow QRS heart failure patients with ejection fraction (EF) ≤ 35% randomized to optimal medical therapy (OMT) plus CCM (n = 215) versus OMT alone (n = 213). Efficacy was assessed by ventilatory anaerobic threshold (VAT), primary end point, peak Vo_2 (pVo_2), and Minnesota Living with Heart Failure Questionnaire (MLWFQ) at six months. The primary safety end point was a test of non-inferiority between groups at 12 months for the composite of all-cause mortality and hospitalizations (12.5% allowable delta). The groups were comparable for age, EF, pVo_2 and other characteristics. While VAT did not improve at six months, CCM significantly improved pVo_2 and MLWHFQ [P = .024] and [P < .0001], respectively) over OMT. Forty-eight percent of OMT and 52% of CCM patients experienced a safety end point, which satisfied non-inferiority criterion (P = .03). Post hoc, hypothesis-generating analysis identified a subgroup (characterized by baseline EF ≥ 25% and New York Heart Association class III symptoms) in which all parameters were improved by CCM. The authors noted that based on the prespecified primary end point, CCM efficacy was not demonstrated and further studies will be required to determine the role of CCM in the treatment of patients with medically refractory heart failure.

Professional Societies/Organizations
The AHA/ACC/HFSA Guideline for the Management of Heart Failure (Heidenreich, et al., 2022) states:

> 7.4.2. Other Implantable Electrical Interventions
> Cardiac contractility modulation (CCM), a device-based therapy that involves applying relatively high-voltage, long duration electric signals to the RV septal wall during the absolute myocardial refractory period, has been associated with augmentation of LV contractile performance. CCM is FDA-approved for patients with NYHA class III with LVEF of 25% to 45% who are not candidates for CRT. Four RCTs have shown benefits in exercise capacity and QOL but, as of yet, no benefits in death or hospitalizations (Abraham, et al., 2018; Kadish et al., 2011; Borggrefe, et al., 2008; Neelagaru, et al., 2006). Most patients in these trials were class III CHF.

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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. Impedance cardiography is utilized in the research setting.

The use of ICG has been proposed for multiple clinical purposes but primarily for use in heart failure patients. 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 ICG 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.

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 thoracic electrical bioimpedance or impedance cardiography (ICG) in the evaluation of patients with acute heart failure syndromes is still under investigation. Studies demonstrating the direct impact of ICG use — as a stand-alone or additional tool — on patient management and long-term health outcomes are needed.

Krzesinski et al. (2022) conducted a RCT to assess whether an outpatient 12 month telecare program based on nurse-led non-invasive assessments could improve clinical outcomes in 300

patients after an episode of acute heart failure, compared to standard care (n = 305). As part of the periodic nurse assessments, impedance cardiography (ICG) (Cardioscreen 2000, Medis, Ilmenau, Germany) was utilized, along with:

- BMI
- body composition analysis / total body water
- heart rate
- systolic and diastolic blood pressure
- thoracic fluid content
- assessment of symptoms including but not limited to:
  - breathlessness
  - orthopnea
  - nocturnal cough
  - wheezing
  - loss of appetite
  - palpitations
  - syncope,
  - weight gain (>2 kg/week)
  - peripheral edema
  - ascites
  - tachypnea

The primary composite outcome of unplanned HF hospitalization or cardiovascular death occurred in 51 (17.1%) patients in the telecare group and 73 (23.9%) patients in the standard care group up to 12 months after randomization (P = 0.044). The direct impact of ICG use as an additional tool on long-term health outcomes was not reported.

Ališauskas et al. (2022) conducted a prospective study between 2019 and 2022 in a single center in Lithuania to evaluate the role of transthoracic impedance cardiography (ICG) in the diagnosis and outcome evaluation of patients who were admitted to the hospital due to HF exacerbation. ICG parameters were recorded immediately after TTE, using a Niccomo™ transthoracic ICG monitor on the last day of patient's in-hospital treatment. A total of 301 consecutive patients with a previous chronic HF diagnosis (166 men, 135 women) admitted to the hospital due to CHF flare-ups. Throughout a median follow-up period of 17 months, there were 128 deaths due to cardiac death in total (42.5%). Ališauskas et al. reported a weak correlation of amino-terminal pro-brain natriuretic peptide (NT-proBNP) with thoracic fluid content (TFC) and thoracic fluid content index (TFCI) was found. There was weak to moderate correlation of 6-min walk distance with main ICG data. There was weak correlation between left ventricular ejection fraction (LVEF) with TFCI, systolic index, and systolic time ratio. The authors concluded the major finding of the present study was that parameters such as TFC ≥36.9 1/kOhm, LVEF ≤40%, and NT-proBNP ≥425.5 pmoL/L were powerful and independent prognostic markers of worsening of HF and increased mortality. The authors noted several study limitations including but not limited only hospitalized patients with moderate to severe HF were included and patients with stable HF were not enrolled. The authors noted that ICG produces controversial data in both diagnostic and prognostic fields; therefore, clinicians cannot rely solely on ICG data.

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 impedance cardiography (ICG) in patients hospitalized with heart failure; the BioImpedance CardioGraphy in Advanced Heart Failure (BIG) substudy from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial. The BIG study was a prospective substudy of a RCT. 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 ($\kappa \leq 0.1$). 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 ($P=0.001$). 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, 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 cannot 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," Packer et al. (2006) 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).

Professional Societies/Organizations

The ACC/AHA Guideline for the Management of Heart Failure (Heidenreich, et al., 2022) notes the following:

- Results from previous clinical trials do not support the alternative remote monitoring strategies (e.g., noninvasive telemonitoring or remote monitoring of physiological parameters such as patient activity, thoracic impedance, heart rate) for this purpose.
- The usefulness of noninvasive telemonitoring or remote monitoring of physiological parameters (e.g., patient activity, thoracic impedance, heart rate) via implanted electrical devices (ICDs or CRT-Ds) to improve clinical outcomes remains uncertain.

The following guidelines do not address recommendations regarding thoracic electrical bioimpedance [TEB] or impedance cardiography [ICG]:

- 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization
- 2021 AHA/ACC/ASE/CHEST/SAEM/ SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain
- 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease
- 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy
- 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation
- 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease
- 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults
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Coronary intravascular lithotripsy (CPT code 0715T, HCPCS code C1761)

Debulking techniques are often necessary for successful lesion preparation in percutaneous coronary intervention (PCI). Rotational atherectomy (RA) is the current gold-standard treatment for severely calcified lesions. Coronary intravascular lithotripsy (IVL) has been proposed for vessel preparation in the presence of coronary artery calcification prior to stent delivery to open the coronary arteries that are narrowed or blocked due to calcification. IVL uses acoustic (sound) pressure shockwaves to break up calcifications.
In contrast to ultrasound technologies which are characterized by low amplitude but very high frequency waveforms, an acoustic pressure shockwave has a very high amplitude but low frequency.

U.S. Food and Drug Administration (FDA)
February 2021, the FDA granted premarket approval (PMA) for Shockwave Intravascular Lithotripsy (IVL) System with the Shockwave C2 Coronary Intravascular Lithotripsy (IVL) Catheter (Shockwave Medical, Inc., Santa Clara, CA). The device is indicated for lithotripsy-enabled, low-pressure balloon dilatation of severely calcified, stenotic de novo coronary arteries prior to stenting.

Contraindications for Use:
The Shockwave C2 Coronary IVL System is contraindicated for the following:
- This device is not intended for stent delivery.
- This device is not intended for use in carotid or cerebrovascular arteries.

The Shockwave Intravascular Lithotripsy (IVL) System consists of the Shockwave C2 Coronary IVL Catheter, the IVL Generator, the IVL Connector Cable, and its accessories. The Shockwave C2 Coronary IVL Catheter is used exclusively with these other components. The IVL Connector Cable is a remote actuator which connects the IVL Generator to the IVL Catheter and is used to activate the lithotripsy therapy from the IVL Generator.

Literature Review
There is a lack of large, randomized trials comparing long term outcomes of IVL versus standard rotational atherectomy (RA).

Oomens et al. (2023) conducted a small, single-center RCT (EXIT-CALC trial) to investigate if pre-treatment with IVL in severely calcified lesions increases stent expansion, assessed by optical coherence tomography (OCT), when compared to predilatation with conventional angioplasty

balloons (scoring- / high pressure- / cutting balloons).
A total of 40 patients were randomized to the IVL group (n = 19) and the conventional group (n=21). The inclusion criteria were:

1) indication for PCI of a calcified lesion in a native coronary artery;
2) optical coherence tomography (OCT)- derived calcium score of 4, defined as a maximum calcium angle of >180◦, maximum calcium thickness > 0.5 mm, and a minimal calcium length of 5 mm, as measured at the target lesion);
3) target vessel reference diameter between 2.5 and 4.0 mm (by visual estimation).

Primary endpoint was stent expansion assessed by OCT. Secondary endpoints were the occurrence of peri-procedural events and major adverse cardiac events (MACE) in hospital and during follow-up. Patients were contacted by telephone at 30-days, 1-year and 2-years after randomization. However, true follow-up timeframes are unclear. OCT was performed after pre-treatment and was successful in 38 patients; in both groups 1 OCT run was insufficient for analysis. The authors reported found no significant difference in minimal stent expansion after plaque modification using IVL or conventional predilatation, in patients with prespecified severe coronary artery disease assessed by OCT. No peri-procedural, in-hospital and 30-day follow-up MACE were reported. Limitations of this study include unclear follow-up timeframes and small sample size

The Disrupt CAD III study (NCT03595176) is prospective, single-arm multicenter study designed for regulatory approval (FDA) of coronary IVL with the purpose to assess the safety and effectiveness of IVL in severely calcified de novo coronary lesions. The primary safety endpoint was freedom from major adverse cardiovascular events (MACE) (cardiac death, myocardial infarction, or target vessel revascularization). Follow-up is scheduled by clinic or telephone visit at 30 days and at 6, 12, and 24 months. According to Kereiakes et al. (2022), 47 patients reported 30 day results (Hill et al. 2020) and follow-up through one year was completed in 97.1% of patients (n=373). There were 384 patients in the intention-to-treat dataset for the primary and secondary endpoint analyses. The primary safety endpoint (freedom from 30-day MACE) was achieved in 92.2% of patients (Hill et al. 2020). The primary effectiveness endpoint (stent delivery with a residual stenosis <50% without in-hospital MACE) was achieved in 92.4% of patients. MACE and target lesion failure (TLF) through 30 days occurred in 7.8% and 7.6% of patients, respectively, and was primarily driven by target vessel MI.
At 1 year, Kereiakes et al. (2022) reported MACE occurred in 13.8% of patients (cardiac death: 1.1%, MI: 10.5%, ischemia-driven target vessel revascularization: 6.0%) and target lesion failure occurred in 11.9% (ID-TLR: 4.3%), both driven by non-Q-wave MI (9.2%). Stent thrombosis (definite or probable) occurred in 1.1% of patients (including 1 event [0.3%] beyond 30 days). The study limitations include the lack of randomization and a control group. The author state that randomized studies would be required to compare the impact of IVL treatment versus other calcium-modifying technologies on longer term outcomes. Second, multiple angiographic and patient demographic subsets were excluded per protocol which limits broader generalization of the observations to a "real-world," all-comers population. These groups include biomarker-positive acute coronary syndromes, severe renal insufficiency, extreme target vessel tortuosity, or unprotected left main, ostial, and saphenous vein bypass graft target lesions.

Honton et al. (2022) reported on a prospective multicenter observational study including 202 consecutive patients (220 lesions). Most patients presented de-novo calcified coronary lesions (DNL) (n = 170; 77.3%) whereas intra-stent restenosis (ISR) related to device underexpansion represented the other 50 patients of the cohort (22.7%). The primary effectiveness endpoint was procedural success, defined as <30% residual stenosis without severe angiographic complications and one year outcomes. On the overall cohort of 202 patient, 7 (3.4%) patients were lost at 12 months follow-up. The rate of MACE-free survival at 1 year was 86.6% in the overall cohort. Rates of target vessel (TVR) and lesion (TLR) revascularization were 6.4% and 2.5%, respectively. The 1-year MACE rate was 91.5% in DNL group and 83.8% in ISR group. Procedural success was

achieved in 95.5% of patients (DNL group: 96.5%; ISR group: 92.0%). In-hospital MACE occurred in 6.4% of cases, mainly driven by periprocedural infarctions. The authors noted that there was no comparative arm and that further studies will be needed comparing IVL with other devices dedicated to plaque preparation.

Leick et al (2023) reported on a prospective, observational study based on an all-comers registry that included consecutive patients with moderate or severe coronary calcification. The authors compared the effectiveness and safety of intravascular lithotripsy (IVL) (n = 86) (Shockwave C2) to that of modified balloon angioplasty (MB) (n = 92) (WOLVERINETM Cutting Balloon™). This all-comers registry included consecutive patients with moderate or severe coronary calcification. The primary endpoint was strategy success (<20% residual stenosis). The secondary endpoint was long-term safety outcomes [cardiac death, acute myocardial infarction (AMI), target lesion failure/ revascularization (TVR)]. Quantitative coronary angiography (QCA) was performed in all patients. Primary and secondary endpoints were compared using inverse probability of treatment weighting (IPTW) for treatment effect estimation. Propensity score matching was waived in order to maintain the sample size; IPTW was applied as an alternative approach. The presence of acute coronary syndrome at the time of admission was less frequent in the IVL group (p = 0.023). In-stent restenosis (ISR) lesions were less frequent in patients treated with IVL (p = 0.001). One patient was lost to follow-up. For all other patients, a follow-up period of at least 450 days was available. The primary endpoint was reached in 152 patients (85.4%) (IVL: 94.2% vs. MB 77.2%; p = 0.001). Five (5.8%) patients in the IVL group had residual stenosis vs. 21 (22.8%) in the MB group (p = 0.001) in quantitative coronary angiography (QCA). The authors concluded that lesion preparation with IVL resulted in a significantly lower rate of residual stenosis than MB angioplasty. During the follow-up period (450 days) there was no difference in cardiovascular mortality rate. The authors noted that randomized trials, which can overcome the selection bias inherent in all-comers registries are needed to compare different lesion preparation methods with IVL.

Sardella et al 2023 conducted a prospective, multicenter, observational study (Rota-Shock or ROTA.Shock registry) to evaluate the efficacy and safety of coronary IVL AFTER rotational atherectomy (RA) in consecutive lesions with severe coronary artery calcification (CAC). Primary efficacy end point was procedural success, defined as final diameter stenosis <30% by quantitative coronary angiography. Primary safety endpoint was freedom from serious angiographic complications. Clinical follow-up was limited to in-hospital outcomes. A total of 160 patients were enrolled with the primary efficacy end point was observed in 155 patients (96.9%). The primary safety end point occurred in 145 cases (90.6%). The authors concluded the following: more than a half of patients underwent IVL after RA failure, IVL as elective or bail-out strategy after RA was found to be effective in terms of procedural success, considering the complexity of lesions treated, the incidence of serious angiographic complications was generally low, with excellent in-hospital outcomes, and the incidence of in-hospital MACCE was low. This study has several limitations including that clinical follow-up was limited to in-hospital events, a small sample size, absence of a control group, and a primary efficacy endpoint of procedural success alone.

Ali et al. (2019) conducted a prospective multicenter, single-arm post-approval study to confirm the safety and effectiveness of IVL for modification of severe coronary artery calcification (CAC) (Disrupt CAD II study). The study included 120 patients with severe CAC with a clinical indication for revascularization who underwent vessel preparation for stent implantation with IVL. The primary end point was in-hospital major adverse cardiac events (cardiac death, myocardial infarction, or target vessel revascularization). An optical coherence tomography substudy was performed to evaluate the mechanism of action of IVL, quantifying CAC characteristics and calcium plaque fracture. Independent core laboratories adjudicated angiography and optical coherence tomography, and an independent clinical events committee adjudicated major adverse

cardiac events. Severe CAC was present in 94.2% of lesions. Successful delivery and use of the IVL catheter was achieved in all patients. The post-IVL angiographic acute luminal gain was 0.83±0.47 mm, and residual stenosis was 32.7±10.4%, which further decreased to 7.8±7.1% after drug-eluting stent implantation. The primary end point occurred in 5.8% of patients, consisting of 7 non-Q-wave myocardial infarctions. There was no procedural abrupt closure, slow or no reflow, or perforations. In 47 patients with post-percutaneous coronary intervention optical coherence tomography, calcium fracture was identified in 78.7% of lesions with 3.4±2.6 fractures per lesion, measuring 5.5±5.0 mm in length. The authors concluded that in patients with severe CAC who require coronary revascularization, IVL was safely performed with high procedural success and minimal complications and resulted in substantial calcific plaque fracture in most lesions, procedural success with low MACE rates in severely calcified lesions in a Japanese population. The study was limited by lack of randomization and lack of a concurrent control group.

Saito et al. (2022) reported on the Disrupt CAD IV trial (NCT04151628), a prospective single-arm multicenter study of IVL performed in a Japanese population with severe coronary artery calcification. There were 72 patients scheduled for PCI who presented with stable, unstable, or silent ischemia, and severely calcified de novo coronary artery lesions, with target lesion length ≤40 mm and target vessel reference diameter between 2.5 and 4.0 mm. Patients with New York Heart Association Class III or IV heart failure, renal failure, active systemic infection, uncontrolled diabetes, uncontrolled severe hypertension, or recent myocardial infarction (MI), stroke, or transient ischemic attack were excluded. A total of 64 patients were available for one year follow up. In all cases, coronary IVL was successfully delivered, and stent placement was successful. The cumulative incidence of events through 1 year of follow-up was 9.4% for MACE, 6.3% for TLF, 4.7% for TVR, and 1.6% for ID-TLR, all of which occurred in 6 patients. No death or stent thrombosis events occurred at 1 year and no MI events occurred after discharge because all 4 MI events were in hospital. The authors concluded favorable safety and effectiveness was observed with coronary IVL through 30 days are durably maintained over 1 year. This was evident by an absence of post-discharge MI, death, or stent thrombosis through 1 year, only 3 (4.7%) TVR procedures through 1 year, and complete resolution of angina in approximately 90% of patients. Limitations noted by the authors include a lack of comparison of IVL to other modalities for vessel preparation, such as atherectomy, in prospective trials, which may complicate the interpretation of comparative results. Furthermore, the adjunctive use of atherectomy in conjunction with coronary IVL was not evaluated in the present study. Complementary use of IVL with atherectomy to treat specific complex coronary lesions warrants further investigation.

