Omnibus Codes (for North Carolina Only)

Policy Number: CSNCT0535.05
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Instructions for Use

Table of Contents Page

Related Policies
None

Application

This Medical Policy only applies to the state of North Carolina.

Coverage Summary

All CPT/HCPCS codes/services addressed in this policy are noted in the table below. Click the code link to be directed to the full coverage rationale and clinical evidence applicable to each of the listed procedures.

Code	Description	Conclusion
0042T	Cerebral perfusion analysis using computed tomography with contrast administration, including post-processing of parametric maps with determination of cerebral blood flow, cerebral blood volume, and mean transit time	Proven in certain circumstances
0061U	Transcutaneous measurement of five biomarkers (tissue oxygenation [StO2], oxyhemoglobin [ctHbO2], deoxyhemoglobin [ctHbR], papillary and reticular dermal hemoglobin concentrations [ctHb1 and ctHb2]), using spatial frequency domain imaging (SFDI) and multi-spectral analysis	Unproven
0100T	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy	Unproven
0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas	Unproven
0174T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)	Unproven

Code	Description	Conclusion
0175T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation	Unproven
0207T	Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral	Unproven
0208T	Pure tone audiometry (threshold), automated; air only	Unproven
0209T	Pure tone audiometry (threshold), automated; air and bone	Unproven
0210T	Speech audiometry threshold, automated	Unproven
0211T	Speech audiometry threshold, automated; with speech recognition	Unproven
0212T	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated	Unproven
0247U	Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth	Unproven
0266T	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0267T	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0268T	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0269T	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0270T	Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0271T	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0272T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day)	Unproven
0273T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming	Unproven

Code	Description	Conclusion
0330T	Tear film imaging, unilateral or bilateral, with interpretation and report	Unproven
0331T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment	Unproven
0332T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment; with tomographic SPECT	Unproven
0335T	Insertion of sinus tarsi implant	Unproven
0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral	Unproven
0339T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral	Unproven
0351T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative	Unproven
0352T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred	Unproven
0353T	Optical coherence tomography of breast, surgical cavity; real-time intraoperative	Unproven
0354T	Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred	Unproven
0358T	Bioelectrical impedance analysis whole body composition assessment, with interpretation and report	Unproven
0394T	High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed	Unproven
0395T	High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed	Unproven
0397T	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)	Unproven
0398T	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed	Unproven
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	Unproven
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	Unproven
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	Unproven

Code	Description	Conclusion
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	Unproven
0412T	Removal of permanent cardiac contractility modulation system; pulse generator only	Unproven
0413T	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)	Unproven
0414T	Removal and replacement of permanent cardiac contractility modulation system pulse generator only	Unproven
0415T	Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)	Unproven
0416T	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator	Unproven
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	Unproven
0418T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system	Unproven
0440T	Ablation, percutaneous, cryoablation, includes imaging guidance; upper extremity distal/peripheral nerve	Unproven
0441T	Ablation, percutaneous, cryoablation, includes imaging guidance; lower extremity distal/peripheral nerve	Unproven
0442T	Ablation, percutaneous, cryoablation, includes imaging guidance; nerve plexus or other truncal nerve (e.g., brachial plexus, pudendal nerve)	Unproven
0444T	Initial placement of a drug-eluting ocular insert under one or more eyelids, including fitting, training, and insertion, unilateral or bilateral	Unproven
0445T	Subsequent placement of a drug-eluting ocular insert under one or more eyelids, including re-training, and removal of existing insert, unilateral or bilateral	Unproven
0469T	Retinal polarization scan, ocular screening with on-site automated results, bilateral	Unproven
0472T	Device evaluation, interrogation, and initial programming of intraocular retinal electrode array (e.g., 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	Unproven
0473T	Device evaluation and interrogation of intraocular retinal electrode array (e.g., retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional	Unproven
0479T	Fractional ablative laser fenestration of burn and traumatic scars for functional improvement; first 100 cm2 or part thereof, or 1% of body surface area of infants and children	Unproven
0480T	Fractional ablative laser fenestration of burn and traumatic scars for functional improvement; each additional 100 cm2, or each additional 1% of body surface	Unproven

Code	Description	Conclusion
	area of infants and children, or part thereof (List separately in addition to code for primary procedure)	
0485T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; unilateral	Unproven
0486T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; bilateral	Unproven
0506T	Macular pigment optical density measurement by heterochromatic flicker photometry, unilateral or bilateral, with interpretation and report	Unproven
0507T	Near-infrared dual imaging (i.e., simultaneous reflective and trans-illuminated light) of meibomian glands, unilateral or bilateral, with interpretation and report	Unproven
0508T	Pulse-echo ultrasound bone density measurement resulting in indicator of axial bone mineral density, tibia	Unproven
0510T	Removal of sinus tarsi implant	Unproven
0511T	Removal and reinsertion of sinus tarsi implant	Unproven
0515T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; complete system (includes electrode and generator [transmitter and battery])	Unproven
0516T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only	Unproven
0517T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; pulse generator component(s) (battery and/or transmitter) only	Unproven
0518T	Removal of only pulse generator component(s) (battery and/or transmitter) of wireless cardiac stimulator for left ventricular pacing	Unproven
0519T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter)	Unproven
0520T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter), including placement of a new electrode	Unproven
0521T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording, and disconnection per patient encounter, wireless cardiac stimulator for left ventricular pacing	Unproven
0522T	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, wireless cardiac stimulator for left ventricular pacing	Unproven
0525T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; complete system (electrode and implantable monitor)	Unproven
0526T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; electrode only	Unproven

Code	Description	Conclusion
0527T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; implantable monitor only	Unproven
0528T	Programming device evaluation (in person) of intracardiac ischemia monitoring system with iterative adjustment of programmed values, with analysis, review, and report	Unproven
0529T	Interrogation device evaluation (in person) of intracardiac ischemia monitoring system with analysis, review, and report	Unproven
0530T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; complete system (electrode and implantable monitor)	Unproven
0531T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; electrode only	Unproven
0532T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; implantable monitor only	Unproven
0559T	Anatomic model 3D-printed from image data set(s); first individually prepared and processed component of an anatomic structure	Unproven
0560T	Anatomic model 3D-printed from image data set(s); each additional individually prepared and processed component of an anatomic structure (List separately in addition to code for primary procedure)	Unproven
0561T	Anatomic guide 3D-printed and designed from image data set(s); first anatomic guide	Unproven
0562T	Anatomic guide 3D-printed and designed from image data set(s); each additional anatomic guide (List separately in addition to code for primary procedure)	Unproven
0563T	Evacuation of meibomian glands, using heat delivered through wearable, open-eye eyelid treatment devices and manual gland expression, bilateral	Unproven
0567T	Permanent fallopian tube occlusion with degradable biopolymer implant, transcervical approach, including transvaginal ultrasound	Unproven
0581T	Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral	Unproven
0583T	Tympanostomy (requiring insertion of ventilating tube), using an automated tube delivery system, iontophoresis local anesthesia	Unproven
0584T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; percutaneous	Unproven
0585T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; laparoscopic	Unproven
0586T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; open	Unproven
0631T	Transcutaneous visible light hyperspectral imaging measurement of oxyhemoglobin, deoxyhemoglobin, and tissue oxygenation, with interpretation and report, per extremity	Unproven