Cubero-Gallego et al. (2020) reported on a prospective, multicenter registry study that reports the initial experience of treatment of calcified lesions with coronary lithoplasty (CL) in an unselected and high-risk population. The study included 57 (66 lesions). Patients that were all consecutive cases with calcified coronary lesions that underwent CL between August, 2018 and August, 2019. The exclusion criteria consisted of a target lesion located in a small vessel (< 2.5mm) and the presence of dissection prior to CL. Quantitative coronary angiography and intravascular ultrasound/optical coherence tomography analysis were completed by an independent central core laboratory. The population was elderly (72.6±9.4 years) with high proportions of patients with diabetes (56%), chronic kidney disease (35%), and multivessel disease (84%). All lesions were classified as type B/C. More than 75% of lesions were predilated with noncompliant/semicompliant balloons or cutting-balloon. Rotablator was used in 5 lesions (7.6%) prelithoplasty. On average, CL required 1.17 balloons delivering a mean of 60 pulses. Successful CL was achieved in 98%. In 13% of cases, lithoplasty balloon was broken during therapy. There were few procedural complications: 2 cases of significant dissections (none related to lithoplasty balloon rupture) were successfully treated with drug-eluting stent implantation. One patient experienced stent thrombosis 2 days after successfully undergoing target lesion revascularization. The authors concluded that the study supports the feasibility, safety, and short-term efficacy of PCI for calcified coronary lesions using CL in an unselected and high-risk population with promising

results. The authors notes that this is an observational study, not a randomized controlled study, with the sample size was relatively small, with a short follow-up time, absence of a comparison group, with heterogeneity of lesions included and with self-reporting of events and that larger multicenter registries with long-term follow-up are required to clarify the role of plaque modification using CL.

Basavarajaiah et al. (2022) reported 23 month results from a retrospective registry of 273 patients from eight European centers. Patients with significant coronary stenosis (>70% on angiography or hemodynamically significant on invasive pressure wire assessment) underwent IVL; 43% had previous PCI. Use of any adjuvant equipment to prepare the lesions (scoring/cutting balloons and/or rotational atherectomy) was at the discretion of the operator, as was subsequent treatment with drug-eluting stents (DES) or drug-coated balloons (DCB).Intravascular imaging was used in 33% (n = 90) of patients. An upfront IVL strategy was adopted in 34% (n = 92), while the rest were bailout procedures. Adjuvant rotational atherectomy ("RotaTripsy") was required in 11% (n = 31) of cases. The procedural success was 99%.
The median follow-up was 687 days (22.9 months) (interquartile range: 549–787).
Cardiac death occurred in 5% (n = 14), TVMI in 3% (n = 8), TLR in 6% (n = 16), and MACE rate was 11% (n = 30). Study limitations include lack of prospective design, lack of a comparator with standard of care.

El Jattari et al. (2022) reported on a prospective registry of observational data obtained from five Belgium facilities. However, follow-up was performed by medical record review. The purpose was to gain insight into the treatment of heavily calcified lesions in a real-world setting, including its use for in-stent restenosis (ISR), which is considered off-label use. The registry included 134 IVL procedures. The indications for coronary angiography (CAG) were diverse (stable angina in 44%, acute coronary syndrome in 33.6%, and silent ischemia in 22.4% of cases). IVL was used to treat de novo lesions in 70.1% of cases and to treat in-stent (re)stenosis in 29.9% of cases.
The primary endpoint was final overall procedural success, which was obtained in 88.1% of cases, an aggregate of 92.6% in de novo lesions and 77.5% in stent underexpansion or in-stent restenosis (ISR). The 1-month major adverse cardiovascular event (MACE) rate was 4 deaths (3%), including 2 cardiovascular deaths (1 in-stent thrombosis and 1 coronary artery perforation). This study had small patient enrollment and lacked long term outcomes.

Rola et al. (2023) reported on a retrospective registry including 131 consecutive patients from two centers who underwent IVL. The two main inclusion criteria the presence of: calcified, resistant lesion (defined by an inadequate non-complaint balloon catheter inflation) or a significantly under-expanded stent (more than 20% of reference diameter). The study had two primary endpoints - successful clinical outcome and safety concerns. Clinical success was defined as effective stent deployment or optimization of a previously under-expanded stent (with less than <20% in-stent residual stenosis). At the 6-month-follow-up, the major adverse cardiac and cerebrovascular events (MACCE) rate was 7.9% with a concomitant target lesion revascularization (TLR) rate of 3.8%. The author noted that if they exclude patients who underwent IVL procedure for post-stenting optimization, the TLR would decrease to 2%. The authors conclude that their mid-term data confirms an acceptable safety and efficacy of intravascular lithotripsy as a valuable strategy for lesion preparation and stent optimization in an all-comers cohort with severely calcified coronary lesions. Limitations of this study include short follow-up, small sample size, and its retrospective method.

Takahashi et al. (2023) retrospectively reported on 109 consecutive patients who underwent IVL at two US facilities to evaluate the complementary utility and safety of IVL with atheroablative devices for the treatment of severely calcified lesions in contemporary, real-world practice.
A total of 33 patients (30.3%) were treated with both IVL and atherectomy and had higher risk features. Patients had severely calcified de novo lesions as well as calcific under-expanded stents.

High prevalence of previous revascularization (58.7%) and LVEF ≤50% (41.3%) was observed, with two-thirds of the included patients presenting with acute coronary syndrome. IVL patients were divided into 2 groups based on the combination of different tools: (1) patients treated with the combined use of IVL and atherectomy; and (2) those treated with non-atherectomy approaches (ie, IVL and balloon angioplasty).
Clinical outcomes through 30 days were available in 104 patients (95.4%). The cumulative incidence of MACE at 30 days was 4.8% (5 patients) including 3 deaths in the combined group (2 cardiac and 1 non-cardiac deaths) and 1 cardiac death and 1 MI in the non-atherectomy group. There was no TVR within 30 days after the index procedure. The authors concluded that procedural success and complications were similar in patients undergoing IVL with and without atherectomy when treating calcified de novo lesions. Those who required a combined approach represented a high-risk population with high mortality, suggesting that a multidisciplinary approach is needed to optimize case selection and care beyond PCI. Two limitations of this study include its retrospective design as well as short follow-up period.

Mhanna et al. (2021/2022) conducted a meta-analysis of studies to evaluate the utility of adjunctive intravascular lithotripsy (IVL). The primary outcomes of our study were the clinical success, defined as the ability of IVL to produce residual diameter stenosis <50% (RDS < 50%) after stenting with no evidence of in-hospital major adverse cardiac events, and the angiographic success, defined as success in facilitating stent delivery with RDS < 50% and without serious angiographic complications. The secondary outcomes included post-IVL and post-stenting changes in lumen area, calcium angle, and the maximum calcium thickness. Proportional analysis was used for binary data and mean difference was used for continuous data. All meta-analyses were conducted using a random-effect model and 95% confidence intervals (CIs) were included. The review included eight single-arm observational studies, with 980 patients (1011 lesions) (6 prospective, 2 retrospective). Acute coronary syndrome was present in 48.8% of the patients and severe calcifications were present in 97% of lesions. Clinical success was achieved in 95.4% of patients. Angiographic success was achieved in 97% of patients. There was an overall increase in postprocedural lumen area as well as significant reduction of calcium angle and maximum calcium thickness. The authors concluded that while IVL seems to have efficacy and safety in the management of calcified coronary lesions, adequately powered RCTs are needed to evaluate IVL compared to other calcium/plaque modifying techniques.

Professional Societies/Organizations
The 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization includes two 'Recommendations for the Treatment of Calcified Lesions':

- In patients with fibrotic or heavily calcified lesions, plaque modification with rotational atherectomy can be useful to improve procedural success (2a B-R).
- In patients with fibrotic or heavily calcified lesions, plaque modification with orbital atherectomy, balloon atherotomy, laser angioplasty, or intracoronary lithotripsy may be considered to improve procedural success (2b B-NR).

In the Background, the ACC states "Other potentially emerging modalities include intracoronary lithotripsy (Kereiakes, et al., 2021; Ali, et al., 2019)".

Class (Strength) of Recommendation:
Class 1 (Strong) (is recommended)
Class 2a (Moderate) (is reasonable)
Class 2b (Weak) (may/might be reasonable)
Class 3 No Benefit (Moderate) (is not recommended)
Class 3 Harm (Strong) (potentially harmful)

Level (Quality) of Evidence:
Level A: High-quality evidence from more than one randomized clinical trial, Meta-analyses of high-quality randomized clinical trials, One or more randomized clinical trials corroborated by high-quality registry.
Level B-R (Randomized): Moderate quality evidence from one or more randomized clinical trials, Meta-analyses of moderate-quality randomized clinical trials.
Level B-NR (Nonrandomized); Moderate-quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies, Meta-analyses of such studies.
Level C-LD (Limited Data); Randomized or nonrandomized observational or registry studies with limitations of design or execution, Meta-analyses of such studies, Physiological or mechanistic studies of human subjects.
Level C-EO (Expert Opinion): Consensus expert opinion based on the clinical experience.

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

CPT®* Codes	Description
34717	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)

Cardiovascular Services Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
33289	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
34718	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 distally in the internal iliac, external iliac, and common femoral artery(ies), and treatment zone angioplasty/stenting, when performed, for other than rupture (eg, for aneurysm, pseudoaneurysm, dissection, arteriovenous malformation, penetrating ulcer), unilateral
0408T	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
0409T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only
0410T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only
0411T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only
0412T	Removal of permanent cardiac contractility modulation system; pulse generator only
0413T	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)
0414T	Removal and replacement of permanent cardiac contractility modulation system pulse generator only
0415T	Repositioning of previously implanted cardiac contractility modulation transvenous electrode (atrial or ventricular lead)
0416T	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator
0417T	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
0418T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system
0715T	Percutaneous transluminal coronary lithotripsy (List separately in addition to code for primary procedure)

HCPCS Codes	Description
C1761	Catheter, transluminal intravascular lithotripsy, coronary
C1824	Generator, cardiac contractility modulation (implantable)

HCPCS Codes	Description
C2624	Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components
K1030	External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only

Cardiovascular Services Not Covered or Reimbursable

CPT®* Codes	Description
93701	Bioimpedance-derived physiologic cardiovascular analysis
99199	Unlisted special service, procedure or report

***Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.**

Endocrinology

Radiofrequency Ablation (RFA) Thyroid Nodules (CPT code 60699)

Radiofrequency ablation (RFA) of thyroid nodules is the application of radiofrequency waves to cause thermal injury and subsequent necrosis of the tissue. Gradual reabsorption of the ablated tissue results in overall volume reduction of the thyroid nodules. RFA of thyroid nodules was first used in 2002. RFA was not approved in the United States until 2018; therefore, RFA has not been commonly used in the United States. Many centers in the United States are establishing RFA programs, and it appears that RFA may be increasing in use as expertise in the technique is developed.

U.S. Food and Drug Administration (FDA)

No information on RFA for benign thyroid nodules is found on the FDA website when searched. A search of other websites and articles suggest the FDA approved RFA for use on benign compressive thyroid nodules in 2018.

Literature Review—Systematic Reviews

Benign: He et al. (2021) conducted a systematic review the literature of ultrasound guided ablation for solid/cyst benign thyroid nodules and a network meta-analysis to evaluate the efficacy and complications of different ablation therapies. The study included 16 randomized controlled trials (843 patients) that compared the following treatments: RFA, laser ablation (LA), high-intensity focused ultrasound (HIFU) and microwave ablation (MWA). Seven studies included RFA. Percentage mean volume change, symptom score change, cosmetic score change and complications were evaluated by network meta-analysis. RFA with two treatment sessions group was associated with the highest reduction for the mean volume change during six-month follow-up. There is no significant difference in the incidence of complications. Subgroup analysis showed that 2 sessions of RFA ranks the highest probability (surface under the cumulative ranking curve (SUCRA) values 77.9) of being the most efficacious treatment for solid or predominantly solid benign nodules. Ethanol ablation (EA) ranked first (SUCRA value 81.1) in the treatment for cyst or predominantly cyst benign nodules. The authors concluded that RFA appears to be superior to other ultrasound-guided percutaneous ablation in reducing benign thyroid nodule volume during short- and long-term follow-up and in the subgroup analysis, RFA with 2 treatment sessions showed the most significant effectiveness for solid benign thyroid nodules and EA showed more effectiveness to decrease the volume of cyst benign thyroid nodules. The authors noted that

further randomized prospective studies focusing on efficacy, side effects, costs, and quality of life in different percutaneous ablation were warranted.

Both benign and cancerous: Muhammad et al. (2021) conducted a systematic review is to evaluate the evidence for current studies and data of safety and efficacy of radiofrequency ablation (RFA) for the management of benign thyroid nodules (BTNs) and differentiated thyroid cancers (DTC). The study notes that while surgery is first-line treatment, for candidates with high surgical risk or those who refuse to undergo repeated surgery, newer techniques such as RFA are an option. The study notes that RFA has been used in Asian and European institutions as an alternative to surgery, but is relatively new in North America and further large-scale studies focusing on a Western population are needed. The review included a total of 75 studies that met the inclusion criteria with 35 studies focused on RFA use for solid nodules; 12 studies on predominantly cystic nodules; 10 for autonomously functioning thyroid nodules, and 18 studies on differentiated thyroid cancer. Prospective and retrospective studies were included in review with inclusion criteria: adult population; persons with DTC; persons with benign functional or nonfunctional thyroid nodules (solid, mixed solid and cystic, or purely cystic. A meta-analysis could not be performed in this systematic analysis due to the heterogeneity of the included studies, lack of a control population in many studies, and differences in inclusion and exclusion criteria; many of the studies were retrospective with a small follow-up duration (around one year); exact breakdown of nodules based on ultrasound features was not mentioned in majority of the studies; and most of the studies were based in Asia or Europe. In conclusion, RFA seems to be an effective and safe alternative to surgery in high-risk surgical patients with thyroid cancers and for selected BTNs. Additional trials with longer follow-up in North American patients are needed to validate its full role in the armamentarium of thyroidologists.

Benign: Monpeyssen et al. (2021) conducted a systematic review to review the outcomes of ultrasound-guided radiofrequency ablation of benign thyroid nodules including solid nonfunctioning and on autonomous thyroid nodules (AFTN). The review included 17 studies that evaluated RFA for the treatment of benign solid (nonfunctioning or autonomous) thyroid nodules, with at least 18 months follow-up. Data extraction and quality assessment were performed by two endocrinologists according to PRISMA guidelines and anthropometric data, safety and efficacy parameters were collected. The majority of the studies were retrospective studies and reported 933 nodules, mostly solid. Baseline volume ranged between 6.1 ± 9.6 and 36.3 ± 59.8 ml. Local analgesia was used and the time duration of the treatment was between 5 ± 2 and 22.1 ± 10.9 min. The volume reduction rate at 12 months ranged from 67% to 75% for the nodule treated with a single procedure and reached to 93.6 ± 9.7% for nodules treated with repeat ablations. The regrowth rate at 12 months ranged from 0% to 34%. The authors concluded that all the studies consistently validated the long-term clinical efficacy and the substantial safety of RFA for the treatment of benign thyroid nodules. It was noted that thermal ablation is an operator-dependent technique and should be performed in centers with specific expertise. The selection of the patients should be rigorous because the nodule size and the structural and functional characteristics influence the appropriateness and the outcomes of the treatment.

Benign: Cho et al. (2020) conducted a systematic review and meta-analysis to determine the efficacy of thermal ablation of benign thyroid nodules of studies with long-term follow-up of more than 3 years. The review included 12 studies that had patients with a benign thyroid nodule treated with thermal ablation; and follow-up data for more than 3 years after ablation (five for RFA and seven for LA) and 695 nodules from 680 patients who underwent RFA. Ten studies were retrospective in design, and the two others were prospective. The pooled volume reduction rate (VRR) for ablated nodules showed rapid volume reduction before 12 months, a plateau from 12 to 36 months, and more volume reduction appearing after 36 months, demonstrating long-term maintenance of treatment efficacy. Thermal ablation had a complication rate of 3.8%. Moreover, patients undergoing nodule ablation showed no unexpected delayed complications during the

follow-up period. In the subgroup analysis, RFA was shown to be superior to LA in terms of the pooled VRR and the number of patients who underwent delayed surgery.

Benign: Trimboli et al. (2020) conducted a meta-analysis and systematic review to obtain solid evidence of the long-term efficacy of image-guided thermal ablations including radiofrequency ablation (RFA) and laser ablation in benign non-functioning solid thyroid nodules (BNFSTN). Studies reporting the effectiveness of RFA or laser ablation in patients with BNFSTN in terms of volume reduction rate (VRR), compressive symptoms and cosmetic concerns were included, and complications were also assessed. The review included 12 studies on RFA and 12 on laser ablation, assessing 1,186 and 2,009 BNFSTNs, respectively. Six studies were prospective cohort, ten retrospective cohorts and seven randomized controlled; and study design not clearly stated in one study. Original papers reporting complete data of BNFSTNs treated by RFA or laser ablation and later followed-up for at least 6 months were included. Overall, VRR at 6, 12, 24, and 36 months was 60%, 66%, 62%, and 53%. VRR of RFA was 68%, 75%, and 87%, respectively. VRR of laser ablation was 48%, 52%, 45%, and 44%, respectively. Baseline volume of nodules undergone RFA was significantly smaller compared to laser ablation (20.1 ± 22.4 versus 24.6 ± 23.6 ml; $p < 0.01$). Nodules smaller than 30 ml obtained better outcomes than larger ones. A significant reduction in compressive symptoms and cosmetic concerns was found after RFA. Results were stable up to 2 years for RFA and 3 years for laser ablation. Improvement in compressive symptoms and cosmetic concerns was demonstrated for RFA. The authors concluded that the meta-analysis showed that both RFA and laser ablation are able to obtain a significant volume reduction in BNFSTNs with a significant volume reduction is evident at 6 months after thermal ablation and results are stable over the time.

Cancerous: Tong et al. (2019) conducted a systematic review and meta-analysis to evaluate the efficacy and safety of radiofrequency ablation (RFA), microwave ablation (MWA) and laser ablation (LA) for treating papillary thyroid microcarcinoma (PTMC). The study assessed the standard mean difference of the tumor volume before and after therapy and the proportion of complete disappearance, local recurrence, distant metastasis and complications using both fixed or random-effects modeling. Heterogeneity among studies was determined using the Q statistic for the pooled estimates and the inconsistency index. The review included 12 studies, including a sample size of 1,187 patients and 1,284 PTMCs, with nine studies retrospective, and three prospective. Eleven studies were single-arm studies (6, 3 and 2 studies treated with RFA, MWA and LA, respectively) and one study comparative. MWA vs RFA, MWA and LA all showed a significant reduction in tumor volume of PTMCs ($p<0.05$). Though MWA demonstrated superior efficacy over the other two therapies for volume reduction, the differences were not statistically significant. The pooled proportion of complete disappearance after RFA was the highest (76.2%), and the pooled proportion of recurrence for RFA was the lowest (0.01%) among the three therapeutic methods, but no significant difference was detected. There was no event of distant metastasis during the follow-up in all of these studies. There were few major complications; the pooled proportion of complications for RFA (1.73%), MWA (6.0%) and LA (0.92%) was low, revealing no significant differences ($p>0.05$).the authors concluded that RFA, MWA and LA are acceptable treatments to manage PTMCs in terms of efficacy and safety for non-surgical candidates.

Both benign and cancerous: Chung et al. (2017) performed a systematic review and meta-analysis to evaluate the safety of radiofrequency ablation (RFA) for the treatment of benign thyroid nodules and recurrent thyroid cancers. The review included 24 studies, with 2,421 patients and 2,786 thyroid nodules. Included were 12 retrospective studies, nine prospective studies, and three studies with unclear study design. Pooled proportions of overall and major complications were assessed using random-effects modelling. Heterogeneity among studies was determined using the $\chi 2$ statistic for the pooled estimates and the inconsistency index I2. The review included 24, with sample size of 2,421 patients and 2,786 thyroid nodules. There were 41 major complications and 48 minor complications of RFA reported, giving a pooled proportion of 2.38% for overall RFA

complications [95% confidence interval (CI): 1.42%-3.34%] and 1.35% for major RFA complications (95% CI: 0.89%-1.81%). There were no heterogeneities in either overall or major complications (I2 = 1.24%-21.79%). On subgroup analysis, the overall and major complication rates were significantly higher for malignant thyroid nodules than for benign thyroid nodules (p=0.0011 and 0.0038, respectively). The authors conclude that RFA was found to be safe for the treatment of benign thyroid nodules and recurrent thyroid cancers.

Literature Review—Studies
Benign: Kandill et al. (2022) conducted a prospective study at two US centers to evaluate the efficacy and safety of RFA in the treatment of benign thyroid nodules. The study included 233 patients, of which 70 patients were available for 12 months follow-up. Inclusion criteria included: 1) benign thyroid nodule on two FNA biopsies prior to ablation or benign sonographic appearance with one benign cytologic result; 2) no history of ethanol injection or radioactive iodine ablation; 3) follow-up for at least three months. Nodule volume during the follow-up period decreased from a median of 4.17 ml (IQR: 0.74–17.90) at baseline to 0.39 ml (IQR: 0.07–2.52) at 12 months (P<0.001). The median and interquartile range of volume reduction rate (VRR) at 12 months was 76% (IQR: 52%–90%) A total of 6 (2.5%) patients encountered complications during the study period. Complications include temporary voice change, drainage from the RFA site, and minor skin burn. A limitation of this study is loss to follow-up and no comparator.

Benign or Indeterminate: Issa et al. (2022) prospectively observed 178 patients with thyroid nodules diagnosed as benign (N=125, Bethesda II) or indeterminate (N=53, Bethesda III/IV) by preoperative cytopathological analysis who underwent RFA. The article stated "By the nature of the study, Bethesda VI nodules were excluded. Since the ETA/AME/AACE all classify only Bethesda III and IV as indeterminate nodules, we excluded patients with Bethesda V nodules". Thyroid nodules were included only if they

(1) were classified by fine needle aspiration as a Bethesda II, III, IV nodule;
(2) have yet to be treated (no previous laser ablation or ethanol ablation or radioactive iodine ablation); and
(3) attended at least one follow-up visit beyond the 1-month mark.

Results showed in the benign and indeterminate cohorts had similar thyroid nodule volume reduction rates at 65.60% and 64.20%, respectively (p = 0.68). The two groups had similar nodular regrowth rates, at 11.2% for benign nodules and 9.40% for indeterminate nodules (p = 0.72). A total of three cases of transient dysphonia were reported. The authors stated that "Moving forward, studies of larger sample sizes and longer follow-up duration could realistically posit RFA as a potential treatment option for indeterminate thyroid nodules".

Benign: Lin et al. (2022) retrospectively reported six month results following RFA in multiple centers. A total of 762 patients presenting with 826 benign solid benign nodules underwent RFA for a single nodule. For those patients presenting with more than one nodule, RFA was performed for a single nodule per session. Nodules included: Large N=180 (>30 mL); Medium N=295 (11–30 mL); and Small N=351 (≤10 mL). All nodules except one were ablated in a single session, and all nodules were classified as solid or predominant solid. At 6-months follow-up, there was no significant difference of volume reduction ratio (VRR) among the three groups. A total of 40 (4.8%) complications were reported. All patients recovered spontaneously without surgery intervention. The overall complication rate showed significant difference among the three groups. Authors noted that the efficacy of RFA for multiple thyroid nodules should be evaluated in another future study to confirm treatment outcomes.

Benign: In a single center randomized trial, Cesareo et al. (2021) compared RFA with laser ablation (LA). A total of 60 patients with solid or predominantly solid benign nonfunctioning thyroid nodules (BNTNs) were followed for 12 months. Only 29 patients in each group completed 12 months. Inclusion criteria included solitary BNTN or dominant nodule characterized by pressure

symptoms/cosmetic problems or patients without symptoms who experienced a volume increase >20% in one year. Primary outcomes included volume reduction rate (VRR) and proportion of nodules with more than 50% reduction. A reduction of >50% in nodule volume at 12 months was observed in 26 (89.7%) and 22 (75.9%) patients in the RFA and LA groups (technical success rate), respectively (P=.149). At the 12-month follow-up, RFA was associated with a statistically significant greater nodule VRR than LA (P=.024). At six months (Cesareo, et al., 2020) the adverse event rates (local pain, dysphonia, thyrotoxicosis, fever, hematoma) were 37% (n = 11) and 43% (n = 13) for RFA and LA, respectively, with no requirement for hospitalization. Cesareo et al. (2021) noted "no further procedure-related complications were documented during the 12-month period".

Benign: Bernardi et al. (2020) conducted a multicenter retrospective study, to evaluate technique efficacy, rate of regrowth, and retreatment over five years after radiofrequency ablation (RFA) or laser ablation (LA) of benign thyroid nodules and to identify predictive factors of outcome. The study included 406 patients treated with either RFA or LA, and followed for five years after initial treatment. Propensity score matching was used to compare treatments. Cumulative incidence studies with hazard models were used to describe regrowth and retreatment trends, and to identify prognostic factors. Logistic regression models and receiver operating characteristic analyses were used for risk factors and their cutoffs. RFA and LA significantly reduced benign thyroid nodule volume, and this reduction was generally maintained for five years. Technique efficacy (defined as a reduction ≥50% after 1 year from the treatment) was achieved in 74% of patients (85% in the RFA and 63% in the LA group). Regrowth occurred in 28% of patients (20% in the RFA and 38% in the LA group). In the majority of cases, further treatment was not required with 18% of patients retreated (12% in the RFA and 24% in the LA group). Data was confirmed by propensity score matching. Cumulative incidence studies indicated that RFA was associated with a lower risk of regrowth and a lower risk of requiring retreatment over time. Overall, technique inefficacy and regrowth were associated with low-energy delivery. Retreatments were more frequent in young patients, in large nodules, in patients with lower volume reduction at one year, and in cases of low-energy delivery (optimal cutoff was 918 J/mL for RFA). The authors concluded that both techniques result in a clinically significant and long-lasting volume reduction of benign thyroid nodules with the risk of regrowth and needing retreatment was lower after RFA.

Benign: Deandrea et al. (2019) retrospectively reported on 215 patients who underwent RFA for benign thyroid nodules who were followed for at least 3 years. Patients were >18 years of age, had normal thyroid function, and had undergone a single RFA procedure. Retrospective analysis showed median volume observed 6 months after the procedure was significantly lower than that at baseline. Further progressive volume reduction was seen at 1 year, as well as at the 2-year follow-up. Nodule volume recorded at 3 and 4 years did not significantly differ from that at 1 and 2 years. An additional small but statistically significant reduction was observed at 5 years (P=0.0089). No major complications occurred.

Benign: In a prospective, multicenter study, Jung et al. (2018) performed RFA on 276 (248 solid and 28 predominantly cystic) benign nodules. The mean number of performed RF sessions was 1.3 ± 0.4 (range 1–2; one session in 206 patients and two in 70). Patients were followed for 12 months. Volume reduction at 12 months after RFA was 80.3 ± 13.7% (n = 276, range 38.7–100%). The therapeutic success rate was 97.8% (270/276) at the 12-month follow-up. No patient experienced a life-threatening or delayed complication during the follow-up. The overall complication rate was 5.1% (14/276). Major and minor complication rates were 1.1% (3/276) and 4.0% (11/276), respectively. The side-effect rate was 4.7% (13/276). Almost all study subjects recovered without sequelae; only one hyperthyroid patient was treated with medication (propylthiouracil, 100–150 mg/day).

Benign: Che et al. (2015) retrospectively compared 200 patients who underwent thyroid surgery to 200 patients who underwent RFA for the treatment of benign thyroid nodules. The surgery methods included total thyroidectomy and lobectomy. Inclusion criteria for both groups was: 1) having a cosmetic problem, 2) having nodule-related symptoms, 3) having hyperfunctioning nodules related to thyrotoxicosis, and 4) having refused surgery. For the RFA group, the nodule volume decreased significantly from 5.4 at baseline to 0.4 mL (P =.002) at the 12-month follow-up. Hypothyroidism was detected in 71.5% of patients after surgery but in none following radiofrequency ablation. The rate of residual nodules (11.9% versus 2.9%, P = .004) and hospitalization days was significantly greater after surgery (6.6 versus 2.1 days, P < .001), but the cost difference was not significant. The incidence of complications was significantly higher from surgery than from radiofrequency ablation (6.0% versus 1.0%, P=.002). This study is limited by its retrospective design.

Benign: Baek et al. (2015) conducted a small, randomized trial at two centers, comparing RFA (N=25) to ethanol ablation (EA) (N=25). The study included 50 patients, followed for six months, who met the following inclusion criteria:

- patients with predominantly cystic thyroid nodules (PCTN) (proportion of cystic component, less than 90% and greater than 50% of the nodule);
- reports of pressure symptoms or cosmetic problems caused by thyroid nodules;
- benign cytological confirmation in at least two separate US-guided, fine-needle aspiration or core needle biopsies; and
- normal serum levels of thyroid hormone, thyrotropin, and calcitonin.

Analysis was performed primarily in an intention-to-treat manner as not all 50 patents were measurable at six months: RFA (n = 22) and EA (n = 24). The mean volume reduction was 87.5 ± 11.5% for RFA and 82.4 ± 28.6% for EA (p = 0.710; mean difference, indicating no significant difference). There were no significant differences in major complications (p > 0.99). This study is limited by the amount of participating patients.

Benign: Bernardi et al. (2014) conducted a study that evaluated RFA efficacy, tolerability, and costs and comparing them to hemithyroidectomy for the treatment of benign thyroid nodules. The study included 37 patients who underwent RFA and then were retrospectively compared to 74 patients surgically treated, either in a standard inpatient or in a short-stay surgical regimen. Efficacy, tolerability, and costs were compared. The contribution of final pathology was also taken into account. RFA reduced nodular volume by 70% after 12 months and appeared to be an effective method for treating nodule-related clinical problems, but it was not as effective as surgery for the treatment of hot nodules. RFA and surgery were both safe, although RFA had less complications and pain was rare. It was noted that RFA did not allow for any pathologic analysis of the nodules, which, in six patients who had undergone surgery (8%), it was revealed that the nodules harbored malignant cells.

Benign: Sung et al. (2013) conducted a small randomized trial, comparing volume reduction of single-session ethanol ablation (EA, N=25 patients) and radiofrequency (RF, N=25 patients) ablation for benign cystic thyroid nodule treatment. Inclusion criteria included:

(a) presence of a cystic thyroid nodule (cystic portion. 90%);
(b) reports of pressure symptoms or cosmetic problems;
(c) cytologic confirmation of benignancy in at least two separate US guided fine-needle aspiration cytologic (FNAC) examinations (ie, two biopsies performed with an interval of several months apart) for cystic fluid and/or a mural, solid component; and
(d) serum levels of thyroid hormone, thyrotropin, and calcitonin within normal limits

Follow-up duration was six months. Volume reduction ratio was reported as a percentage. Analysis was performed primarily in intention-to-treat manner (N = 21 for each).

Mean volume reduction was 96.9% in EA and 93.3% in RF ablation. Authors state the mean volume reduction of the EA group was noninferior to and also significantly superior to that of the RF ablation group. There were no major complications (P > .99).

Benign: Lim et al. (2013) conducted a retrospective study including 111 patients with a mean follow-up duration of 49.4 ± 13.6 months. A total of 126 benign non-functioning thyroid nodules underwent RFA. Inclusion criteria included but was not limited to reported cosmetic and/or symptomatic problems, largest diameter of nodule exceeding 2 cm; cytologically confirmed benign nodule on two separate US-guided fine-needle aspiration biopsy (FNAB),
US imaging finding without suspicious malignant features, serum thyroid hormone and thyrotropin levels within normal ranges, refusal of or ineligible for surgery. Results demonstrated thyroid nodule volume decreased significantly, from 9.8 ± 8.5 ml before ablation to 0.9 ± 3.3 ml (P < 0.001) at final evaluation: a mean volume reduction of 93.4 ± 11.7 %. Overall complication rate was 3.6 % (4/111). Major complications were observed in two patients (one with voice change and one with brachial plexus injury), and minor complications were observed in two patients (one with a haematoma and one with vomiting). A limitation of this study is its retrospective design.

Benign: Baek et al. (2012) reported results of a retrospective analysis of complications following RFA for benign thyroid nodules. A total of 1459 patients underwent RFA of 1543 thyroid nodules at 13 thyroid centers. Patients who underwent RFA met these criteria: pressure symptoms or cosmetic problems; had benign nodules greater than 2 cm in largest diameter; had serum thyroid hormone levels within normal limits; and refused or were ineligible for surgery. Of the 1459 patients, 48 (3.3%) experienced complications (2.2% per session), including 20 major and 28 minor complications. None of these complications was life threatening, and 46 patients recovered without sequelae. Of the remaining two patients, one had permanent hypothyroidism and the other underwent left thyroidectomy due to nodule rupture. The authors concluded the complication rate is low, but various complications may occur during thyroid RF ablation.

Professional Societies/Organizations

National Comprehensive Cancer Network™ (NCCN™): NCCN guideline for thyroid carcinoma, includes radiofrequency ablation as a treatment option for differentiated thyroid cancer (includes papillary, follicular, and Hürthle cell) and medullary thyroid cancer (NCCN 3.2022 – November 1, 2022) Category 2A

> Category 2A: based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

The American Association of Clinical Endocrinology published a Disease State Clinical Review titled The Clinical Utility of Minimally Invasive Interventional Procedures in the Management of Benign and Malignant Thyroid Lesions (Jasim, et al., 2022). The AACE states:

> Minimally invasive thyroid techniques are effective and safe when performed by experienced centers. To date, percutaneous ethanol injection therapy is recommended for recurrent benign thyroid cysts. Both ultrasound-guided laser and radiofrequency ablation (RFA) can be safely used for symptomatic solid nodules, both toxic and nontoxic. Microwave ablation and high-intensity focused ultrasound are newer approaches that need further clinical evaluation. Despite limited data, encouraging results suggest that minimally invasive techniques can also be used in small-size primary and locally recurrent thyroid cancer.
>
> Specific to RFA, the AACE states that the indications to perform RFA differ according to the lesion's nature and treatment intent. There are three well-established indications for RFA of benign nodules:

(1) esthetic concern
(2) compressive symptoms, and
(3) autonomously functioning nodules.

One indication that may be considered is the growing nodule prior to becoming symptomatic, since smaller nodules respond with better volume reduction rate (VRR) than larger nodules (Jasim, et al., 2022)

Benign Nonfunctional Nodules: Several studies suggest that RFA is a safe option in benign nonfunctional nodules. The volume reduction can range from 50% to 85%.Volume reduction can be maintained a few years after initial treatment, especially in smaller-volume nodules (<10 mL), while larger benign nodules tend to require more than one treatment over time.

Benign Autonomously Functioning Thyroid Nodules: Growing international data have demonstrated the safety and efficacy of the RFA technique in benign autonomously functioning thyroid nodules (AFTNs) as an alternative choice to surgery or radioactive iodine (RAI) treatment, although limited data are available in the United States.

American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE) and Associazione Medici Endocrinology (AME): these organizations published medical guidelines for clinical practice for the diagnosis and management of thyroid nodules (Gharib, et al., 2016). The guidelines include the recommendations:

- Image-guided thermal ablation for benign nodules:
  - Consider laser or radiofrequency ablation for the treatment of solid or complex thyroid nodules that progressively enlarge, are symptomatic or cause cosmetic concern (best evidence level [BEL] 2, GRADE C).
  - Repeat FNA for cytologic confirmation before thermal ablation treatment [BEL 3, GRADE B].
  - Discuss alternative therapy options and their efficacy, limitations, and adverse effects with the patient [BEL 3, GRADE B].