Code	Description	Conclusion
0640T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); image acquisition, interpretation and report, each flap or wound	Unproven
0641T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); image acquisition only interpretation and report, each flap or wound	Unproven
0642T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); interpretation and report only, each flap or wound	Unproven
0647T	Insertion of gastrostomy tube, percutaneous, with magnetic gastropexy, under ultrasound guidance, image documentation and report	Unproven
0651T	Magnetically controlled capsule endoscopy, esophagus through stomach, including intraprocedural positioning of capsule, with interpretation and report	Unproven
0658T	Electrical impedance spectroscopy of 1 or more skin lesions for automated melanoma risk score	Unproven
0664T	Donor hysterectomy (including cold preservation); open, from cadaver donor	Unproven
0665T	Donor hysterectomy (including cold preservation); open, from living donor	Unproven
0666T	Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor	Unproven
0667T	Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor	Unproven
0668T	Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary	Unproven
0669T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each	Unproven
0670T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each	Unproven
0672T	Endovaginal cryogen-cooled, monopolar radiofrequency remodeling of the tissues surrounding the female bladder neck and proximal urethra for urinary incontinence	Unproven
0692T	Therapeutic ultrafiltration	Unproven
0694T	3-dimensional volumetric imaging and reconstruction of breast or axillary lymph node tissue, each excised specimen, 3-dimensional automatic specimen reorientation, interpretation and report, real-time intraoperative	Unproven
0766T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, initial treatment, with identification and marking of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; each additional nerve (List separately in addition to code for primary procedure)	Unproven
0767T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, initial treatment, with identification and marking of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; first nerve	Unproven

Code	Description	Conclusion
0768T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, subsequent treatment, including noninvasive electroneurographic localization (nerve conduction localization), when performed; first nerve	Unproven
0769T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, subsequent treatment, including noninvasive electroneurographic localization (nerve conduction localization), when performed; each additional nerve (List separately in addition to code for primary procedure)	Unproven
19105	Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma	Unproven
31634	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, with assessment of air leak, with administration of occlusive substance (e.g., fibrin glue), if performed	Unproven
33274	Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (e.g., fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (e.g., interrogation or programming), when performed	Unproven
33275	Transcatheter removal of permanent leadless pacemaker, right ventricular, including imaging guidance (e.g., fluoroscopy, venous ultrasound, ventriculography, femoral venography), when performed	Unproven
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	Unproven
43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy	Unproven
43252	Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy	Unproven
53451	Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance	Unproven
53452	Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance	Unproven
53453	Periurethral transperineal adjustable balloon continence device; removal, each balloon	Unproven
53454	Periurethral transperineal adjustable balloon continence device; percutaneous adjustment of balloon(s) fluid volume	Unproven
53860	Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence	Unproven
60659	Unlisted laparoscopy procedure, endocrine system	Proven in certain circumstances
69705	Nasopharyngoscopy, surgical, with dilation of eustachian tube (i.e., balloon dilation); unilateral	Unproven
69706	Nasopharyngoscopy, surgical, with dilation of eustachian tube (i.e., balloon dilation); bilateral	Unproven
80145	Adalimumab	Unproven

Code	Description	Conclusion
80230	Infliximab	Unproven
80280	Vedolizumab	Unproven
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score	Unproven
81599	Unlisted multianalyte assay with algorithmic analysis (when used to report PreTrm)	Unproven
88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session	Unproven
93264	Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional	Covered in certain circumstances
93702	Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)	Unproven
C2624	Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components	Unproven
G0341	Percutaneous islet cell transplant, includes portal vein catheterization and infusion	Unproven
G0342	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion	Unproven
G0343	Laparotomy for islet cell transplant, includes portal vein catheterization and infusion	Unproven
G0429	Dermal Filler injection(s) for the treatment of facial lipodystrophy syndrome (LDS) (e.g., as a result of highly active antiretroviral therapy)	Proven in certain circumstances
K1006	Suction pump, home model, portable or stationary, electric, any type, for use with external urine management system.	Unproven
K1007	Bilateral hip, knee, ankle, foot (HKAFO) device, powered, includes pelvic component, single or double upright(s), knee joints any type, with or without ankle joints any type, includes all components and accessories, motors, microprocessors, sensors	Unproven
K1018	External upper limb tremor stimulator of the peripheral nerves of the wrist	Unproven
K1019	Monthly supplies for use of device coded at K1018	Unproven
K1030	External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only	Unproven
L8607	Injectable bulking agent for vocal cord medialization, 0.1 ml, includes shipping and necessary supplies	Proven in certain circumstances
L8608	Miscellaneous external component, supply or accessory for use with the Argus II Retinal Prosthesis System	Unproven
L8699	Prosthetic implant, not otherwise specified [when used to report an absorbable nasal cartilage support implant] [when used to report three-dimensional (3-D) printed cranial implants]	Unproven

Code	Description	Conclusion
L8701	Powered upper extremity range of motion assist device, elbow, wrist, hand with single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated	Unproven
L8702	Powered upper extremity range of motion assist device, elbow, wrist, hand, finger, single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated	Unproven
P2031	Hair analysis (excluding arsenic)	Unproven
Q2026	Injection Radiesse 0. 1ml	Proven in certain circumstances
Q2028	Injection, sculptra, 0.5 mg	Proven in certain circumstances
S2117	Arthroereisis, subtalar	Unproven

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Coverage Rationale/Clinical Evidence

Code	Description
0042T	Cerebral perfusion analysis using computed tomography with contrast administration, including post-processing of parametric maps with determination of cerebral blood flow, cerebral blood volume, and mean transit time

Cerebral computed tomography perfusion (CTP) with contrast administration is proven and medically necessary for evaluation of acute ischemic stroke. For medical necessity clinical coverage criteria, refer to the InterQual® CP: Imaging, Imaging, Brain.

Click here to view the InterQual® criteria.

Cerebral computed tomography perfusion (CTP) with contrast administration is unproven and not medically necessary for all other indications due to insufficient evidence of safety and/or efficacy.

Code	Description
0061U	Transcutaneous measurement of five biomarkers (tissue oxygenation [StO2], oxyhemoglobin [ctHbO2], deoxyhemoglobin [ctHbR], papillary and reticular dermal hemoglobin concentrations [ctHb1 and ctHb2]), using spatial frequency domain imaging (SFDI) and multi-spectral analysis

Transcutaneous measurement of biomarkers using spatial frequency domain imaging (SFDI) and multi-spectral analysis is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Spatial Frequency Domain Imaging (SFDI) technology is an optical technique used to quantitatively characterize turbid (multiple scattering) materials. The Clarifi® Imaging System (Modulated Imaging, Inc.) is a non-contact, noninvasive tissue oxygenation measurement system that reports an approximate value of oxygen saturation, oxy-hemoglobin, and deoxy-hemoglobin into 2D/3D visual presentations. It is indicated for use to determine oxygenation levels in superficial tissues for patients with potential circulatory compromise.

According to the manufacturer, the Clarifi® Imaging System itself does not provide any medical diagnosis or prescribe a medical course of treatment. It is intended to be part of a larger assessment battery and used in conjunction with other clinical assessment and diagnostic tests.

Weinkauf et al. (2019) analyzed 47 patients (94 limbs) with and without diabetes. The SFDI Reflect RS machine was used to collect maps showing StO2 and hemoglobin content within the papillary dermis or microcirculation (HbT1) and reticular dermis or macro - circulation (HbT2) of the plantar aspects of each foot. The authors evaluated the SFDI hemoglobin maps, which identified the total hemoglobin present in the papillary and reticular dermis in addition to the pedal Doppler waveforms; these were used as standards for estimating lower extremity blood supply. After review and analysis of the data, the authors concluded that the SFDI technology is a noninvasive technology that can be a tool to manage patients with peripheral arterial disease; however, further studies will need to be designed to fully evaluate the applicability of this new technology. Limitations of the study included small sample size, the absence of a "gold standard" for non-invasive imaging of lower extremity perfusion, and a design that did not allow assessment of whether the use of SFDI improves patient care or patient outcomes.

The U.S. Food and Drug Administration (FDA) cleared the Clarifi® Imaging System under its 510(k) premarket notification process as substantially equivalent to predicate devices. For additional information, refer to the following:

- https://www.accessdata.fda.gov/cdrh_docs/pdf18/K181623.pdf
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K181623

(Accessed March 14, 2022)

Three clinical trials were found for multispectral imaging, and spatial frequency domain imaging related to tissue perfusion. One trial is not yet recruiting (NCT03516864), one is in the process of recruiting (NCT03144050), and one has been completed but no study results have been posted as yet (NCT03341559).

Reference(s)

https://clinicaltrials.gov/ct2/show/NCT03516864.

https://clinicaltrials.gov/ct2/show/NCT03144050.

https://clinicaltrials.gov/ct2/show/NCT03341559.

Modulin. https://www.modulim.com/clarifi/. (Accessed March 14, 2022) .

Weinkauf C, Mazhar A, Vaishnav K, et al. Near-instant noninvasive optical imaging of tissue perfusion for vascular assessment. *J Vasc Surg*. 2019;69(2):555–562.

Code	Description
0100T	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy
0472T	Device evaluation, interrogation, and initial programming of intraocular retinal electrode array (e.g., 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
0473T	Device evaluation and interrogation of intraocular retinal electrode array (e.g., retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional
L8608	Miscellaneous external component, supply or accessory for use with the Argus II Retinal Prosthesis System

The use of retinal prosthetic devices is unproven and not medically necessary for inducing visual perception in individuals with retinitis pigmentosa due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The Argus® II Retinal Prosthesis System (Second Sight Medical Products, Inc.) is a retinal implant that requires use of an external device to provide electrical stimulation to the retina to induce some visual perception in blind individuals with severe to profound retinitis pigmentosa (RP). The Argus II Retinal Prosthesis System received a Humanitarian Device Exemption (HDE) from the U.S. Food and Drug Administration (FDA) in February 2013. According to FDA documentation, the device is indicated for use in individuals with severe to profound retinitis pigmentosa who meet the following criteria:

- Age 25 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)

- A previous history of useful form vision
- Aphakic or pseudophakic eyes (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 postimplant clinical follow-up, device fitting, and visual rehabilitation

The device is intended for use in one eye—the worse-seeing eye. The HDE approval required the company to conduct 2 post-approval studies, including an extended (10-year) follow-up of patients receiving the implant and a 5-year, prospective, multicenter study of the visual function, device reliability, and adverse events (AEs) in patients receiving the implant. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H110002. (Accessed March 16, 2022)

Schuffert et al. (2019) conducted a post approval multi-center case series (with on/off tests) to assess the safety and visual outcomes of the Argus II Retinal Prosthesis System. The primary end point was the nature and rate of adverse events. Secondary end points included 3 visual function tests: square localization (SL), direction of motion, and grating visual acuity (GVA). Multicenter, post approval clinical trial was conducted at 9 sites in Germany and Italy. Data were collected from December 2, 2011, to September 30, 2017, and 47 patients were followed-up for 12 months or longer. The results showed during the first 12 months post-implantation, 23 patients (49%) experienced 51 nonserious adverse events and 12 (26%) experienced 13 serious adverse events (SAEs), 9 of which were judged to be related to the Argus II, and 4 of which were judged to be related to the procedure. The most common SAE was conjunctival erosion, reported in 4 patients. No significance testing was done for group analysis for the SL or direction-of-motion tests. 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 safety and visual function outcomes in this clinical practice setting cohort of patients with Argus II implants were consistent with previously reported results. 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.