Level of evidence: 2
Randomized controlled trials with limited body of data
Well-conducted prospective cohort studies
Well-conducted meta-analyses of cohort studies

Level of evidence: 3
Methodologically flawed randomized clinical trials
Observational studies
Case series or case reports
Conflicting evidence, with weight of evidence supporting the recommendation

Grade C
No conclusive level 1 or 2 publications - Action recommended for indications reflected by the published reports
≥1 Conclusive level 3 publication demonstrating benefit >> risk Or No conclusive risk at all and no benefit at all:
Use when the patient declines or does not respond to conventional therapy, provided there are no important adverse effects

American Association of Endocrine Surgeons (AAES): this organization published guidelines for the definitive surgical management of thyroid disease in adults (Patel, et al., 2020). The guidelines note that for toxic adenoma (TA), two other therapeutic approaches are ethanol injection and

radiofrequency ablation, neither of which have gained popularity in the United States nor are recommended as initial treatment, but which may be considered when patients are not candidates for conventional treatment. They note that, in most cases a surgeon should be consulted prior to proceeding, as surgery after one of these interventions can be more difficult if a euthyroid state does not result, hyperthyroidism recurs, or a nodule persists.

American Thyroid Association (ATA): The 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer only addresses RFA for treatment of thyroid cancer and does not address RFA for benign nodules (Haugen, et al., 2016).

The American Thyroid Association Guideline on Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer (Francis, et al., 2015) does not address radiofrequency ablation**.**

The American Academy of Otolaryngology — Head and Neck Surgery does not address thyroid nodules in their published Clinical Practice Guidelines.

American Head and Neck Society Endocrine Surgery Section with the Asia Pacific Society of Thyroid Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, European Thyroid Association, Italian Society of Endocrine Surgery Units, Korean Society of Thyroid Radiology, Latin American Thyroid Society, and Thyroid Nodules Therapies Association: these organizations published an international multidisciplinary consensus statement for radiofrequency ablation (RFA) and related ultrasound-guided ablation technologies for treatment of benign and malignant thyroid disease (Orloff, et al., 2022). The document notes that while RFA is the dominant focus of the statement, the clinical framework presented applies to other ablation techniques, including Laser thermal ablation (LTA), microwave ablation (MWA), high-intensity focused ultrasound (HIFU), and ethanol ablation. Future efforts will elucidate patient- and nodule-specific factors in which one technique should be preferred over others. While all methods may be appropriate for some patients, not all clinicians should seek to offer each of these techniques. Further investigation is required to address areas of evolving understanding, including:

- Optimal role of thermal ablation in primary malignancy and indeterminate nodules.
- Optimal role of thermal ablation vs. surgery in cytologically benign thyroid nodules.
- The role of thermal ablation in managing metastatic disease primarily.
- Criteria for determining treatment efficacy and outcomes.
- Prognostic factors for successful ablation and regrowth.
- Timing of additional treatment following an incomplete treatment or regrowth.
- Cost effectiveness for ablation procedures vs. surgical approaches.
- Patient-related outcome measures for ablation procedures versus surgical approaches.
- Comparative efficacy, safety, and ideal applications of varied thermal ablation techniques.
- Long-term efficacy in all clinical applications.
- Minimum expectations for training and experience prior to offering thermal ablation.
- Disseminating and securing global availability of ablation technologies

Recommendations in this consensus statement include:

- Ultrasound (US)-guided ablation procedures may be used as a first-line alternative to surgery for patients with benign thyroid nodules contributing to compressive and/or cosmetic symptoms
- Although less efficacious than surgery or RAI in normalizing thyroid function, thermal ablation procedures can be a safe therapeutic alternative in patients with an autonomously functional thyroid nodule and contraindications to first-line techniques

- US-guided ablation procedures may be considered in patients with suitable primary papillary microcarcinoma who are unfit for surgery or decline surgery or active surveillance
- Following thermal ablation for benign nodules, primary objective measures of efficacy include ultrasonographic measurement of volume reduction and preservation or normalization of thyroid function
- Patient-reported outcomes, including validated symptom, cosmetic, and quality of life instruments may be used to determine efficacy
- Repeat ablation of a benign nodule can be considered for remnant nodular tissue contributing to unresolved symptomatic or cosmetic concerns
- Retreatment for persistent hyperthyroidism may be performed

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Coding Information Endocrinology

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

Radiofrequency Ablation (RFA) Thyroid Nodules

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

CPT®* Codes	Description	Comment
60699	Unlisted procedure, endocrine system	Considered Medically Necessary when used to report treatment of ANY of the following: • differentiated thyroid cancer (i.e., papillary, follicular, and Hürthle cell) • medullary thyroid cancer • benign thyroid nodule when BOTH of the following criteria are met: ➢ compressive symptoms (e.g., changes of voice, dysphagia, dyspnea, pain) ➢ limited to a single RFA treatment in a 12-month period

Gastroenterology

Ingestible devices for the treatment of constipation (CPT 91299, HCPCS A9999)

An orally ingested transient device for constipation is an electric swallowable capsule that naturally passes through the gastrointestinal tract for the treatment of constipation. It is proposed the vibration may mechanically stimulate the intestinal wall and thereby augment the circadian rhythm of colonic contractile activity, resulting in increased number of complete spontaneous bowel movements.

U.S. Food and Drug Administration (FDA)
On August 26, 2022, the FDA completed its review of a De Novo request for classification of the Vibrant® System (Vibrant Ltd., Philadelphia, PA) and concluded that this device should be classified into Class II under the generic name 'orally ingested transient device for constipation'.

Literature Review
There is a lack of long-term, large studies demonstrating that ingestible vibrating capsules are a safe and effective treatment for chronic constipation. The safety, efficacy, and potential inferiority or superiority over established treatments remains unknown.

Rao et al. (2023) conducted a randomized, placebo-controlled trial in centers in the US to assess the efficacy and safety of the vibrating capsule in the treatment of chronic constipation:

Inclusion criteria:
- adults (≥22 years) with chronic idiopathic constipation according to Rome III criteria
- had not experienced relief of their symptoms from available therapies (osmotic and stimulant laxatives for at least one month)
- had an average of ≥1 spontaneous bowel movements (SBM) per week and ≤2.5 SBMs per week
- had a colonoscopy within the previous 5 years, (unless patients were <50 years old) with no alarm features

Exclusion criteria included history of complicated/obstructing diverticular disease, intestinal obstruction, inflammatory bowel disease or gastrointestinal malignancy, gastroparesis, Zenker's diverticulum, dysphagia, esophageal stricture, pelvic floor dysfunction, megarectum, history of bariatric surgery, significant systemic illnesses or pregnancy/lactation or with pacemaker.

Patients were randomized to receive either the vibrating capsule (Vibrant®, Vibrant Ltd, Hakochav Yokneam, Israel) or an identical placebo. Patients were asked to completed daily eDiaries as well as take one capsule orally between 9-10 pm each night, 5 times a week (excluding Wednesdays and Sundays).

The study design initially comprised of 3 arms; 2 active vibrating capsule arms (Modes 1 and 2) and one placebo arm. In the activation Mode 1, the capsule was preprogramed to start vibrating from noon the next day and in Mode 2, from 6 am the next day. The objective of this first phase analysis was to identify which of the two activation modes was superior, and to recommend that mode for the remainder of the study. Based on the analysis of the first phase of the study, Mode 2 was discontinued and the trial was completed using Mode 1.

The vibrating capsule was programmed to induce two separate vibration cycles over a 2-day period, with each cycle lasting 2 hours and comprised of 3 seconds of stimulation and 16 seconds

of rest, i.e. approximately 3 oscillation cycles per minute. The placebo capsule was identical in size, shape, weight and color to the vibrating capsule and required activation using the Pod, but was designed not to vibrate and dissolve in the small intestine.

Patients were allowed to use only one of the following rescue treatments (bisacodyl 5 mg suppository or tablet, phosphosoda enema [Fleet Enema®]), if they had no bowel movement for 3 consecutive days, and its use was recorded in the eDiary.

The primary efficacy end points were defined as the proportions of patients with an increase of one or more complete spontaneous bowel movement (CSBM1) per week, OR with an increase of two or more CSBMs per week (CSBM2), during at least 6 of the 8 weeks of treatment when compared to the baseline period. A total of 312 patients (269 women, 43 men) were randomized to the vibrating capsule activation Mode 1 (n=163) or the placebo (n=149) arms and were included in the final analysis. Authors report a significantly greater proportion of patients in the vibrating capsule arm achieved the primary efficacy end point of CSBM1, 39.26% (64/163) compared to 22.15% (33/149) in the placebo arm (p = 0.001), as well as the CSBM2, 22.70% (37/163) compared to 11.41% (17/149) in the placebo group (p = 0.008).

In total, 49 adverse events were considered possibly or probably related to study treatments (36 in mode 1 and 5 in mode 2 of the vibrating capsule arms and 8 in the placebo arm). A vibrating sensation was reported by 11% in the vibrating capsule arm, but all completed the trial. Larger and long-term trials are needed to establish its long-term efficacy and safety.

Professional Societies/Organizations
The following professional society guidelines do NOT address ingestible vibrating capsules:

- American Gastroenterological Association 2013 Medical Position statement on Constipation
- American Gastroenterological Association Institute 2019 Guideline on the Medical Management of Opioid-Induced Constipation
- American Society of Colon and Rectal Surgeons' 2016 Clinical Practice Guideline for the Evaluation and Management of Constipation

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Excision of rectal tumor, transanal endoscopic microsurgical approach (ie, TEMS), including muscularis propria (ie, full thickness) (CPT Code 0184T)

A variety of surgical approaches are used to treat primary rectal cancer lesions, including transanal local excision and transabdominal resection. According to the NCCN, when the lesion can be adequately localized to the rectum, local excision of more proximal lesions may be technically feasible using advanced techniques, such as transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS) (page REC-C, 1 of 3). According to the American Society of Colon & Rectal Surgeons (ASCRS), the correct code for TAMIS is 0184T. The ASCRS states although TAMIS carries a different name, it is essentially the same procedure, just performed with non-proprietary instruments and a slightly different access device.

According to the NCCN, TEM can facilitate excision of small tumors through the anus when lesions can be adequately identified in the rectum. TEM may be technically feasible for more proximal lesions. Both transanal local excision and TEM involve a full-thickness excision performed perpendicularly through the bowel wall into the perirectal fat. Negative (>3 mm) deep and mucosal margins are required, and tumor fragmentation should be avoided. (NCCN, 2023; MS-12, MS-13).

U.S. Food and Drug Administration (FDA)
The Transanal Endoscopic Microsurgery (TEM) Combination System and Instrument Set (Richard Wolf Medical Instruments, Inc., Vernon Hills, IL) received FDA 50(k) approval in March 2001 as a substantially equivalent device. It is designed to provide access to the rectal cavity and accessible part of the lower sigmoid colon using a stereo and/or monocular endoscope under gas tight conditions for the excision of polyps and/or the removal of tumors that have previously been staged.

A May 28, 2015 PRNewswire press release states that SurgiQuest, Inc., today announced that its AirSeal® System recently received 510(k) Clearance from the FDA for Transanal Endoscopic Surgery (TES). A search of the FDA website and the SurgiQuest website was unable to confirm this approval.

Literature Review
Evidence for TEMS for the treatment of T1N0 rectal cancer, in the published peer-reviewed scientific literature includes a RCT performed in the U.S., several systematic reviews, and a number of prospective and retrospective clinical trials. There is insufficient published evidence regarding the efficacy of this treatment for other stages of rectal cancer.

Ahmad et al. (2021) meta-analysis was to compare the oncological outcomes and report on the evidence-based clinical results of transanal endoscopic microsurgery (TEMS) or total mesorectal excision (TME) in the treatment of early rectal cancers. The review included three randomized controlled trials with a total number of 208 patients. A local recurrence and postoperative complications were analyzed as primary end points. Intraoperative blood loss, operation time, and duration of hospital stay were compared as secondary end points. The findings noted that there was no statistical difference in the local recurrence or postoperative complications with a risk ratio of 1.898 and 0.753 and p -values of 0.296 and 0.306, respectively, for TEMS and TME. A marked statistical significance in favor of TEMS was observed for secondary end points. There was standard difference in means of −4.697, −6.940, and −5.685 with p -values of 0.001, 0.005, and 0.001 for blood loss, operation time, and hospital stay, respectively. The authors concluded that TEMS procedure is a viable alternative to TME in the treatment of early rectal cancers and that TME surgery remains the standard of care in more advanced rectal cancers.

Lezoche et al. (2008) reported results of a RCT involving 70 patients with stage T2N0M0 rectal cancer who underwent radiotherapy followed by chemotherapy. After chemotherapy the patients were randomized to either local excision by TEMS (Group A, n=35) or laparoscopic resection (Group B, n=35). Inclusion criteria for the TEMS group included a diameter of <3cm, located within 6cm of the anal verge, negative lymph nodes, no signs of systemic or metastatic disease, and a minimum follow-up of five years. The patients undergoing TEMS had significantly less operative time, blood loss, and hospital stay than the patients undergoing laparoscopic resection ($p<0.001$). For both approaches the 30-day mortality was zero. In group A, no intraoperative complications or conversion to other surgical procedures occurred. In group B, four procedures were converted to open surgery; in nine cases a laparoscopic abdominoperineal resection was performed. In the postoperative period, no significant differences in complication rates were observed between the two groups ($p=0.111$). The median follow-up period was 84 months. The probability of local and distant failure at the end of the follow-up period was similar in both groups: 9% and 6% in the TEMS and laparoscopic groups, respectively. The probability of disease-free survival at the end of the follow-up period was 94% in both groups.

Doornebosch et al. (2009) reported outcomes of a systematic review involving four studies totaling 282 patients with T1 carcinoma comparing TEMS, local excision (LE) and/or radical surgery (RS). One study was a RCT; the other studies were retrospective. In the RCT patients were randomized to TEMS or RS. With median follow-up of more than 40 months, local recurrence rate after TEMS was 4.1%. In the RS group no local recurrence occurred. Five-year procedure specific survival rates were 96% for both groups. Two retrospective studies could be identified comparing TEMS to RS. Local recurrence rates are comparable (4% versus 3%, after TEMS and radical surgery, respectively) for low-risk (i.e., T1 cancer) carcinomas. Overall survival rates between both treatment groups were comparable (TEMS 79% versus RS 81%, respectively).

Professional Societies/Organizations
American Society of Colon and Rectal Surgeons (ASCRS): The ASCRS Clinical Practice Guideline for the Management of Rectal cancer (2020) notes that local excision is an appropriate treatment modality for carefully selected patients with cT1N0 rectal cancer without high-risk features. The procedure can be performed as a conventional transanal excision or by using a transanal endoscopic platform like transanal endoscopic microsurgery (TEMS) or transanal minimally invasive surgery (TAMIS). While there is a paucity of well-designed randomized, controlled trials, studies suggest that TEMS offers better visualization and access to more proximal lesions than conventional transanal excision, and TEMS and TAMIS appear to be comparable
Grade of recommendation:
Strong recommendation based on moderate-quality evidence, 1B.

National Comprehensive Cancer Network™ (NCCN™): The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer (Version 4.2022 — January 25, 2023) states the following under Principles of Surgery:

Transanal Local Excision Criteria:
- <30% circumference of bowel;
- <3 cm in size;
- Margin clear (>3 mm);
- Mobile, nonfixed;
- Within 8 cm of anal verge;
- T1 only;
- Endoscopically removed polyp with cancer or indeterminate pathology;
- No lymphovascular invasion or PNI;
- Well to moderately differentiated;

- No evidence of lymphadenopathy on pretreatment imaging;
- Full-thickness excision must be feasible

When the lesion can be adequately localized to the rectum, local excision of more proximal lesions may be technically feasible using advanced techniques, such as transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS) (NCCN, 2023)

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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 anoscopic 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 Takahashi-Monroy et al. (2008) (19 patients, 5 year

study) and Lam et al. (2014) (31 patients, 3 year study), 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). Simillis et al. (2019) reported on a meta-analysis of RCTs that compare the clinical outcomes and effectiveness of treatments for fecal incontinence. The review found that pairwise comparisons of the treatments demonstrated significantly more adverse events with transanal delivery of radiofrequency energy compared to placebo. 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): The ACG clinical guideline for management of benign anorectal disorders (Wald, et al., 2021) addresses Radiofrequency stimulation (SECCA procedure), stating that the SECCA procedure involves radiofrequency stimulation of the muscles in the anal canal to increase muscle connective tissue ratio and scarring via a probe with needles in the anal canal performed under local anesthesia and sedation. Despite initial positive studies including a multi-center trial from 2003, more recent reports suggest poor long-term results (Wald, 2021).

American Society of Colon and Rectal Surgeons: The American Society of Colon and Rectal Surgeons' 2023 Clinical Practice Guidelines for the Management of Fecal Incontinence states:

- 17. Application of temperature-controlled radiofrequency energy to the sphincter complex is not recommended to treat fecal incontinence.

Based on the available data, radiofrequency energy delivery is not recommended for the treatment of FI. Additionally, no new studies evaluating this modality have been published since 2014 (Bordeianou, et al., 2023).

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13C-Spirulina Gastric Emptying Breath Test (GEBT) (CPT code 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. 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 this test has the advantage of avoiding radiation associated with scintigraphy, further studies are needed before they can be routinely recommended for evaluation of delayed gastric emptying.

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 CO_2, or $^{13}CO2$, which can be measured in the breath samples.

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.

Advanced Breath Diagnostics' (Brentwood, TN) 13C-Spirulina Gastric Emptying Breath Test (GEBT) received FDA Approval 08/10/2021 for a change to labeling that will facilitate telehealth administration of the device (PMA Number P110015, Supplement Number S008).

Literature Review
There is a lack of large, well-designed clinical trials comparing scintigraphy and spirulina 13C breath test.
Currently, spirulina 13C breath test appears to be used in a clinical research setting.

Sanges conducted a study to compare gastric emptying of radiopaque markers (ROM) and 13carbon-labelled gastric emptying breath tests for solids (GEBT) and to determine any association between gastric emptying and patient-reported symptoms, glycemic control and the patients' age, diabetes duration and occurrence of other late complications. The study included 45 patients with diabetes mellitus types 1 or 2 (40, 5) and symptoms of gastroparesis were examined with ROM and GEBT. Patients were interviewed, symptom questionnaires completed and HbA1c levels measured. Forty percent of patients had delayed gastric emptying of ROM, while 55% had delayed gastric emptying of GEBT. Correlation between ROM and GEBT was not significant. Compared to GEBT, sensitivity for a positive ROM test was 0.52, while specificity was 0.74 and in women, there was a higher specificity of 0.92, sensitivity 0.47. Difference in HbA1c between patients with positive and negative results was of borderline significance for both tests. GEBT ($r=0.41$, $P=0.008$) correlated with HbA1c. Patients with any late complications of diabetes had higher gastric retention of ROM ($P=0.028$), while patients with polyneuropathy ($P=0.014$) and diabetic wounds ($P=0.004$) had slower emptying with GEBT. None of the methods identified significant associations between gastric emptying and symptom scores, age or diabetes duration. The study did not compare ROM and GEBT to scintigraphy, which is the standard in diagnostic assessment of diabetic gastroparesis of gastric emptying. The study is limited by the small number of participants and lack of randomization.