Dagnelie et al. (2017) conducted a multi-center case series (with on/off tests) study to test Argus II subjects on three real-world functional vision tasks. Testing was conducted in a hospital/research laboratory setting at the various participating centers. Twenty-eight Argus II subjects, all profoundly blind, were included in the study. Subjects were tested on the three real-world functional vision tasks: Sock Sorting, Sidewalk Tracking and Walking Direction Discrimination Task for the Sock Sorting task, percentage correct was computed based on how accurately subjects sorted the piles on a cloth-covered table and on a bare table. In the Sidewalk Tracking task, an 'out of bounds' count was recorded, signifying how often the subject veered away from the test course. During the Walking Direction Discrimination task, subjects were tested on the number of times they correctly identified the direction of testers walking across their field of view. The mean percentage correct OFF versus ON for the Sock Sorting task was found to be significantly different for both testing conditions. On the Sidewalk Tracking task, subjects performed significantly better with the system ON than they did with the system OFF. 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 the Argus II subjects performed better on all three tasks with their systems ON than they did with their systems OFF. The study is however limited by the lack of comparison group with a different treatment mode or no treatment that could provide data on quality of life (QOL) and day-to-day function. These findings require confirmation in a larger study.
Health Quality Ontario (2017) updated the 2016 Health Technology Assessment that examined the effects of the Argus II retinal prosthesis system in patients with advanced retinitis pigmentosa and appraised the evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. The focus of the review included visual function, functional outcomes, QOL, and AEs in a total of 30 patients. One multicenter international study and one single-center study were included in the clinical review. In both studies, patients showed improved visual function with the Argus II system. At 5 years after implantation, 18/30 experienced no device or surgery related adverse effects, and 12/30 patients reported severe adverse events that were all treated with standard ophthalmic approaches. The authors concluded that based on evidence of moderate quality, patients with advanced retinitis pigmentosa who were implanted with the Argus II retinal prosthesis system showed significant improvement in visual function, real-life functional outcomes, and QOL that appeared sustained over time. Adverse events can be managed through standard ophthalmologic treatments.

In 2016, a technology assessment was completed for the Agency for Health Care Research and Quality (AHRQ) on retinal prostheses in the Medicare population. Eleven studies of retinal prosthesis systems (RPS) effectiveness were included. Although some patients clearly improve on tests of visual function, visual acuity, visual field, color vision, laboratory-based function, and day-to-day function from an RPS, the evidence was insufficient to estimate the proportion of patients who would benefit. Intraoperative AEs were typically mild, but some serious AEs were reported, including intraocular pressure increase, hypotony, and presumed endophthalmitis. Three studies pointed to the possibility that RPSs may provide neuroprotection. Of the 74 outcomes reported in the 11 included studies, only 4 (Early Treatment of Diabetic Retinopathy Study visual acuity test [ETDRS], Grating Acuity Test [GAT], Chow Color Test [CCT], and Functional Low-Vision Observer Rated Assessment [FLORA]) had evidence of validity and/or reliability. Measures with evidence of validity and reliability that could be used in future RPS studies include full-field flash test, Grating Contrast Sensitivity (GCS), FAST instrument (Functional Assessment of Self-Reliance on Tasks), Very Low Vision Instrumental Activities of Daily Living (IADL-VLV), Modified National Eye Institute Visual Function Questionnaire 25-item (NEI-VFQ-25) plus supplement, and the Modified Impact of Vision Impairment (IVI). According to the authors, some patients clearly benefit from RPSs. The magnitude of that benefit is unknown because of a paucity of evidence on quality of life (QOL) and day-to-day function. The authors concluded that future studies of retinal prosthesis should make an effort to report valid and reliable measures of day-to-day function and QOL (Fontanarosa et al., 2016).

da Cruz et al. (2016) reported in a multi-center case series (with on/off tests) the results at 5 years after Argus II implantation in 30 subjects. Twenty-four of 30 patients remained implanted with functioning Argus II Systems at 5 years after implantation. Only 1 additional serious AE was experienced after the 3-year time point. Patients performed significantly better with the Argus II on than off on all visual function tests and functional vision tasks. According to the authors, the 5-year results of the Argus II trial support the long-term safety profile and benefit of the Argus II System for patients blind as a result of retinitis pigmentosa (RP). This study is limited by a small study population which makes it is difficult to complete a robust statistical analysis of the safety results because of limited power. It is further limited by the lack of comparison group with a different treatment mode or no treatment that could provide data on quality of life (QOL) and real-life day-to-day function.

Geruschat et al. (2016) compared observer-rated tasks in patients implanted with the Argus II Retinal Prosthesis System, when the device is ON versus OFF. The Functional Low-Vision Observer Rated Assessment (FLORA) instrument was administered to 26 blind patients implanted with the Argus II Retinal Prosthesis System at a mean follow-up of 36 months. The tasks are evaluated individually and organized into four discrete domains, including 'Visual orientation', 'Visual mobility', 'Daily life and 'Interaction with others. Twenty-six patients completed each of the 35 tasks. Overall, 24 out of 35 tasks (69 percent) were statistically significantly easier to achieve with the device ON versus OFF. This study is however limited by the lack of comparison group with a different treatment mode or no treatment that could provide data on quality of life (QOL) and real-life day-to-day function. These findings require confirmation in a larger study.

In a 2015 interventional procedures guidance entitled *Insertion of a subretinal prosthesis system for retinitis pigmentosa*, The National Institute for Health and Care Excellence (NICE) states that the evidence on the safety and efficacy is limited in quality and quantity and this procedure should only be used within the context of research. Furthermore, NICE encourages research and recommends it includes outcomes that measure the impact on quality of life, activities of daily living, and the durability of the implants.

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Code	Description
0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas

The use of a biomarker panel based algorithmic analysis test (e.g., BeScreened using three tumor proteins teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]) to screen for colorectal cancer or advanced adenomas is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Blood-based biomarker panels are tests to assess the expression of genes to theoretically calculate a risk of having CRC. BeScreened™-CRC is manufactured by Beacon Medical Inc. and partnered with Sonora Quest Laboratories is an ELISA-based multiplexed, CLIA laboratory developed colorectal cancer (CRC) screening test. It tests three plasma or serum cancer related proteins (carcinoembryonic antigen, extracellular matrix protein involved in early-stage tumor stroma changes, teratocarcinoma derived growth factor-1 (TGDF-1, Cripto-1) to determine an algorithmic analysis reported as a positive or negative result. https://www.beaconbiomedical.com/about-bescreened-crc. (Accessed May 12, 2022)

In a systematic review, Harlid et al. (2021) summarized the evidence from 53 studies (between 2011 and 2021) that used blood-based colorectal cancer biomarkers in pre-diagnostic, asymptomatic settings. The quality of the studies was mostly high, but very few possible biomarkers showed consistent results in more than one study. The most promising biomarkers was the anti-p53 antibodies which performed well with constant findings in one screening cohort and in the 3-4 years prior to diagnosis in two prospective cohort studies. Proteins were the most common type of biomarker assessed, particularly carcinoembryonic antigen (CEA) and C-reactive protein (CRP), with uncertain results. Other possible promising biomarkers included proteins, such as AREG, MIC-1/GDF15, LRG1 and FGF-21, metabolites and/or metabolite profiles, non-coding RNAs and DNA methylation, as well as re-purposed routine lab tests, such as ferritin and the triglyceride-glucose index. Biomarker panels generally achieved higher discriminatory performance than single markers. There were study limitations which included: general search topic in a many different exposures, lack of define criteria to differentiate the etiology verses the biomarkers between the studies and relevant studies before 2011 were not included which could have missed other biomarkers. In conclusion, this systematic review highlighted anti-p53 antibodies as a promising blood-based biomarker for use in colorectal screening panels, together with other specific proteins. Additional research is needed to evaluate these promising biomarkers in independent pre-diagnostic settings.