Szarka et al. (2008) 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 samples combined were 93% sensitive to identify accelerated GE, and 150- and 180-minute combined were 89% sensitive for delayed GE.

Professional Societies/Organizations
American College of Gastroenterology (ACG)**:** The 2022 ACG Clinical Guideline on Gastroparesis (Camilleri, et al., 2022) states the following Recommendation: Stable isotope (13C-spirulina) breath test is a reliable test for the evaluation of GP in patients with upper GI symptoms. (Level of evidence: Low; Strength of Recommendation: Conditional)

The 2022 AGA Clinical Practice Update on Management of Medically Refractory Gastroparesis: Expert Review does not make any Best Practice Advice Statements specific to breath testing (Lacy, et al., 2022).

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Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (i.e., ELISA) (CPT code 0176U; IBSchek irritable bowel syndrome [IBS])

IBSchek (Commonwealth Diagnostics International Inc., [CDI], Salem, MA, acquired by Valeant in 2015) is an enzyme-linked immunosorbent assay (or ELISA) blood test that is proposed for the diagnosis of irritable bowel syndrome (IBS). IBSchek detects antibodies against cytolethal distending toxin B (anti-CdtB) and the cell adhesion protein vinculin (antivinculin). These serum biomarkers are thought to be involved in the pathophysiology of postinfectious IBS.

Literature Review
Pimentel et al. (2015) conducted a validation study of circulating anti-CdtB and anti-vinculin antibodies as biomarkers for D-IBS in 2375 subjects with D-IBS based on Rome criteria. Subjects with inflammatory bowel disease (IBD) (n=142), with celiac disease (n=121), and healthy controls (n=43) were obtained for comparison. For anti-CdtB the specificity, sensitivity and likelihood ratio were 91.6%, 43.7 and 5.2, respectively, and for anti-vinculin were 83.8%, 32.6 and 2.0, respectively. The study is limited by the lack of randomization.

Professional Societies/Organizations
American College of Gastroenterology (ACG): ACG published clinical guideline for the management of IBS (Lacy, et al., 2021). The guidelines do not include a recommendation for IBSchek or testing for presence of two antibodies—anti-CdtB and anti-vinculin. Included in the recommendations:

- suggest that either fecal calprotectin or fecal lactoferrin and C-reactive protein be checked in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease.

Strong recommendation; moderate quality of evidence (CRP, fecal calprotectin).
Strong recommendation; very low quality of evidence (fecal lactoferrin).

American Gastroenterological Association (AGA): AGA published a technical review on the evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults note regarding these biomarkers that properly designed and powered prospective validation trials in consecutive uninvestigated patients with IBS-D symptoms are needed. The AGA review notes that the analysis indicates that the specificity of anti-CdtB and antivinculin antibodies for IBS-D is reasonably good with a high positive predictive value, however, the sensitivity was <50% (Carrasco-Labra, et al., 2019)

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Esophageal mucosal integrity testing by electrical impedance, transoral (HCPCS code C9777)

Esophageal mucosal integrity testing has been proposed as a method to diagnosis gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EoE). Mucosal Integrity is affected by the presence of dilated intercellular spaces (DIS), or spongiosis, which affects paracellular permeability of the esophageal lumen. DIS is an important histologic feature in GERD and EoE where the degree of dilation inversely correlates with MI measurements (i.e., lower impedance values occur with increasing DIS). The diagnosis of gastroesophageal reflux disease (GERD) may be based on clinical symptoms alone in patients with classic symptoms such as heartburn and/or regurgitation. However, patients may require additional evaluation if they have alarm features, risk factors for Barrett's esophagus, or abnormal gastrointestinal imaging performed for evaluation of their symptoms. An upper endoscopy is indicated in patients with suspected GERD to evaluate alarm features or abnormal imaging. An upper endoscopy may also be performed to screen for Barrett's esophagus in patients with risk factors. On upper endoscopy, biopsies can be performed and should target any areas of suspected metaplasia, dysplasia, or, in the absence of visual abnormalities, normal mucosa to evaluate for eosinophilic esophagitis.

According to the vendor's website, the MiVu™ Mucosal Integrity Testing System (Diversatek Healthcare, Inc.) utilizes a balloon probe and proprietary software to instantly detect changes in esophageal mucosal integrity during endoscopy. The MiVu™ Balloon Probe incorporates both radial and axial sensors mounted at 180-degree intervals along a 10 cm segment of the esophagus to measure esophageal mucosal integrity. Real time impedance values, a mucosal integrity contour pattern and disease probability are displayed which distinguishes various esophageal pathologies (GERD, EoE, or Non-GERD).

U.S. Food and Drug Administration (FDA)
On 12/23/2019, the Mucosal Integrity Conductivity (MI) Test System (Diversatek Healthcare Inc.) received FDA De Novo approval as a Class II device as an esophageal tissue characterization system. An esophageal tissue characterization system is a device intended for obtaining measurements of electrical properties within esophageal tissue.

The indications for use: the Mucosal Integrity Conductivity Test System is indicated for use by gastroenterologists, surgeons, and medically trained personnel during an endoscopy to obtain a real time measurement of esophageal epithelial impedance. The device is not for use as a sole diagnostic screening tool.

Literature Review
Patel et al. (2019) reported on a prospective study to evaluate the ability of a balloon-incorporated mucosal impedance (MI) catheter to detect and evaluate esophageal disorders, including gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EoE).the study included 69 patients undergoing esophagogastroduodenoscopy with or without wireless pH

monitoring. Patients were classified as having GERD (erosive esophagitis or abnormal pH; n = 24), EoE (confirmed with pathology analysis of tissues from both distal and proximal esophagus; n = 21), or non-GERD (normal results from esophagogastroduodenoscopy and pH tests; n = 24). Receiver operating characteristic curves (ROC) and area under the ROC curve (AUC) were used to compare the accuracy of balloon MI in diagnosis. Probabilities of assignment to each group (GERD, non-GERD, or EoE) were estimated using multinomial logistic regression. Association between MI patterns and diagnoses were validated using data from patients seen at 3 separate institutions. The MI pattern along the esophageal axis differed significantly ($p<0.01$) among patients with GERD, EoE and non-GERD. Patients with non-GERD had higher MI values along all measured segments. The MI pattern for GERD was easily distinguished from that of EoE: in patients with GERD, MI values were low in the distal esophagus and normalized along the proximal esophagus, whereas in patients with EoE, measurements were low in all segments of the esophagus. Intercept and rate of rise of MI value (slope) as distance increased from the squamo-columnar junction identified patients with GERD with an AUC = 0.69, patients with EoE with an AUC of 0.89, and patients with non-GERD with an AUC = 0.84 in the development cohort. One patient had an adverse event of mild chest pain after the procedure and was discharged from the hospital without further events.

Choksi et al. (2018) reported on a retrospective analysis of 91 patients to quantify mucosal impedance (MI) along the esophagus and identify patterns that differentiated patients with and without gastroesophageal reflux disease (GERD) from those with eosinophilic esophagitis (EoE), and determine whether MI values and patterns are sufficient to identify patients with EoE using histologic findings as a reference. During the first endoscopy, MI measurements were obtained at two, five, and 10 cm from the squamocolumnar junction. GERD was confirmed by ambulatory pH tests, and histologic analyses of biopsies were used to confirm EoE. Statistical modeling was used to identify MI patterns along the esophagus that associated with GERD vs EoE. Findings were validated in a prospective cohort of 49 patients undergoing elective upper endoscopy for dysphagia. It was noted that patients with EoE have a unique MI pattern, with low values along the esophageal axis. MI measurements at five cm could discern patients with normal vs abnormal mucosa with 83% sensitivity and 79% specificity, and patients with EoE vs GERD with 84% sensitivity and 70% specificity; the measurements differentiated the patient populations with the highest level of accuracy of any of the six measurements tested. In the validation study, a rater using the esophageal MI pattern identified patients with EoE with 100% sensitivity and 96% specificity. The study is limited by retrospective nature and lack of randomization.

Lowry et al. (2018) conducted a prospective study to investigate whether mucosal impedance measurements can be used to monitor disease activity in 173 pediatric patients with Eosinophilic esophagitis (EoE). Mucosal impedance was measured at three locations in the esophagus in pediatric patients (1-18 years old; 32 with active EoE, 10 with inactive EoE, 32 with nonerosive reflux disease [NERD]) and 53 children with symptoms but normal findings from histologic analyses (controls) undergoing routine esophagogastroduodenoscopy. Pathologists reviewed biopsies per routine protocol, determined eosinophilic density, and graded spongiosis on an ordinal visual scale. Mucosal impedance measurements were compared within patient groups. The primary outcome was correlation of mucosal impedance measurements with disease activity, based on severity of spongiosis and eosinophil counts. Mucosal impedance measurements were significantly lower in patients with active EoE at 2, 5, and 10 cm above the squamo-columnar junction (median values of 1069, 1368, and 1707, respectively) compared to patients with inactive EoE (median values of 3663, 3657, and 4494, respectively), NERD (median values of 2754, 3243, and 4387), and controls (median values of 3091, 3760, and 4509) ($P < 0.001$ for all comparisons to patients with active EoE). Inverse correlations were found between mucosal impedance measurements and eosinophil count ($P < 0.001$), and spongiosis severity ($P < 0.001$). The authors concluded that mucosal impedance measurements may provide immediate

information about mucosal inflammation in children and this needs to be confirmed by further, prospective studies.

Professional Societies/Organizations
American College of Gastroenterology (ACG): The ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease states "Mucosal integrity testing, e.g., is available commercially but is not developed sufficiently to warrant discussion in this guideline" (Katz, et al., 2022).

The American Gastroenterological Association (AGA): The AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review (Yadlapati, et al., 2022) does not address mucosal integrity testing.

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Wide-Area Transepithelial Tissue Sampling with Computer-Assisted 3D Analysis (WATS3D) (CPT codes 88104, 88112, 88305, 88312, 88361)

Wide-area transepithelial sampling with 3-dimensional sampling (WATS/WATS3D) (CDx Diagnostics, Suffern, NY) is proposed as an endoscopic method of sampling tissue from the esophagus for detection and surveillance of Barrett's esophagus. It is proposed to be used in addition to the standard biopsy protocol. The first-generation WATS3D system was formerly known as EndoCDx. WATS-3D is a novel method that uses an abrasive brush to sample larger surface areas of the esophagus. These specimens allow for analysis of large sheets of cells while maintaining the 3-dimensional aspects of the tissue. The tissue is analyzed by software that uses convoluted neural networks to identify abnormal cells, which are confirmed by an expert pathologist.

U.S. Food and Drug Administration (FDA)
No information on WATS3D (CDx Diagnostics) is found on FDA website search.

Literature Review
DeMeester et al. (2021) conducted a multicenter, randomized controlled trial to compare the frequency of Intestinal metaplasia (IM) detection during upper endoscopy by forceps biopsy sampling (FB) versus wide-area transepithelial sampling (WATS) brush. Patients presenting for upper endoscopy for foregut symptoms or surveillance of Barrett's esophagus (BE) at nine centers in the United States were randomized to either FB or WATS. The study included 1,002 patients with FB was done in 505 and WATS in 497. The overall frequency of finding IM was 21% and was similar with FB (19.6%) and WATS (22.7%, P = .2). Low-grade dysplasia was found in eight patients and no patient had high-grade dysplasia. There was no difference in detection of dysplasia between FB and WATS. In patients with no history of IM, WATS found significantly more IM compared with FB when a columnar-lined esophagus (CLE) was present (32.4% with WATS vs 15.2% with FB, P = .004). In 184 patients with known BE, FB and WATS found IM with similar frequency (38.5% FB vs 41.9% WATS, P = .6) with no difference in short- or long-segment BE. The authors concluded that overall, FB and WATS detected a similar frequency of IM and dysplasia with WATS was twice as likely as FB to find IM in patients without a history of BE who had CLE on endoscopy. In patients with known BE, WATS and FB showed IM and dysplasia with similar frequency. Limitations of this study noted by the authors include most patients were women with no history of intestinal metaplasia (IM), and this influenced the frequency of finding IM. Another cited limitation is only 30 patients with long-segment BE underwent surveillance. In these patients, 14 had FB and16 had WATS, and although both techniques found IM and dysplasia with a similar frequency, this should be studied further in a larger group of patients given the potential for a Type II error. The authors noted in this series there was a paucity of patients with dysplasia, and future studies in a larger group of patients with dysplasia may allow better assessment of WATS versus FB in this setting.

Vennalaganti et al. (2018) conducted a randomized non-controlled trial of referred Barrett's esophagus (BE) patients undergoing surveillance at 16 medical centers. The study included 160 patients (mean age, 63.4 years; 76% men; 95% white) who received either biopsy sampling followed by WATS or WATS followed by biopsy sampling. The primary outcome was rate of detection of high-grade dysplasia/esophageal adenocarcinoma (HGD/EAC) using WATS in conjunction with biopsy sampling compared with biopsy sampling alone using standard histopathologic criteria. Secondary aims included evaluating neoplasia detection rates based on the procedure order (WATS vs biopsy sampling first), of each procedure separately, and the

additional time required for WATS. The median circumferential and maximal BE extents were 1.0 cm (interquartile range: .0-5.0) and 4.0 cm (interquartile range, 2.0-8.0), respectively. The diagnostic yield for biopsy sampling alone was as follows: HGD/EAC, 7 (4.4%); low-grade dysplasia (LGD), 28 (17.5%); nondysplastic BE (NDBE), 106 (66.25%); and no BE, 19 (11.9%). The addition of WATS to biopsy sampling yielded an additional 23 cases of HGD/EAC (absolute increase, 14.4%; 95% confidence interval, 7.5%-21.2%). Among these 23 patients, 11 were classified by biopsy sampling as NDBE and 12 as LGD/indefinite for dysplasia (IND); 14 received biopsy sampling first and nine WATS first (not significant) and most (n = 21; 91.7%) had a prior dysplasia history. WATS added an average of 4.5 minutes to the procedure. The authors concluded that results of this multicenter, prospective, randomized trial demonstrate that the use of WATS in a referral BE population increases the detection of HGD/EAC. The authors noted that at the time of the trial WATS specimens were evaluated only by pathologists at a single central laboratory and that in the study population (20%) were enriched with BE patients with a known history of dysplasia or referred for endoscopic therapy, and the results may not be generalizable to a low-risk BE surveillance population.

Smith et al. (2019) conducted a multicenter, prospective trial to investigate the benefit of wide area
transepithelial sampling with 3-dimensional computer-assisted analysis (WATS) used adjunctively to the combination of random and targeted forcep biopsy (FB) in the detection of esophageal dysplasia (ED), and as a secondary outcome, Barrett's esophagus (BE). The study included 12,899 patients ages 18 years and older undergoing screening for suspected BE as well as those with known BE undergoing surveillance for dysplasia. Of these, 14% of patients had a history of known BE. Patients with a suspicious lesion concerning for invasive cancer on endoscopy and requiring endoscopic resection were excluded from the study. Investigators were instructed to use both WATS and FB to sample suspected BE only in patients displaying salmon-colored mucosa in the tubular esophagus. Community endoscopists at 21 sites utilized WATS as an adjunct to both targeted and random FB in patients undergoing BE screening and surveillance. The investigators alternated taking FB and WATS samples first. WATS specimens were analyzed at CDx Diagnostics (Suffern, NY) while FB samples were analyzed by each site's regular pathologists. FB identified 88 cases of ED, and WATS detected an additional 213 cases missed by FB. These 213 cases represented an absolute increase of 1.65%, raising the yield from 0.68% to 2.33%. Adding WATS to FB increased the overall detection of ED by 242% (95% CI: 191%-315%). Fewer than 61 patients needed to be tested with WATS to identify an additional case of ED. The combination of random and targeted FB identified 1,684 cases of BE, and WATS detected an additional 2,570 BE cases. The absolute incremental yield of adding WATS to FB is 19.9%, increasing the rate of detection from 13.1% to 33%. Adding WATS to FB increased the overall detection of BE by 153% (95% CI: 144-162%). The number needed to test with WATS in order to detect an additional case of BE was 5. Whether FB or WATS was done first did not impact the results. The authors concluded that these results underscore the shortcomings of FB in detecting BE-associated neoplasia, which can potentially impact the management and clinical outcomes of these patients. The authors noted that although routine screening for BE in women is not recommended, women accounted for 61% of patients in the study and data regarding females in our study who would be potential candidates for BE screening by exhibiting multiple risk factors for BE or EAC (age >50 years of age, Caucasian race, chronic or frequent GERD, central obesity, waist circumference >88 cm, waist to hip ratio >0.8, current or past history of smoking, a confirmed family history of BE or EAC) was not collected.

Gross et al. (2018) conducted a multicenter, prospective trial to determine if wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS) used adjunctively with forceps biopsy (FB) can increase the detection of Barrett's esophagus (BE) and esophageal dysplasia (ED). The study included 4,203 patients, that were screened for suspected BE and undergoing surveillance for BE. The patients at 25 community-based practices underwent

WATS adjunctively to targeted FB and random four-quadrant FB. Findings included that 594 were diagnosed with BE by FB alone, and 493 additional cases were detected by adding WATS, increasing the overall detection of BE by 83% (493/594, 95% CI 74%–93%). Low-grade dysplasia (LGD) was diagnosed in 26 patients by FB alone, and 23 additional cases were detected by adding WATS, increasing the detection of LGD by 88.5% (23/26, 95% CI 48%–160%). It was noted in the study that there were 288 cases of BE and 16 cases of ED identified by FB that were undetected by WATS. These discrepant results are not unexpected as FB was used both to target any visible mucosal abnormality and to obtain random four-quadrant biopsy samples and WATS was used only to test large segments of the esophagus that would have remained untested by both targeted and random FB. The authors note that the study was not designed to address the question of whether WATS is more or less effective than FB in identifying BE and ED. The authors concluded that the study demonstrates that the increased adjunctive use of WATS to FB increases the detection of BE and ED.

Johanson et al. (2010) prospectively evaluated 1,183 patients (from original cohort of 1,266 pts) to determine if and by how much the detection of BE and esophageal dysplasia can be increased by the addition of EndoCDx to a standard esophageal biopsy protocol. Included patients were over age 18, scheduled for mucosal forceps biopsies for screening or surveillance of BE and dysplasia including with symptoms of gastroesophageal reflux and suspected BE as well as those with known BE undergoing surveillance for dysplasia. Patients were excluded if inadequate brush biopsy or forceps biopsy results or those with missing pathology reports. Each patient had two brush biopsies (BB) and then random four-quadrant FB every 1–2 cm of the esophagus. Among the 1,183 patients, BE was diagnosed in 363 patients by FB and in 340 patients by BB. Of the 340 patients with BE detected by the BB, 146 had negative FB results. The authors note the addition of two brush biopsies to the standard multiple forceps biopsy protocol increased the detection of BE by 39.8% (146/363, 95% confidence interval 32–48%). This added detection of BE in 11.5% of all patients tested with the BB (146/1,266) resulted in a number of patients needed to test (NNT) to obtain each additional positive finding of Barrett's esophagus of 8.7.
Esophageal dysplasia was diagnosed in 16 patients by forceps biopsy and in 19 patients by brush biopsy. Of the
19 patients diagnosed with esophageal dysplasia by brush biopsy, 14 had negative forceps biopsy results. It is unknown if there were adverse events or complications.

Shaheen et al. (2022) retrospectively analyzed a prospective registry to evaluate the outcome, measured in terms of progression to high-grade dysplasia (HGD) or EAC, of a cohort of 4545 BE patients diagnosed with either no dysplasia, BE-associated crypt dysplasia (CD), or low-grade dysplasia (LGD) by WATS3D.The primary outcome was the crude progression rate, defined as the proportion of patients per patient-year who demonstrated progression on forceps biopsy sampling to either HGD or EAC, stratified by baseline WATS3D histologic grade. Crude progression rate was calculated by dividing the number of patients progressing to HGD/EAC by the total patient-years of observation for each baseline disease stage (NDBE, CD, and LGD).
Shaheen et al. defined a cohort of 4545 patients undergoing a WATS3D procedure for either screening or surveillance of BE, with no prior history of esophageal dysplasia or endoscopic eradication therapy, fulfilling the following criteria:
1. Initial endoscopy demonstrating ≥1 cm of columnar-lined mucosa in the esophagus.
2. Forceps biopsy sampling of the esophageal columnar metaplasia showing intestinal metaplasia.
3. WATS3D sampling of the esophagus demonstrating intestinal metaplasia and either nondysplastic BE (NDBE), CD, or LGD. Patients with WATS3D findings considered indefinite for dysplasia were excluded.
4. At least 1 additional follow-up endoscopy with WATS3D administration, separated by a minimum of 12 months from the index endoscopy.
The 4545 patients had 2 WATS3D separated by ≥12 months. The mean follow-up was 1.97 years.

Reported results included but are not limited to the following: Overall, .33% of patients progressed to HGD/EAC, as diagnosed by forceps biopsy sampling, over the follow-up period. Overall, 55% of the baseline WATS3D samples had accompanying forceps biopsy sampling data available for analysis, and of these, over 98% of the forceps biopsy samples were diagnosed as nondysplastic BE (NDBE). No patient was diagnosed with CD or HGD on forceps biopsy sampling. In patients with baseline NDBE, progression was .08% per patient-year (95% confidence interval [CI], .02%-.14%). Progression of baseline CD was significantly higher, at 1.42% per patient-year (95% CI, 0%-3.01%). For baseline LGD, progression was 5.79% per patient-year (95% CI, 1.02%-10.55%). Other risk factors for progression were increasing age and BE segment length. Adverse events are unknown as they were not reported.

Corbett et al. (2022) retrospectively analyzed two prospective registries, defining a cohort of 1114 patients.
The analysis purpose was to determine the "adjunctive and absolute yield of WATS3D for detection of post ablation IM". Specifically, Corbett et al. evaluated the diagnostic efficacy of WATS3D for detection of intestinal metaplasia (IM) and dysplasia / esophageal adenocarcinoma (EAC) in Barrett's esophagus (BE) patients who have undergone endoscopic eradication therapy (EET).
The characteristics of the included cohort are unclear. Corbett et al. reports including patients who had undergone radiofrequency ablation (77.7%) and had a preablation history of nondysplastic BE (NDBE) (47.9%), high-grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) (18.7%), or indefinite dysplasia, crypt dysplasia, low-grade dysplasia, and/or unspecified dysplasia (33.4%) on prior preablation endoscopies. Most patients also had a hiatus hernia (60.3%). Patients were included if they were being surveyed for BE after endoscopic eradication therapy (EET) (≥1 EET session) and did not have prior esophageal surgery other than endoscopic mucosal resection (EMR).The cohort included patients whose baseline diagnosis preablation was nondysplastic BE (NDBE), most of whom were derived from 2 large studies specifically looking at this group as well as patients with dysplasia. Additionally, the cohort included patients who had not yet completed EET as well as some deemed refractory to EET. Patients were excluded if information regarding endoscopy or histology were incomplete or unavailable for analysis. All patients underwent both WATS-3D and FB sampling at the time of postablation endoscopy.IM adjunctive yield of WATS was defined as the number of IM cases added by WATS (that were negative for IM by FB sampling) divided by the number of IM cases detected by FB sampling (including dysplasia cases).The absolute yield of WATS was defined as the number of cases that WATS detected (that were not detected by FB sampling) divided by the total number of cases.
Reported results from the cohort analysis include but are not limited to the following: the WATS-3D adjunctive yield for detection of residual/recurrent IM or dysplasia was 52.5% and 91.5%, respectively. The absolute yield for IM and dysplasia detection was 16% and 4.4%, respectively. Of 29 patients with high-grade dysplasia or esophageal adenocarcinoma detected by WATS3D, FB sampling missed 11, including 7 where FB sampling did not detect any IM. The added yield of detection of BE was found to be greater in patients with either no endoscopic evidence of residual BE (260%) or in those with short segments of residual BE (66.9%) compared with long-segment BE (21.1%). However, for dysplasia, no differences were noted according to either the presence or length of visible BE at endoscopy. Adverse events are unknown as they were not reported. Most patients were white (88%). A limitation of this study is the potentially conflicting reported inclusion criteria.

Kaul et al. (2020) conducted a retrospective review to evaluate the clinical utility of WATS3D and its impact on the management of patients with BE and dysplasia. The study included 432 consecutive patients who had a WATS3D positive and an accompanying forcep biopsy (FB) negative result. Physicians were contacted to determine if the WATS3D result impacted their decision to enroll patients in surveillance or increase the frequency of surveillance, recommend ablation, and/or initiate or increase the dose of proton pump inhibitors (PPIs). WATS3D directly

impacted the management of 97.8% of 317 BE patients; 96.2% were enrolled in surveillance and 60.2% were started on PPIs or their dose was increased. WATS3D impacted the management of 94.9% and 94.1% of the 98 low-grade dysplasia and 17 high-grade dysplasia patients, respectively. As a result of WATS3D, 33.7% of low-grade dysplasia and 70.6% of high-grade dysplasia patients underwent endoscopic therapy. More than 37% of all dysplasia patients were enrolled in a surveillance program, and nearly 30% were scheduled to be surveilled more frequently. PPIs were either initiated, or the dose was increased in more than 54% of all dysplasia patients.

Agha et al. (2021) conducted a retrospective observational cohort study and included 108 patients who underwent screening for BE with WATS3D and forceps biopsy (FB) between across three endoscopy centers. The FB specimens were reviewed by community pathologists, while the WATS3D samples were sent to CDX technology labs, NY. The review included 108 patients that were screened for BE using both modalities concurrently. FB and WATS3D detected 62 (57.4%) and 83 (76%) cases of BE, respectively. The absolute difference of 21 cases (18.6%) of BE was attributed to the addition of WATS3D. The number needed to test with
WATS3D was 5. The samples were divided into four groups to compare the agreement across all groups:
(FB−; WATS3D+), (FB−; WATS3D−), (FB+; WATS3D+), and (FB+ and WATS3D−). Overall agreement by kappa statistic was 0.74. The authors concluded that WATS3D identified 21 cases of BE missed by FB. Using WATS3D in addition to FB increased the yield of BE during surveillance endoscopy, with no increase in complications.

Professional Societies/Organizations
American College of Gastroenterology (ACG): The 2022 ACG Updated Guideline on the Diagnosis and Management of Barrett's Esophagus makes 21 recommendations. They are broken up by:

- Diagnosis
- Screening
- Surveillance
- Treatment (Medical)
- Treatment (Endoscopic).

Under Surveillance, the ACG recommends:

Surveillance-specific Recommendations	Quality of evidence	Strength of recommendation
8. We recommend both white light endoscopy and chromoendoscopy in patients undergoing endoscopic surveillance of BE.	Moderate	Strong
9. We recommend a structured biopsy protocol be applied to minimize detection bias in patients undergoing endoscopic surveillance of BE.	Low	Strong
10. We suggest endoscopic surveillance be performed in patients with BE at intervals dictated by the degree of dysplasia noted on previous biopsies.	Very low	Conditional
11. We recommend that length of BE segment be considered when assigning surveillance intervals with longer intervals reserved for those with BE segments of <3 cm.	Moderate	Strong
12. We could not make a recommendation on the use of wide-area transepithelial sampling with computer-		

Surveillance-specific Recommendations	Quality of evidence	Strength of recommendation
assisted 3-dimensional analysis in patients undergoing endoscopic surveillance of BE.		
13. We could not make a recommendation on the use of predictive tools (p53 staining and TissueCypher) in addition to standard histopathology in patients undergoing endoscopic surveillance of BE (Shaheen, et al., 2022).		

American Gastroenterology Association (AGA): The AGA 2022 Clinical Practice Update on New Technology and Innovation for Surveillance and Screening in Barrett's Esophagus: Expert Review states the following:

- Best Practice Advice 7: Wide-area transepithelial sampling (WATS-3D) may be used as an adjunctive technique to sample the suspected or established Barrett's segment (in addition to the Seattle biopsy protocol)

Further prospective studies directly comparing WATS-3D and Seattle protocol are needed to understand if WATS-3D sampling might be as or more effective (Muthusamy, et al., 2022).

American Society for Gastrointestinal Endoscopy (ASGE): ASGE published guidelines on the screening and surveillance of Barrett's esophagus (ASGE, 2019).
In patients with known or suspected BE, we suggest using WATS-3D in addition to Seattle protocol biopsy sampling compared with white-light endoscopy with Seattle protocol biopsy sampling.
Strength of recommendation: conditional
Quality of evidence: low

Strength of recommendations-conditional:
- Patients: Most individuals in this situation would want the suggested course of action, but many would not.
- Clinicians: Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
- Policymakers: Policymaking will require substantial debate and involvement of various stakeholders.

Quality of evidence- low:
- Meaning: Our confidence in the estimate of the effect is limited; the true effect may be substantially different from the estimate of the effect.
- Interpretation: Further research is very likely to have an impact on our confidence in the estimate of the effect and is likely to change the estimate.

National Comprehensive Cancer Network® (NCCN): NCCN clinical guideline for esophageal and esophagogastric junction cancers (Version 1.2023 — February 28, 2023) notes that the use of wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS3D) is a relatively new sampling technique combining an abrasive brush biopsy of the Barrett esophagus mucosa with computer-assisted pathology analysis to highlight abnormal cells, may help increase the detection of esophageal dysplasia in patients with Barrett esophagus. It does not include this test in the screening/testing recommendations for esophageal cancer. It is noted in the guideline,

"the utility and accuracy of WATS for detecting HGD/adenocarcinoma inpatients with Barrett's esophagus needs to be evaluated in larger phase III randomized trials."

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Coding Information Gastroenterology

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.

Transanal Endoscopic Microsurgical Approach (TEMS)

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

CPT®* Codes	Description
0184T	Excision of rectal tumor, transanal endoscopic microsurgical approach (ie, TEMS), including muscularis propria (ie, full thickness)

Services Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description	Comment
46999	Unlisted procedure, anus	Considered Experimental/Investigational/Unp

CPT®* Codes	Description	Comment
		roven when used to report transanal radiofrequency therapy for fecal Incontinence (e.g., SECCA procedure)
0106U	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	13C-Spirulina Platensis Gastric Emptying Breath Test Gastric Emptying Breath Test (GEBT) (Advanced Breath Diagnostics LLC)
0176U	Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (ie, ELISA)	IBSchek (Commonwealth Diagnostics International Inc.)
91299	Unlisted diagnostic gastroenterology procedure	Considered Experimental/Investigational/Unproven when used to report Ingestible devices for the treatment of constipation (e.g., Vibrant® System (Vibrant Ltd., Philadelphia, PA)

HCPCS Codes	Description
A9999	Miscellaneous DME supply or accessory, not otherwise specified
C9777	Esophageal mucosal integrity testing by electrical impedance, transoral includes esophagoscopy or esophagogastroduodenoscopy

Considered Experimental/Investigational/Unproven when used to report Wide-Area Transepithelial Tissue Sampling with Computer-Assisted 3D Analysis (WATS3D)

CPT®* Codes	Description
88104	Cytopathology, fluids, washings or brushings, except cervical or vaginal; smears with interpretation
88112	Cytopathology, selective cellular enhancement technique with interpretation (eg, liquid based slide preparation method), except cervical or vaginal
88305	Level IV - Surgical pathology, gross and microscopic examination
88312	Special stain including interpretation and report; Group I for microorganisms (eg, acid fast, methenamine silver)
88361	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology

ICD-10-CM Diagnosis Codes	Description
	All Codes

Neurology

Current perception threshold/sensory nerve conduction threshold (sNCT) test (HCPCS Code G0255)

Various testing methods and devices used determine sensory abnormalities and include electrical current testing such as current perception threshold (CPT) testing also known as sensory nerve conduction testing (sNCT). Determination of current perception threshold has been proposed for evaluation of patients with peripheral nervous system diseases resulting in altered cutaneous sensation. This type of testing is proposed to complement needle EMG and NCSs, to assist with evaluating treatment response or disease progression after a diagnosis is made. However, conflicting information and methodologic problems exist regarding the utility of this testing for the diagnostic evaluation of specific disease conditions such as carpal tunnel syndrome and polyneuropathy.

U.S. Food and Drug Administration (FDA)
Several devices have received 501(k) clearance as devices for current perception threshold/sensory nerve conduction test (sNCT). The indication is for quantitative detection of sensory neurological impairments. The FDA states Medi-Dx 7000 (K964622, 1997) is a device 'for the examination of peripheral neuropathies'.
The devices include but are not limited to:

- Medi-Dx 7000 (Neuro Diagnostic Associates, Inc.)
- Neurometer® (Neurotron, Inc.)
- NC-stat (NeuroMetrix Inc.)

Literature Review
The published evidence is insufficient to determine the effectiveness of this testing.

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 CPT for diagnosis of carpal tunnel syndrome (AAOS, 2016).

American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM): this organization published Model Policy for Needle Electromyography and Nerve Conduction Studies (2010, last updated March 2021). It is noted that, "Current Perception Threshold/Sensory Nerve Conduction Threshold Test (sNCT) is investigational and not covered. This procedure is different and distinct from assessment of nerve conduction velocity, amplitude, and latency. It is also different from short-latency somatosensory evoked potentials (SSEPs)."

American Academy of Neurology: In a 2003 report from the Therapeutics and Technology Assessment Subcommittee of the AAN titled 'Quantitative Sensory Testing', the AAN concluded "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. Because malingering and other nonorganic factors can influence the test results, QST is not currently useful for the purpose of resolving medicolegal matters. Well-designed studies comparing different QST devices and methodologies are needed and should include patients with abnormalities detected solely by QST."

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Physiologic Recording of Tremor Using Accelerometer/Gyroscope (CPT Code 95999, 0533T, 0534T, 0535T, 0536T)

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. Kinesia ONE and Kinesia 360 (Great Lakes NeuroTechnologies Inc., Cleveland, OH) are systems that include wearable sensors for measuring PD motor symptoms. Kinesia ONE measures tremor, bradykinesia, and dyskinesia using a sensor worn on one finger during standardized motor tasks. It provides objective tracking of a subset of the Unified Parkinson's Disease Rating Scale (UPDRS) Part III items. Kinesia 360 allows continuous motor symptom monitoring throughout the day during activities of daily living (ADL) using sensor bands worn on the wrist and ankle on one side of the body.

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.

The Personal Kinetigraph (PKG) System (Global Kinetics Corporation, Australia) received 510(k) approval on August 22, 2014 (K140086). Indications for Use include "The Personal Kinetigraph (PKG) System is intended to quantify kinematics of movement disorder symptoms in conditions such as Parkinson's disease, including tremor, bradykinesia and dyskinesia. It includes a medication reminder, an event marker and is intended to monitor activity associated with movement during sleep. The device is indicated for use in individuals 46 to 83 years of age."

Literature Review
Joshi et al. (2019) reported on 63 Parkinson's disease (PD) patients who wore a watch-device called the Personal KinetiGraph (PKG) for six continuous days before their visit. The authors reported the PKG system provided clinical utility through improved characterization of motor manifestations of Parkinson's disease, both the type and timing.

Santiago et al. (2019) conducted a prospective physician survey study to evaluate the impact of using continuous objective measurement provided by the PKG in the routine clinical care of patients with PD. Four physicians employed the use of the PKG in 89 patients for whom they were seeking objective measurement. Patients wore a PKG data logger for ≥6 days during routine daily living activities. Of the 89 patients, 45 had one PKG, 44 had two PKGs, and 10 of the 44 patients went on to have three PKGs completed as part of their routine clinical evaluation and follow-up PD care visits. The survey completion rate was 83% (119/143). Results reported included that

physicians' adjusted treatment nearly a third of the time based on the real-time clinical status captured during objective continuous monitoring outside the clinic setting, rather than solely based on the traditionally obtained historical survey provided during a routine clinical visit.