Voronova et al. 2020 in a pilot study evaluated the performance of 20 blood markers including tumor antigens, inflammatory markers, and apolipoproteins as well as their combinations in colorectal cancer screening programs. This study consisted of 203 healthy volunteers and 102 patients with CRC were enrolled into the study. Differences between healthy and cancer subjects were evaluated using Wilcoxon rank-sum test. Several classification algorithms were employed using information about different combinations of biomarkers altered in CRC patients as well as age and gender of the subjects; random sub-sampling cross-validation was done to overcome overfitting problem. Diagnostic performance of single biomarkers and the different classification models was evaluated by receiver operating characteristic (ROC) analysis. Of 20 biomarkers, 16 were significantly different between the groups; ApoA1, ApoA2 and ApoA4 levels were decreased, while levels of tumor antigens (e.g., carcinoembriogenic antigen) and inflammatory markers (e.g., C-reactive protein) were increased in CRC patients verses healthy subjects. Combination markers including information about all 16 significant analytes, age, and gender of patients, demonstrated better performance over single biomarkers with average accuracy on test datasets ≥ 95% and area under ROC curve ≥ 98%. The combination biomarkers showed more accurate discrimination between healthy subjects and CRC patients, compared to a univariate biomarker. Limitations included small sample size and variations in algorithms. Larger studies are necessary to confirm the clinical efficacy of biomarker and algorithm screening.

Bhardwaj et, al. (2020) used a two-stage design to measure 275 protein markers by proximity extension assay (PEA), first in plasma samples of a discovery set consisting of 98 newly diagnosed CRC cases and 100 age- and gender-matched controls

free of neoplasm at screening colonoscopy. An algorithm predicting the presence of early- or late-stage CRC was derived by least absolute shrinkage and selection operator regression with .632 + bootstrap method, and the algorithms were then validated using PEA again in an independent validation set consisting of participants of screening colonoscopy with and without CRC (n = 56 and 102, respectively). Three different signatures for all-, early-, and late-stage CRC consisting of 9, 12, and 11 protein markers were obtained in the discovery set with areas under the curves (AUCs) after .632 + bootstrap adjustment of 0.92, 0.91, and 0.96, respectively. External validation among participants of screening colonoscopy yielded AUCs of 0.76 [95% confidence interval (95% CI), 0.67-0.84], 0.75 (95% CI, 0.62-0.87), and 0.80 (95% CI, 0.68-0.89) for all-, early-, and late-stage CRC, respectively. The authors concluded that although the identified protein markers are not competitive with the best available stool tests, the combination of identified protein markers with other informative blood-based markers could contribute to the development of a promising blood-based test for CRC screening. Additionally, this study is based on more biomarkers and a different algorithm from BeScreened™-CRC.

Gawel et, al. (2019) Screening programs for colorectal cancer (CRC) often rely on detection of blood in stools, which is unspecific and leads to a large number of colonoscopies of healthy subjects. Research has led to the identification of many different types of biomarkers, few of which are in general clinical use. Here, the authors searched for highly accurate combinations of biomarkers by meta-analyses of genome- and proteome-wide data from CRC tumors. They focused on secreted proteins identified by the Human Protein Atlas and used recently described algorithms to find optimal combinations of proteins. The authors identified nine proteins, three of which had been previously identified as potential biomarkers for CRC, namely CEACAM5, LCN2 and TRIM28. The remaining proteins were PLOD1, MAD1L1, P4HA1, GNS, C12orf10 and P3H1. They analyzed these proteins in plasma from 80 patients with newly diagnosed CRC and 80 healthy controls. A combination of four of these proteins, TRIM28, PLOD1, CEACAM5 and P4HA1, separated a training set consisting of 90% patients and 90% of the controls with high accuracy, which was verified in a test set consisting of the remaining 10%. Further studies are warranted to test algorithms and proteins for early CRC diagnosis. Additionally, this study is based on different biomarkers and a different algorithm from BeScreened™-CRC.

Hayes (2019) For use of liquid biopsy tests for colorectal cancer (CRC) screening to reduce CRC morbidity and mortality. Evidence from 3 studies suggests that CRC screening-eligible adults, especially those who reject a colonoscopy screen, prefer a blood-based test for mSEPTIN9 to a standard stool-based test. However, evidence comparing new versus established screening test performance in an unselected, prospective screening population is insufficient to support conclusions. Similarly, evidence for other types of liquid biopsy CRC screening tests is lacking.

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Voronova V, Glybochko P, Svistunov A, et al. Diagnostic value of combinatorial markers in colorectal carcinoma. Front Oncol. 2020 May 22; 10:832.

Code	Description
0174T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)
0175T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation

Computer aided detection (CAD) of chest radiographs is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Computer aided detection (CAD) systems are adjunctive tools used in assessing chest radiographs. The basic function of CAD is to provide radiologists with a computer algorithm that assists with interpreting these radiological images. CAD is thought to improve the accuracy and consistency of radiological diagnosis by reducing the time it takes to interpret images.

The published literature regarding CAD for chest radiographs consists primarily of the technical capabilities of CAD systems. High-quality, randomized trials examining the effect of CAD systems for chest radiographs are necessary to determine the true impact of this technology on health outcomes.

In a systematic review, Haber et al. (2020) aimed to identify whether there was an advantage to using Computer Aided Detection (CAD) to support CXR interpretation of pulmonary nodules; our findings were inconclusive. From initial 290 articles retrieved; seven studies were included in the review following a systematic screening process. The average CAD sensitivity in these studies was 58.67% (range; 44.2%–71%) alongside a mean 2.22 (range; 0.19–3.9) FP rates per image. No correlation between CAD sensitivity and false positive rates was identified. The findings suggest that further work is needed with larger sample sizes to improve confidence in synthesized findings. While future studies to evaluate CAD in the detection of PNs could be recommended, the recent research related to the higher potential effectiveness of Artificial Intelligence (AI) systems to support CXR interpretation suggests that this may no longer be an appropriate recommendation. Future research in either CAD or AI should explore and evaluate the risk versus benefit of computer-assisted technologies, as well as the impact on the imaging workforce and workflow. These technologies offer huge potential for diagnosis at an earlier stage, with a focus on saving more lives and improving the quality of life for those diagnosed with disease.