Isaacson et al. (2019) reported on a 12-week pilot study conducted to investigate whether motor symptom management in patients with PD starting transdermal rotigotine could be improved by using Kinesia 360 at home (NCT03103919). A total of 39 PD patients were included: 20 in the Control group (CG) and 19 in the Experimental group (EG). Two patients each in the CG (10%) and EG (10.5%) discontinued from the study; for all four, the primary reason was treatment-emergent adverse events (TEAEs). The study was not powered to detect statistically significant differences between the two study sets.

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 accelerometry 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.

Professional Societies/Organizations
The American Academy of Neurology Practice parameter: therapies for essential tremor (2005/2011) does not address remote monitoring using Accelerometer/Gyroscope technology.

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Adrenal and Fetal Mesencephalic Transplantation for Parkinson’s disease (HCPCS Code S2103)

Researchers have been looking for alternative strategies to supplement dopamine by replacing the dopaminergic neurons lost in Parkinson’s disease with stem-cell-derived equivalents. According to

a review of emerging treatment approaches for Parkinson's disease, Stoker et al. (2018) notes the following:

- Adrenal medullary tissue has been studied in humans, with poor graft survival and neuropsychiatric complications.
- The use of human fetal ventral mesencephalon tissue grafts has been studied in humans. Ethical and logistical barriers (chiefly the unpredictable and inadequate supply of fetal tissue) means that this approach will never be a viable mainline therapy for this condition.
- Mesenchymal stem cells have been studied in humans. Limitations include not possible to generate authentic dopaminergic neurons and theoretical risk of tumorigenesis
- Porcine ventral mesencephalon, retinal pigment epithelium cells, carotid body cells have been studied in humans, with little clinical benefit.
- Human trials evaluating embryonic stem cell (ESC)-derived neural progenitors and induced pluripotent stem cell (iPSC)-derived neural progenitors dopaminergic neuron progenitors are scheduled.

The main concern regarding the use of stem cell-based therapies for PD is the theoretical potential for tumor formation. This may occur due to overgrowth of the graft or the presence of mutations in oncogenes or tumor suppressor genes in the grafted cells. Interpretation of genetic abnormalities within a graft product is challenging, and because of this, forthcoming clinical trials have adopted different strategies for genetic testing. Robust investigation of safety, and thorough surveillance will be vital to ensure that the risk of tumor formation is negligible, if these treatments are to be successful.

Literature Review
Wang et al. (2022) conducted a meta-analysis aimed at assessing the efficacy and safety of cell transplantation for PD. It included 120 patients in 10 studies (9 single-arm clinical trials and 1 RCT studies). Five types of cell therapy were involved, including 1) human fetus 2) pig embryo 3) bone-marrow-derived mesenchymal stem cells (BM-MSCs) 4) human retinal pigment epithelial (HRPE) and 5) neural progenitor cells (NPC). Seven studies reported significant improvement in Unified Parkinson's Disease Rating Scale (UPDRS) III, 2 studies showed poor results. In terms of safety, 7 papers reported that cell transplantation was safe and well-tolerated, whereas 3 papers reported cell transplantation related complications, including depressive suicidal tendencies, cell transplantation-related cerebral infarction (with sequelae), and cell transplantation procedure-related death. The authors stated their results require additional long-term prospective clinical studies with large samples. With the establishment of best practice guidelines for stem cell therapies, it will be possible to develop more effective and Safety approaches to treating PD.

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
International Parkinson and Movement Disorder Society**:** The International Parkinson and Movement Disorder Society (MDS) January 2021 Position Paper on Use of Stem Cell Therapies for Parkinson's Disease concludes "Cell-based therapies should demonstrate efficacy and safety particularly lacking adverse immune reactions, tumor formation or dyskinesias. There have been great advances in the research of stem-cell therapy, especially for PD, and clinical trials are ongoing. However, for the time being there is still not enough evidence to support the widespread use of cell-based therapies for PD outside of carefully controlled clinical trials._We are hopeful for the future progress of such therapies based on extensive translational studies in proper animal models, and international clinical approaches with properly designed trials."

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.

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Coding 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:

CPT®* Codes	Description	Comment
95999	Unlisted neurological or neuromuscular diagnostic procedure	Considered Experimental/Investigational/Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s)

CPT®* Codes	Description	Comment
0533T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; includes set-up, patient training, configuration of monitor, data upload, analysis and initial report configuration, download review, interpretation and report	Considered Experimental/Investigational/Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
0534T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; set-up, patient training, configuration of monitor	Considered Experimental/Investigational/Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
0535T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; data upload, analysis and initial report configuration	Considered Experimental/Investigational/Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s)
0536T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; download review, interpretation and report	Considered Experimental/Investigational/Unproven when used to report tremor measurement with accelerometer(s) and/or gyroscope(s)

HCPCS Codes	Description
G0255	Current perception threshold/sensory nerve conduction test, (sNCT) per limb, any nerve
S2103	Adrenal tissue transplant to brain

Ophthalmology

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

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], 2022). 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 (SECOND SIGHT, LLC., Sylmar, CA, [now Vivani Medical, Inc.]) received a Humanitarian Device Exemption (HDE) from the FDA in February 2013 (H110002). 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.

According to ClinicalTrials.gov, NCT01860092 recruitment was terminated. Manufacturing ceased for all Argus II and Argus 2s devices (FDA notified of and subsequently approved discontinuation of post approval study in Oct 2021).

The SecondSight (now Vivani Medical, Inc.) website states the following:

> About Argus® II
> The world's first FDA-approved prosthetic retina implant, Argus II provides artificial vision to blind individuals with retinitis pigmentosa (RP) by stimulating remaining viable retinal cells to induce visual perception.*
>
> *Authorized by Federal (U.S.) law to provide electrical stimulation of the retina to induce visual perception in blind patients with severe to profound retinitis pigmentosa and bare light or no light perception in both eyes. The effectiveness of this device for this use has NOT been demonstrated."

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 et al. (2016) 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 nine 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 three 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.

Ghani et al. (2023) retrospectively reported results of five patients diagnosed with profound retinal dystrophy who had undergone implantation of retinal prosthesis at Stony Brook University Hospital. The authors noted that the electrode array is fixed to the retina by a single titanium tack. Analysis of fundus images at each patient’s routine post-operative appointments revealed that the electrode array was shifting in its position in both a linear and rotational fashion between each appointment. Over a two-year postoperative timeframe, there was a counterclockwise rotation around the implant’s surgical tack.

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

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Coding 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

Ophthalmology Services Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description	Comment
0100T	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intraocular retinal electrode array, with vitrectomy	Argus II Retinal Prosthesis System (Argus II) (Second Sight Medical Products, Inc.)
0472T	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	Argus II Retinal Prosthesis System (Argus II) (Second Sight Medical Products, Inc.)
0473T	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	Argus II Retinal Prosthesis System (Argus II) (Second Sight Medical Products, Inc.)

Other

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.

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 ImpediMed SOZO® device received 510(k) approval on January 12, 2018.The SOZO Body Fluid Analyzer has the following uses for adult human patients at risk of lymphedema:

- A bioimpedance spectroscopy device for use on adult human patients, utilizing impedance ratios that are displayed as an L-Dex ratio that supports the measurement of extracellular volume differences between the limbs and is presented to the clinician on an L-Dex scale as an aid to their clinical assessment of lymphedema.
- The use of the device to obtain an L-Dex score is only indicated for patients who will have or who have had lymph nodes, from the axillary and/or pelvic regions, either removed, damaged or irradiated.

The SOZO® device received 510(k) approval on April 19, 2021 (K203473) for use in heart failure patients. The SOZO Body Fluid Analyzer is intended for use, under the direction of a physician, for the noninvasive monitoring of patients with fluid management problems suffering from heart failure. Data from the device should be considered in conjunction with other clinical data.

Literature Review

Ridner et al. (2022) reported results from a multicenter, randomized clinical trial that compared bioimpedance spectroscopy (BIS) and tape measure (TM) measurements for breast cancer-related lymphedema (BCRL)
surveillance among newly diagnosed breast cancer patients. Median follow-up was 32.9 months. A total of 963 (BIS n = 482; TM n = 481) patients were randomized and 879 analyzed (BIS n = 442; TM n = 437). The authors concluded that use of BIS as part of prospective BCRL surveillance, coupled with early compression sleeve and gauntlet intervention, significantly reduced chronic BCRL (progression to complex decongestive physiotherapy [CDP]), (7.9% vs. 19.2%, p = 0.016) compared to TM.

Shah et al. (2021) conducted a meta-analysis to evaluate the impact of monitoring techniques on the incidence of chronic breast cancer-related lymphedema (BCRL) among patients monitored by bioimpedance spectroscopy (BIS) and circumference. Incidence rates from 50 studies (>67,000 women) were classified by BCRL monitoring method: background (no standardized BIS or circumference assessments), BIS or circumference. Authors concluded that monitoring with BIS allowing for early intervention significantly reduces the relative risk of chronic BCRL with a 69% and 81% reduction compared to background and circumference, respectively.

Cho et al. (2020) reported on a prospective cohort study to evaluate the use of bioimpedance analysis (BIA) as a tool to measure lymphedema before and after treatment. The study included 29 patients with cancer treatment-related lymphedema (CTRL) who were admitted to a secondary university hospital for complex decongestive therapy (CDT) (12 upper- and 17 lower-extremity CTRL). Circumferential measure (CM) and BIA were used to evaluate lymphedema at admission (initial) and before discharge (follow-up, FU). The authors concluded that BIA data correlates significantly with clinical measurement, and therefore can be a practical tool in monitoring outcome measure after lymphedema treatment. The study was limited by the small number of participants and lack of randomization.

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%. 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) conducted 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 spectroscope (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.

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. 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.

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
The NCCN® Practice Guidelines in Oncology (NCCN Guidelines®) Survivorship (Version 1.2023 — March 24, 2023) states under Principles of Lymphedema:

- Early detection/diagnosis and early referral are key for optimal lymphedema management because stages 0 and 1 are reversible, whereas stages 2 and 3 are less responsive to treatment. Therefore, survivors at risk for lymphedema should be regularly screened for lymphedema by symptom assessment, clinical exam, and, if available, bioimpedance spectroscopy. Patients should be educated about early symptoms and signs of lymphedema including fullness, tightness, heaviness, and pain (page SLYMPH-2).

On page SLYMPH-3, the algorithm for Screening of Survivor at risk for lymphedema includes:

- Perform clinical examination, which may include, but is not limited to:
  - Range of motion
  - Muscle performance
  - Circulation
  - Sensation
  - Hemodynamic functioning
  - Functional mobility
  - If available, obtain objective measurements to identify early signs of lymphedema; tools may include bioimpedance spectroscopy

The NCCN® Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer (Version 4.2023 — March 23, 2023) states:

- Lymphedema is a potential side effect after the treatment of axillary lymph node surgery resulting from damage to the lymphatic system. Early detection/diagnosis of lymphedema is key for optimal management. Consider pretreatment measurement of both arms as a baseline for patients with risk factors for lymphedema.

American Society of Breast Surgeons (ASBrS)
The American Society of Breast Surgeons Lymphatic Surgery Working Group conducted a large review of the literature in order to develop guidelines on breast cancer- related lymphedema (BCRL) prevention and treatment.
The article discusses tape measure, perometry, water displacement and bioimpedance spectroscopy as assessment tools for BCRL but does not make any recommendations (McEvoy, et al., 2022).

The ASBrS 2022 Consensus Guideline on Axillary Management for Patients With In-Situ and Invasive Breast Cancer addresses surgical techniques only, when discussing prevention of lymphedema.

The ASBrS 'Considerations for Clinicians in the Diagnosis, Prevention, and Treatment of Breast Cancer-Related Lymphedema: Recommendations from a Multidisciplinary Expert ASBrS Panel : Part 1: Definitions, Assessments, Education, and Future Directions' (McLaughlin, et al., 2017) states these recommendations:

- Recommendation 1: The panel agrees that clinicians should establish a surveillance plan because early diagnosis leads to early treatment and increases the likelihood for limited disease burden.
- Recommendation 2: The panel agrees that baseline and follow-up measurements of the ipsilateral and contralateral arms of all breast cancer patients are critical. All measurement techniques have advantages and disadvantages that should be considered when a comprehensive measurement strategy is developed that includes a combination of objective and subjective measures.

American College of Cardiology (ACC)
The 2022 American College of Cardiology (ACC) and the American Heart Association (AHA) Guideline for the Management of Heart Failure (Heidenreich, et al., 2022) does not address bioimpedance spectroscopy.

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Frequency of Physical, Occupational, and Chiropractic Services

Physical and occupational therapists provide services to patients who have impairments, functional limitations, disabilities, or changes in physical function and health status resulting from injury, disease, or other causes. Medically necessary therapy services must relate to a written treatment plan of care and be of a level of complexity that requires the judgment, knowledge and skills of a physical and/or occupational therapist to perform and/or supervise the services. The plan of care for medically necessary physical therapy and/or occupational therapy services is established by a licensed physical or occupational therapist. The amount, frequency and duration of the therapy services must be reasonable (within regional norms and commonly accepted practice patterns); the services must be considered appropriate and needed for the treatment of the condition and must not be palliative in nature. Thus, once therapeutic benefit has been achieved, or a home exercise program could be used for further gains without the need for skilled therapy, continuing supervised physical and/or occupational therapy is not considered medically necessary.

Chiropractic is a health care profession that focuses on disorders of the musculoskeletal system and the nervous system, and the effects of these disorders on general health. Chiropractic services are used most often to treat musculoskeletal and related conditions. Chiropractic services are intended to improve, adapt or restore functions which have been impaired or permanently lost as a result of illness, injury, loss of a body part, or congenital abnormality involving goals an individual can reach in a reasonable period of time. Spinal manipulation (sometimes referred to as a "chiropractic adjustment") is a common, therapeutic procedure performed by doctors of chiropractic. The purpose of spinal manipulation is to restore joint mobility by manually applying a controlled force into joints that have become hypomobile, or restricted in their movement, as a result of a tissue injury. Manipulation, or adjustment of the affected joint and tissues, restores mobility, thereby alleviating pain and muscle tightness allowing tissues to heal. In addition to manual therapy other procedures/modalities, both passive and active, are often used as adjunct treatments throughout the treatment program. The medical necessity of continued chiropractic care is dependent on documented progress toward therapeutic goals. Maximum therapeutic benefit has been reached when the patient fails to show improvement, or when a pre-injury level of functioning has been reached.

Physical, occupational and chiropractic care involve the use of a variety of physical medicine and rehabilitation modalities and procedures depending on the patient’s condition, response to care, and treatment tolerance. The outpatient level of care is the most medically appropriate setting for these services unless the individual independently meets coverage criteria for a different level of care. Each of these treatment sessions last up to one-hour on any given day, and all services must be supported in the treatment plan and be based on an individual's medical condition. Consistent with Centers for Medicare & Medicaid Services (CMS) Local Coverage Determinations (LCDs), up to a maximum of 4 timed codes (modalities and procedures) will be allowed. Services in excess of 60 minutes per day are generally not demonstrated to have additional medical benefit in an outpatient setting.

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   Section 230 - Practice of Physical Therapy, Occupational Therapy, and Speech-Language Pathology. Rev. 63, Issued: 12-29-06, Effective: 01-01-07, Implementation: on or before 01-29-07)
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Coding 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

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

CPT®* Codes	Description	Comment
93702	Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)	L-Dex U400 ExtraCellular Fluid analyzer, and SOZO® device (ImpediMed Inc.)

Other - Physical Therapy, Occupational Therapy and Chiropractic Care Considered Not Medically When Treatment Visit Extends Beyond 4 Timed Unit Services (Equivalent to One Hour), Per Date of Service, Per Provider:

CPT®* Codes	Description
97032	Application of a modality to 1 or more areas; electrical stimulation (manual), each 15 minutes
97033	Application of a modality to 1 or more areas; iontophoresis, each 15 minutes
97034	Application of a modality to 1 or more areas; contrast baths, each 15 minutes
97035	Application of a modality to 1 or more areas; ultrasound, each 15 minutes

CPT®* Codes	Description
97036	Application of a modality to 1 or more areas; Hubbard tank, each 15 minutes
97110	Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility
97112	Therapeutic procedure, 1 or more areas, each 15 minutes; neuromuscular reeducation of movement, balance, coordination, kinesthetic sense, posture, and/or proprioception for sitting and/or standing activities
97113	Therapeutic procedure, 1 or more areas, each 15 minutes; aquatic therapy with therapeutic exercises
97116	Therapeutic procedure, 1 or more areas, each 15 minutes; gait training (includes stair climbing)
97124	Therapeutic procedure, 1 or more areas, each 15 minutes; massage, including effleurage, petrissage and/or tapotement (stroking, compression, percussion)
97140	Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes
97530	Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes
97535	Self-care/home management training (eg, activities of daily living (ADL) and compensatory training, meal preparation, safety procedures, and instructions in use of assistive technology devices/adaptive equipment) direct one-on-one contact, each 15 minutes
97542	Wheelchair management (eg, assessment, fitting, training), each 15 minutes
97760	Orthotic(s) management and training (including assessment and fitting when not otherwise reported), upper extremity(ies), lower extremity(ies) and/or trunk, initial orthotic(s) encounter, each 15 minutes
97761	Prosthetic(s) training, upper and/or lower extremity(ies), initial prosthetic(s) encounter, each 15 minutes
97763	Orthotic(s)/prosthetic(s) management and/or training, upper extremity(ies), lower extremity(ies), and/or trunk, subsequent orthotic(s)/prosthetic(s) encounter, each 15 minutes
G0151	Services performed by a qualified physical therapist in the home health or hospice setting, each 15 minutes
G0152	Services performed by a qualified occupational therapist in the home health or hospice setting, each 15 minutes
G0160	Services performed by a qualified occupational therapist, in the home health setting, in the establishment or delivery of a safe and effective occupational therapy maintenance program, each 15 minutes
G0237	Therapeutic procedures to increase strength or endurance of respiratory muscles, face-to-face, one-on-one, each 15 minutes (includes monitoring)
G0238	Therapeutic procedures to improve respiratory function, other than described by G0237, one-on-one, face-to-face, per 15 minutes (includes monitoring)

Otolaryngology

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) H_20 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
A Cochrane review evaluated the benefits and risks of positive pressure therapy for Ménière's disease. The review included three studies with a total of 238 participants, all of which compared positive pressure using the Meniett device to sham treatment. The duration of follow-up was a maximum of four months. Key findings included:

- Due to a lack of robust evidence, it is not clear whether positive pressure therapy works to improve the symptoms of people with Ménière's disease. We did not find any information on whether this treatment may cause any harm.
- Larger, well-conducted studies are needed in order to identify whether positive pressure therapy may be effective, and make sure that there are no harmful effects of treatment.
- Further work also needs to be done to find out how best to measure the symptoms of people with Ménière's disease, in order to assess whether treatments are beneficial or not. This should include the development of a 'core outcome set' - a list of things that should be measured in all studies on Ménière's disease (Webster, et al., 2023).

Devantier et al. (2019) reported on a systematic review to critically assess the current evidence investigating the efficacy of using a positive pressure device in patients with definite or probable Menière's disease. The review included both systematic reviews and primary literature [randomized controlled trials (RCTs)] investigating positive pressure treatment, in patients (≥ 18 years of age), with Menière's disease. The review included five randomized controlled trials. The data synthesis showed no effect of positive pressure treatment on primary nor secondary outcomes. No serious adverse events were reported. The overall certainty of evidence ranged from very low to low, due to the serious risk of bias and imprecision. The authors concluded that

the current available evidence does not support positive pressure device treatment in patients with Menière's disease, the authors note that the limitations of the current literature hinder the possibility of any solid conclusion and there remains a need for randomized controlled trials of high quality to fully access the utility of this treatment.

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.

Professional Societies/Organizations
American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS): AAO-HNS published clinical practice guideline for Ménière's disease (Basura, et al., 2020). The guidelines address positive pressure therapy:

- Clinicians should not prescribe positive pressure therapy to patients with Ménière's disease. Recommendation against based on a systematic review and randomized trials showing ineffectiveness of devices like the Meniett devices with a preponderance of benefit over harm for not using.

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Tympanostomy (requiring insertion of ventilating tube), using an automated tube delivery system, iontophoresis local anesthesia (CPT® 0583T)

Over 6 million children in the United States have tympanostomy tubes, with a prevalence of 8.6% based on data from the 2014 National Health Interview Survey. Tube insertion in children is usually performed in a surgical setting under general anesthesia, but interest in office insertion has grown because of convenience and concerns over potential anesthetic-related adverse events.

U.S. Food and Drug Administration (FDA)

Initial approval occurred April 1, 2011 (K103595) for the Acciarent Tympanostomy Tube and Tympanostomy Tube Delivery System (Acclarent, Inc., USA, now Tusker Medical Inc.). Several related approvals occurred since then including but not limited to:

- June 16 2011 (K110636 Tula™ Iontophoresis System , Acclarent, Inc., USA)
- May 20, 2015 (K150453, Tula Iontophoresis System with Earset, Acclarent, Inc., USA)
- June 28, 2017 (K171239, TULA Tube Delivery System, Tusker Medical, USA)

On November 25, 2019, Tula® System (Tusker Medical Inc., USA) received PMA approval (P190016):

- Device Description: The Tula® System is a combination product that consists of an Iontophoresis System (IPS), a Tube Delivery System (TDS), and a lidocaine hydrochloride 2% and epinephrine 1:100,000 (0.01 mg/mL) otic iontophoretic drug solution (TYMBION) to be used with the IPS.
- Indications for Use:
  - Tula System: The Tula® System is intended to create a myringotomy and insert a tympanostomy tube using the Tula Tube Delivery System in pediatric (aged 6 months and older) and adult patients indicated to receive tympanostomy tubes. The Tula System is used to deliver a tympanostomy tube under local anesthesia induced using the Tula Iontophoresis System and TYMBION™, a combination of an amide local anesthetic and an alpha- and beta-adrenergic agonist.
  - TYMBION: TYMBION™, a combination of an amide local anesthetic and an alpha- and betaadrenergic agonist, is indicated for the induction of local anesthesia of the tympanic membrane via iontophoresis using the Tula® Iontophoresis System in pediatric (aged 6 months and older) and adult patients undergoing tympanostomy tube placement using the Tula Tube Delivery System.

The use of the Tula® System is CONTRAINDICATED in the following patients:

- Cases in which the tympanic membrane is significantly atrophic, significantly retracted in the target location for tube delivery, or completely atelectatic.
- Patients presenting with tympanic membrane (TM) perforation(s). It is recommended that otoscopy and tympanometry be used in the assessment of the TM.
- Active or recent conditions of the tympanic membrane (e.g., prior myringotomy with incomplete wound healing or re-epithelialization)
- Hemotympanum or other suspicion of aberrant vasculature (e.g., carotid artery; high riding jugular bulb, vascular tumors) impacting the tympanic membrane or middle ear.
- Patients presenting with lacerations/abrasions to the external auditory canal.
- Patients presenting with dimeric or monomeric tympanic membrane.
- Presence of otitis externa.
- Patients with electrically sensitive medical support systems (e.g., pacemakers, defibrillators, cochlear implants).
- Patients with a history of sensitivity or allergic reaction to lidocaine hydrochloride (HCl), tetracaine, epinephrine, or any hypersensitivity to local anesthetics of the amide type, or any component of the anesthetic drug formulation.
- Patients with a familial history of insensitivity to lidocaine or other local anesthetics.
- Anatomical or visualization reasons preventing tympanostomy tube placement in the anterior half of the tympanic membrane.

Literature Review

FDA approval was primarily based upon the Tusker Medical 'OTTER' clinical trial (in-Office Tympanostomy Tube placEment in childRen; NCT03323736; Lustig, et al., 2020). The study established a reasonable assurance of safety and effectiveness of the Tula® System for the placement of tympanostomy tubes in unsedated and unrestrained children in a physician office setting. The OTTER study was a prospective, single-arm, multi-center, non-randomized study in pediatric subjects undergoing tympanostomy tube placement. There were 18 investigational sites.

Each investigator was required to treat a minimum of two 'OR Lead-In' subjects under general anesthesia using the TDS alone without iontophoresis. Following completion of the OR procedures, each investigator was required to treat a minimum of two 'Office Lead-In' subjects undergoing tympanostomy tube placement under local anesthesia using the TDS and IPS with TYMBION. Upon

completion of the OR and Office subjects, investigators were permitted to begin treating subjects to obtain study findings (the Pivotal Cohort). Exclusion criteria included behavioral intolerance.

The studied "Pivotal' cohort included 222 pediatric individuals (N=120 < age 5 years, N=102 age 5-12 years).

Technology explanation: An iontophoresis system (IPS) together with an iontophoretic otic anesthesia solution were used to provide local anesthesia to the tympanic membrane (TM), and a tube delivery system (TDS) was used to rapidly create the myringotomy and deliver the tube.

The TM was anesthetized using the IPS and an iontophoretic otic solution (TYMBION™) consisting of 2% lidocaine HCl and 1:100,000 epinephrine (Tusker Medical, Menlo Park, CA), henceforth referred to collectively as IPS. The IPS accelerates tissue uptake of the local anesthetic using a submilliamp electrical current that mobilizes ions of lidocaine and epinephrine achieving local anesthesia of the TM in approximately 10 minutes (unilateral or simultaneous bilateral). The IPS system includes specialized earplugs that maintain the otic solution in the ear canal during the iontophoresis process.

Once the TM was anesthetized, the lidocaine and epinephrine solution was drained from the ear canal by gravity or wicking, and TTs were placed using the TDS (Tusker Medical). The TDS automates myringotomy and tube placement. Upon device actuation, an incision is created, and the tube is placed in <500 milliseconds. The myringotomy blade is recessed within the device except for a brief exposure during myringotomy creation.

Results: Twelve patients treated in-office were determined to have inadequate anesthesia for tube placement in one or both ears following iontophoresis. Tubes were successfully placed in all indicated ears in 85.8% (103/120) of children <5 and 89.2% (91/102) of children 5 to 12 years old. Patients 5 to 12 years old self-reported tube placement pain using the Faces Pain Scale–Revised (FPS-R) instrument, which ranges from 0 (no pain) to 10 (very much pain). Mean FPS-R score was 3.30 (mild range) (standard deviation [SD] = 3.39) for tube placement and 1.69 (SD = 2.43) at 5 minutes post-procedure. There were no serious AEs in any study cohorts that were associated with the study devices, drug, or procedure. Nonserious adverse events occurred at rates similar to standard tympanostomy procedures. Study limitations included only 3 week post-procedure follow-up and exclusion criteria of 'behavioral intolerance' (Lustig, et al., 2020).

Waldman et al. (2023) reported results on the above (Lustig, et al., 2020) patient cohort (mean follow-up was 14.3 months). Patients were followed for 2 years or until tube extrusion, whichever occurred first. Patient compliance with protocol-required follow-up visits was 94.5% (189/200) in the OR Lead-In and 92.3% (930/1008) in the In-Office cohorts.

- Tube retention: At the 3-week visit, 99.7% of tubes were present across the TM, with 91.7% at 6 months, 67.1% at 12 months, 39.1% at 18 months, and 22.7% at 24 months for all subjects. In a small number of patients, a tube was removed by the physician. Six patients (9 ears) had tubes removed due to a history of infection or tube occlusion, and 5 patients (5 ears) had a tube removed and replaced during a subsequent tube placement procedure for the contralateral ear.
- Time to Extrusion: The estimated median and mean times to tube extrusion for the combined OR and In-Office cohorts were 15.82 and 16.79 months, respectively. When removed tubes were included in the analysis, the estimated median and mean times to tube extrusion or removal were 15.77 and 16.72 months, respectively.
- Sequelae included ongoing perforation for 1.9% of ears (11/580) and medial tube displacement for 0.2% (1/580) observed at 18 months. Over a mean follow-up of 14.3 months, 30.3% (176/580) of ears had otorrhea and 14.3% (83/580) had occluded tubes.

The authors concluded that in-office placement of tubes using the Tula System results in rates of tube retention and patency within the ranges described for similar short term tympanostomy tubes. Complications were of a type and rate consistent with expectations for tube placement via traditional methods in the OR (Waldman, et al., 2023).

Cohen 2022 reported a sub-analysis from the above (Lustig, et al., 2020) patient cohort. Behavioral strategies were used to minimize procedural distress. Anxiolytics, sedation, or papoose board were not used. Face, legs, activity, cry, consolability (FLACC) behavior observational rating scale to quantify children's distress. Mean tube placement FLACC score was 4.0 (out of a maximum score of 10) for children ages 6 months to 4 years and was 0.4 for children age 5–12 years. Mean FLACC score 3-min post-tube placement was 1.3 for children ages 6 months to 4 years and was 0.2 for children age 5 12 years. FLACC scores were inversely correlated with age, with older children displaying lower distress.

Professional Societies/Organizations
The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) has published several recent related articles:

- Position Statement: In-office Placement of Tubes in Pediatric Patients While Awake (2019)
  The statement says "The position of the AAO-HNS is that tympanostomy tubes are safe and effective for managing otitis media in children who meet current guidelines for tube insertion [Rosenfeld, 2013]. Although insertion of tympanostomy tubes in children is generally accomplished in the operating room under general anesthesia, insertion in the clinic in appropriately selected patients using shared decision making between clinicians and families can be appropriate" (Adopted 7/09/2019).

- Clinical Practice Guideline: Tympanostomy Tubes in Children (Update) (Rosenfeld 2022a)
  This update does not include any recommendations regarding office insertion of tubes in children without general anesthesia.
  The group consensus was that the quality and breadth of published research (November 2020) was insufficient to facilitate evidence-based recommendations on in-office tube insertion.
  Readers are referred to a 'Companion Article' that is a 'State of the Art' Review.

- State of the Art Review: The existing literature is too sparse to make recommendations about procedure setting and optimal technique or assess long-term outcomes. The role of automated devices is uncertain, given the increased equipment cost and limited information on characteristics of the proprietary preloaded tubes, including intubation duration and rates of otorrhea, obstruction, medialization, granulation tissue, and persistent perforation (Rosenfeld 2022b).

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Coding 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 - Tympanostomy using an automated tube delivery system, iontophoresis local anesthesia (TULA):

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

CPT® Codes	Description
0583T	Tympanostomy (requiring insertion of ventilating tube), using an automated tube delivery system, iontophoresis local anesthesia

Otolaryngology Considered Experimental/Investigational/Unproven:

HCPCS Codes	Description
E2120	Pulse generator system for tympanic treatment of inner ear endolymphatic fluid

***Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.**

Urology

Transperineal Periurethral Balloon Continence Device (CPT codes 53451, 53452)

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 that 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—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.

The ACT device for women is currently undergoing clinical trials. The Adjustable Continence Therapy (ACT) for the Treatment of Female SUI study is a prospective, single arm, non-randomized, multicenter, prospective case-series trial. It includes 167 participants to examine the effectiveness of this device.

de Guerry et al. (2022) reported on a retrospective cohort study involving five French academic institutions.
A total of 281 women were implanted with ACT® balloons to treat SUI. At baseline, 137 women (48.8%) complained of mixed UI and 70 (24.9%) were receiving a concomitant overactive bladder (OAB) therapy. In addition, 182 women (64.6%) had a history of previous SUI surgery, and 88 (31.3%) had a history of vaginal prolapse surgery. The primary endpoint was the effectiveness

assessed 1 year after implantation. Success was defined as a maximum 1 pad/24 h associated with a numerical rating scale (NRS) ≥ 8/10. Improvement was defined as a decrease in daily pad use associated with a NRS ≥ 5/10. Failure was defined as an increase or stability in daily pad use or a NRS < 5/10. At 1 year, 70.5% of women achieved success or improvement, while intra- or postoperative surgical complications occurred in 36.1% of them. Intraoperative surgical complications occurred in 13 women (4.6%) while early and late postoperative surgical complications were reported in 35 (12.5%) and 75 (26.7%), respectively. Uni- or bilateral explantation was performed in 26.7% of women—mainly due to surgical complications—almost half of them (46.7%) were reimplanted the same year. Study limitations include retrospective design and short follow-up duration.

Ronzi et al. (2019) conducted a retrospective cohort study in France 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.

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. Explanation 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), which was reduced to an average of 1.1 PPD after ProACT implantation. The number of patients that were considered "dry" was 60.2% and the number of patients who were found to be either "dry" or improved greater than 50% was 81.9%. The meta-analysis estimate for intraoperative perforation of the bladder or urethra is 5.3%. Estimates for infection and urinary retention were 2.2% and 1.5%, respectively. The estimated overall revision rate for all causes is 22.2% 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.

Angulo et al. (2019) conducted a meta-analysis to determine the safety and efficacy of Adjustable Transobturator Male System (ATOMS) and ProACT for male SUI. Combined data of 41 observational studies with 3059 patients showed higher dryness (68 vs. 55%; p = .01) and improvement (91 vs. 80%; p = .007) rate for ATOMS than ProACT. Mean pad-count (-4 vs. -2.5 pads/day; p = .005) and pad-test decrease (-425.7 vs. -211.4 cc; p < .0001) were also significantly lower. Satisfaction was higher for ATOMS (87 vs. 56%; p = .002) and explant rate was higher for proACT (5 vs. 24%; p < .0001). Complication rate for ProACT was also higher, but not statistically significant (17 vs. 26%; p = .07). Mean follow-up was 25.7 months, lower for ATOMS than ProACT (20.8 vs. 30.6 months; p = .02). The rate of working devices favored ATOMS at 1-year (92 vs. 76; p < .0001), 2-years (85 vs. 61%; p = .0008) and 3-years (81 vs. 58%; p = .0001). The authors concluded that both the ProACT and the ATOMS system appear efficacious and safe procedures to treat male stress incontinence. However, taking into account the statistical summary of effect size ATOMS is a more efficacious alternative compared to ProACT with higher dryness, improvement and patient satisfaction rates, lower explant rate and higher durability.

Munier et al. (2020) reported results of a retrospective study in France that evaluated 27 patients who underwent second-line ProACT balloon implantation for persistent SUI post-radical prostatectomy (RP) after insufficient improvement from a sling. Five patients previously had adjuvant radiotherapy (18%). The mean follow-up was 36 months. All patients presented with persistent SUI after sling implantation. After ProACT with an average 3 mL refilling (±1.2 min 2–max 6), 18 patients (66.7%) were continent. Eight of the remaining patients (29.6%) were improved; their number of pads per day (PPD) decreased from 2.6 to 1. Three patients (14.8%) needed ProACT replacement. The authors concluded that ProACT as a second-line intervention does not seem to bring a high risk of infection. Limitations of this study include the lack of prospective randomized comparison and the small study population.

Noordhoff et al. (2019) retrospectively reported on a case series that evaluated the use of ProACT in the treatment of SUI after transurethral resection of the prostate (TURP). ProACT was implanted in 29 patients with post-TURP SUI between 2007 and 2018 in two facilities. Preoperative UI was mild in 7 (24%), moderate in 12 (41%), and severe in 10 (35%) patients. After a median follow-up of 21 months, two-thirds (22 of 29) of the patients reported to use fewer pads daily, and 13 of the 29 patients were even dry. All but one patient reported improvement on the PGI-I scale. Within 30 days postoperatively, a Clavien-Dindo grade less than or equal to II complication had occurred in 24% of the patients. These findings are limited by lack of comparison group and small sample size. The authors noted that future research is needed to compare different devices and determine outcome predictors.

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. Out 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.

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 at some point during the 18-month follow-up, of which 22 were ultimately re-implanted and continued in the study. The most common reason for explant was device migration. Thirty-one procedure-related adverse events (AEs) were recorded, with the most common being urethral or bladder perforation during implant.

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 due to device-related problems (2), infection or erosion (5), migration (1), iatrogenique traumatism (2), or nonresponse (9). Of these patients, four were reimplanted with ProACT balloons, and two went on to have artificial urinary sphincters implanted.

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): The AUA/SUFU 2017 guideline Surgical Treatment of Female Stress Urinary Incontinence does not include adjustable continence therapy (ACT) (Kobashi, et al., 2017).

AUA/SUFU 2019 guideline Incontinence after Prostate Treatment states "Adjustable balloon devices may be offered to patients with mild stress urinary incontinence after prostate treatment (Moderate Recommendation; Evidence Level: Grade B)". The guideline notes, "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 (Sandhu, et al., 2019).

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Coding Information Urology

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:

CPT®* Codes	Description
53451	Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance
53452	Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance

Revision Details

Type of Revision	Summary of Changes	Date
Focused Review	• Updated policy statements	12/03/2023