In a small retrospective study, Dellios et al. (2017) applied two CAD systems, SoftView™ 2.4A and OnGuard™ 5.2, to 100 posteroanterior chest radiographs with pulmonary lesions larger than 5 mm. Of these initial 100 radiographs, 75 of them had been confirmed via CT scans and histologically as malignant prior to the application of the software. The number of detected lesions by observation in unprocessed images was compared to the number of CAD-detected lesions in bone-suppressed images. 20% of the true positive lesions were proven benign while 80% were malignant whereas the false negative lesions were 47% benign and 53% malignant. The false positive rate was 0.88/image, and the false negative rate was 0.35/image. The researchers concluded a “hybrid” approach of CAD implementation with a critical radiological reading is effective for the detection of lung nodules. They noted that it does increase the amount of time necessary to complete the radiograph readings.

Mazzone et al. (2013) stated that the sensitivity of CT-based lung cancer screening for the detection of early lung cancer is balanced by the high number of benign lung nodules identified, the unknown consequences of radiation from the test, and the potential costs of a CT-based screening program. CAD chest radiography may improve the sensitivity of standard chest radiography while minimizing the risks of CT-based screening. Study subjects were age 40 to 75 years with 10 + pack-years of smoking and/or an additional risk for developing lung cancer. Subjects were randomized to receive a PA view chest radiograph or placebo control (went through the process of being imaged but were not imaged). Images were reviewed first without then with the assistance of CAD. Actionable nodules were reported, and additional evaluation was tracked. The primary outcome was the rate of developing symptomatic advanced stage lung cancer. A total of 1,424 subjects were enrolled; 710 received a CAD chest radiograph, 29 of whom were found to have an actionable lung nodule on prevalence screening. Of the 15 subjects who had a chest CT performed for additional evaluation, a lung nodule was confirmed in 4, 2 of which represented lung cancer. The authors concluded that further evaluation is needed to determine if CAD chest radiography has a role as a lung cancer screening tool.

de Hoop et al. (2010) assessed how CAD affects reader performance in detecting early lung cancer on chest radiographs. A total of 46 individuals with 49 CT-detected and histologically proved lung cancers and 65 patients without nodules at CT were retrospectively included in the study. Chest radiographs were obtained within 2 months after screening CT. Four radiology residents and two experienced radiologists were asked to identify and localize potential cancers on the chest radiographs, first without and subsequently with the use of CAD software. The investigators concluded that the sensitivity of CAD in identifying lung cancers depicted with CT screening was similar to that of experienced radiologists. However, CAD did not improve cancer detection because, especially for subtle lesions, observers were unable to sufficiently differentiate true-positive from false-positive annotations.

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Code	Description
0207T	Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral
0563T	Evacuation of meibomian glands, using heat delivered through wearable, open-eye eyelid treatment devices and manual gland expression, bilateral

Due to insufficient evidence of safety and/or efficacy, the following are unproven and not medically necessary for the evaluation or evacuation of meibomian glands:

- Thermal pulsation or automated evacuation using heat and intermittent pressure
- Wearable, open-eye eyelid treatment devices used for application of localized heat

Clinical Evidence

Eyelid Thermal Pulsation

The LipiFlow® Vectored Thermal Pulsation (VTP) System (Johnson & Johnson Vision) is an eyelid thermal pulsation device that uses heat and intermittent pressure to automatically evacuate the meibomian glands. The iLUX MGD Treatment System (Alcon) is a thermal pulsation device that simultaneously applies localized heat and compression to safely and effectively treat MGD. These devices are intended to treat individuals with dry eye disease and other conditions that cause meibomian gland dysfunction.

A Hayes report for Thermal Pulsation System for Chronic Dry Eye Syndrome and Meibomian Gland Dysfunction indicates that there is low-quality evidence that thermal pulsation therapy has efficacy similar to or somewhat better than standard warm compress treatment. However, the durability of benefit is unclear due to inadequate follow-up times. There is limited evidence comparing thermal pulsation therapy with established medications to treat dry eye or meibomian gland dysfunction. The authors conclude that there is potential but unproven benefit of this technology. (Hayes Comparative Effectiveness Review, Thermal Pulsation for Chronic Dry Eye Syndrome and Meibomian Gland Dysfunction, 2020).

Hu et al. (2022) conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to examine the efficacy and safety of a vectored thermal pulsation system (Lipiflow®) for the treatment of dry eye disease related to MGD. Subjective symptoms, objective tests of dry eye, meibomian gland function, and the incidence of adverse events were evaluated from RCTs thru January 2021. Results were based off ten qualified RCTs incorporating 761 patients with a range of comparison groups. Findings were stratified by whether the study analysis took into account the correlation between two eyes included per participants. In the comparison of Lipiflow® treatment and lid hygiene, the subgroup with inconsistent units of randomization and analysis (not taking into consideration correlation between the two eyes of study participants) showed that the Lipiflow® treatment brought slight improvement in corneal fluorescein staining (mean difference (MD), -0.42; 95% CI, -0.75 to -0.1), significant improvements in ocular surface disease index (OSDI) score (MD, -7.4; 95% CI, -11.06 to -3.74), Standard Patient Evaluation of Eye Dryness (SPEED) score (MD, -2.7; 95% CI, -3.95 to -1.45), meibomian glands yielding liquid secretion (MGYLS) (MD, 1.3; 95% CI, 0.78 to 1.82), and meibomian glands yielding secretion score (MGYSS) (MD, 4.09; 95% CI, 1.18 to 6.99). Significant improvements were detected in OSDI score, SPEED score, MGYLS, and MGYSS with patients who received Lipiflow® treatment compared with those who received nontreatment. The adverse events were similar in the two control groups. Findings were not significant or less consistent among studies with data analysis strategies taking into account correlation between participants eyes. The authors also noted that no individual trial was assessed as having a low risk of bias for all domains. They however concluded that Lipiflow® treatment can improve the subjective and objective outcomes of MGD and does not increase the incidence of adverse events. Further well-designed, large-scale randomized controlled trials are essential to reach a stronger conclusion. (Tauber 2020 and Blackie 2018 included in this study)

Tauber (2020) conducted a single-center, 6-week, prospective, randomized, single-masked study of adults with inflammatory meibomian gland dysfunction (MGD), defined as having all of the following: burning, stinging, dryness; thickened secretions or occlusion of glands; eyelid redness; and elevated matrix metalloproteinase-9. Patients received lifitegrast ophthalmic solution 5% twice daily for 42 days or one thermal pulsation procedure (TPP) treatment at day 0. Seven symptoms and 8 objective measures of dry eye disease were assessed. Overall, 40 of 50 randomized patients (80%) were women with mean (SD) age 65.8 (8.9) years. Lifitegrast-treated (n = 25) versus TPP-treated (n = 25) patients had greater improvement from baseline to day 42 in eye dryness [mean (SD) change from baseline: -1.05 (0.79), lifitegrast; -0.48 (0.96), TPP; p = 0.0340], corneal staining [-0.55 (0.80), lifitegrast; 0.12 (1.09), TPP; p = 0.0230], and eyelid redness [-0.77 (0.43), lifitegrast; -0.38 (0.58), TPP; p = 0.0115]; trend favored lifitegrast for best corrected visual acuity and gland patency. The author notes that unexpectedly, TPP treatment did not improve lipid layer thickness or gland patency compared with lifitegrast. No adverse events were reported. The authors concluded that although MGD is often considered a disease of gland obstruction, these findings demonstrate anti-inflammatory treatment with lifitegrast significantly improved patient symptoms and signs compared with treatment for obstruction. Furthermore, this study does not support the superiority of thermal pulsation over ophthalmic solutions.

Pang et al. (2019) conducted a systematic review and meta-analysis of randomized controlled trials that compared the efficacy of vectored thermal pulsation treatment (VTPT) and warm compress treatment (WCT) in treating dry eye disease (DED). The primary outcome was the gland function. The analysis consisted of 4 trials with 385 patients. Significantly greater improvement was observed in meibomian gland function, tear breakup time, and Standard Patient Evaluation for Eye Dryness at 2 to 4 weeks in the VTPT group than in the WCT group. A significantly greater decrease in Ocular Surface Disease Index was observed at 2 to 4 weeks and 3 months in the VTPT group than in the WCT group. The authors concluded that a single 12-minute VTPT was more efficacious than traditional WCT in treating DED either in objective or subjective measurements. There were several study limitations. All four included trial were considered at high risk of overall bias. All participants belonged to an age group (45-65 years) therefore the results may not apply to the younger population. The authors also notes that it was not known if the WCT group was treated per the protocol. Lastly the included trials were limited up to three-months follow-up. These findings require confirmation in randomized controlled trials with larger patient populations, confirmed treatment protocols and long-term follow-up. (Blackie et al. 2016 included in this review).

In a prospective randomized, multi-center clinical trial, Blackie et al. (2018) evaluated the effect of a single vectored thermal pulsation (VTP) treatment in contact lens wearers with (MGD) and dry eye symptoms. The trial included 55 soft contact lens (SCL) wearers with MGD and evaporative dry eye. Subjects were randomized to the single VTP treatment group or an untreated control. The controls received a crossover VTP treatment at 3 months (crossover treatment group). Primary effectiveness measures were meibomian gland secretion (MGS) score and Standard Patient Evaluation of Eye Dryness (SPEED) that were evaluated at baseline, at 1 and 3 months post-VTP treatment, and at 1-month post-VTP treatment in the crossover treatment group. Exploratory variables included fluorescein tear break-up time (TBUT), lid wiper epitheliopathy (LWE), lid parallel conjunctival folds (LIPCOF), ocular surface staining, frequency of over-the-counter (OTC) drop use, and hours of comfortable contact lens wear. At 3 months, the treatment group showed significantly greater mean change from baseline in MGS, SPEED and significantly greater improvement in exploratory variables (TBUT, LWE, and frequency of OTC drop use) relative to the controls. Mean comfortable contact lens wearing time increased by 4.0 ±3.9 hours at 1 month. This was sustained for 3 months with no change in the control group. The crossover treatment group demonstrated similar results to the treatment group at 1-month post-VTP. The authors concluded that in SCL wearers with MGD, a single VTP treatment significantly improved mean meibomian gland function and significantly reduced dry eye signs and symptoms compared to an untreated control. This was a small study intended to assess the value of performing a larger clinical study in contact lens wearing patients with MGD. The authors indicated that they cannot rule out investigator bias or the placebo effect, especially in the context of an open-label trial. Furthermore, this study was funded by the manufacturer of Lipiflow (TearScience, Inc) and lack comparison to established treatments.

In a prospective, randomized, parallel-group, single-masked study, Hagen et al. (2018) compared the efficacy of a single bilateral 12-minute vectored thermal pulsation (VTP) procedure versus daily oral doxycycline for 3 months for moderate-to-severe (MGD). This study included 28 subjects who received either a single-dose VTP with the LipiFlow System (TearScience, Inc) or 3 months of doxycycline treatment. At baseline and 3 months post treatment, all subjects were evaluated for the following: dry eye symptoms with a standard dry eye questionnaire (the Standard Patient Evaluation for Eye Dryness [SPEED]), meibomian gland (MG) function by counting the number of glands yielding liquid secretion with the MG evaluator (MGE), tear breakup time (TBUT) and corneal and conjunctival staining. In the VTP group, at 3 months, there was a significant improvement in MG function, SPEED score, TBUT, corneal staining and conjunctival staining. In the doxycycline group, there was a

significant improvement in MG function, SPEED score and conjunctival staining, but the improvement in TBUT and corneal staining was not statistically significant. At 3 months, SPEED score was significantly better in the VTP group; other parameters were comparable between the two groups. The authors concluded that a single 12-minute bilateral VTP procedure was significantly more effective than the 3-month daily course of oral doxycycline at improving the dry eye symptoms secondary to MGD and that a single 12-minute VTP treatment was at least as effective as a dose of doxycycline for 3 months, in improving MG function and all measured signs of MGD. According to the authors, given the minimal risk profile of the single VTP procedure over long-term doxycycline use, a single VTP presents a favorable alternative to long-term antibiotic use. According to the authors, this is a small study that can serve as a pilot study for additional investigations. It was disclosed that 2 of the authors are either a consultant or employee of TearScience, Inc. Furthermore, the study may have been too small to detect clinically significant differences between groups.

Blackie et al. (2016) evaluated the sustained effect (up to 1 year) of a single, 12-minute vectored thermal pulsation (VTP) treatment in improving MGD and dry eye symptoms in patients with meibomian gland dysfunction and evaporative dry eye. The prospective, multicenter, open-label clinical trial included 200 subjects (400 eyes) who were randomized to a single VTP treatment (treatment group) or twice-daily, 3-month, conventional warm compress and eyelid hygiene therapy (control group). Control group subjects received crossover VTP treatment at 3 months (crossover group). Effectiveness measures of meibomian gland secretion (MGS) and dry eye symptoms were evaluated at baseline and 1, 3, 6, 9, and 12 months. Subjects with inadequate symptom relief could receive additional MGD therapy after 3 (treatment group) and 6 months (crossover group). At 3 months, the treatment group had greater mean improvement in MGS and dry eye symptoms, compared to controls. At 12 months, 86% of the treatment group had received only one VTP treatment, and sustained a mean improvement in MGS from 6.4 ±3.7 (baseline) to 17.3 ±9.1 and dry eye symptoms from 44.1 ±20.4 to 21.6 ±21.3; 89% of the crossover group had received only one VTP treatment with sustained mean improvement in MGS from 6.3 ±3.6 to 18.4 ±11.1 and dry eye symptoms from 49.1 ±21.0 to 24.0 ±23.2The authors concluded that a single VTP treatment can deliver a sustained mean improvement in meibomian gland function and mean reduction in dry eye symptoms, over 12 months. A single VTP treatment provides significantly greater mean improvement in meibomian gland function and dry eye symptoms as compared to a conventional, twice-daily, 3-month regimen. According to the authors, a significant limitation of this study is that the investigators were not masked, which could have introduced a bias in the findings. This study was funded by the manufacturer of Lipiflow (TearScience, Inc) and the lead authors are affiliated with TearScience, Inc.

Clinical Practice Guidelines

Tear Film and Ocular Surface Society (TFOS)

The Tear Film and Ocular Surface Society (TFOS) recommends LipiFlow as a second-line option for treatment of dry eye disease (Craig et al., 2017).

American Academy of Ophthalmology

The American Academy of Ophthalmology Preferred Practice Pattern Guidelines on dry eye syndrome (2018b) lists LipiFlow as a second-stage option for treatment of dry eye disease.

The American Academy of Ophthalmology Preferred Practice Pattern Guidelines for Blepharitis (2018a) indicates that multiple industry-sponsored studies have demonstrated that a single vectored thermal pulsation (VTP) treatment can be effective at improving meibomian gland function and reducing dry eye symptoms for a year or more post procedure. However, there have been no independent, randomized, clinical trials confirming or refuting these industry-sponsored studies.

Wearable, Open-Eye Eyelid Treatment Devices Used for Application of Localized Heat

TearCare® (Sight Sciences) is a software-controlled, wearable eyelid technology that provides targeted and adjustable heat energy to the meibomian glands. It is intended to treat eye conditions such as meibomian gland dysfunction, dry eye, and blepharitis.

An ECRI report for TearCare indicated that the evidence for TearCare is inconclusive due to too few data on outcomes and comparisons with other treatments (ECRI, TearCare for Treatment of Dry Eye Disease, 2020).

Gupta et al., (2022) in a masked randomized controlled trial evaluated the safety and effectiveness of a single TearCare procedure compared with a single LipiFlow procedure in the treatment of dry eye disease associated with MGD. 135 subjects

received a single TearCare (TC) treatment (n = 67) or a single LipiFlow (LF) treatment (n = 68) at baseline and were followed up for 1 month posttreatment. Tear film breakup time, meibomian gland function, and corneal and conjunctival staining scores were assessed as dry eye signs at baseline, 2 weeks, and 1 month; dry eye symptoms were assessed using the Ocular Surface Disease Index, Symptom Assessment in Dry Eye, and eye dryness questionnaires at baseline and 1 month. At 1 month post-treatment, both groups demonstrated significant improvements ($p < 0.0001$) in mean tear film breakup time and meibomian gland secretion score to 3.0 ±4.4 and 11.2 ±11.1 in the TC group and 2.6 ±3.3 and 11.0 ±10.4 in the LF group, respectively. The mean eye dryness, Symptom Assessment in Dry Eye, and Ocular Surface Disease Index scores were significantly reduced ($p < 0.0001$) by 35.4 ±34.1, 38.2 ±31.0, and 27.9 ±20.5 in the TC group and 34.9 ±26.9, 38.0 ±25.9, and 23.4 ±17.7 in the LF group, respectively. The groups showed no statistically significant differences for any one result. The TC group demonstrated numerically greater improvements consistently in all signs and symptoms. Device-related ocular adverse events were reported in 3 patients in the TC group (superficial punctate keratitis, chalazion, and blepharitis) and 4 patients in the LF group (blepharitis, 2 cases of foreign body sensation, and severe eye dryness). Study limitations included outcomes were subjective, interpretation of results from the examiner even though masked and lack of long-term follow-up. The authors concluded that a single TearCare treatment alleviates the signs and symptoms of dry eye disease in patients with MGD and is equivalent in its safety and effectiveness profile to LipiFlow treatment as shown in this 1-month follow-up study. Due to study limitations, further well-controlled studies that includes long-term efficacy are needed.

Badawi (2019) evaluated the safety and effectiveness of TearCare retreatment in adults with clinically significant dry eye disease (DED) that was an extension of an initial 6-month, prospective, single-center, randomized, parallel-group pilot study (Badawi, 2018). In the case series, subjects were evaluated for the clinical signs and symptoms of DED prior to retreatment in the extension study that would measure the safety, effectiveness, and durability of a TearCare retreatment for another 6 months through a 12-month end point. The TearCare retreatment procedure consisted of 12 minutes of thermal eyelid treatment immediately followed by manual meibomian gland clearance. The primary effectiveness end point was the change in tear break-up time TBUT from baseline to 1-month follow-up. Twelve subjects participated in the 6-month extension study. At 1-month clinic visit following retreatment, a significant improvement from baseline in mean (±SD) TBUT of 12.4 (±3.3) seconds was observed. Significant improvements in the mean change from baseline in meibomian gland scores, corneal and conjunctival staining scores, and symptoms of DED were also observed following retreatment. The second treatment was well tolerated. The investigator concluded that the findings of the extension study through 12 months suggest that a second TearCare treatment after 6 months provides additional improvement in the signs and symptoms of DED. According to the investigator, there are some limitations to this study. This was a single-treatment, single-investigator study so it was not possible to mask subjects or the investigator. Also, the study population was small. This and the original studies were funded by the manufacturer of the device and the author disclosed that he is an employee of the manufacturer. Independent confirmation of these findings would be helpful.

Badawi (2018) evaluated the safety and effectiveness of the TearCare System in adult patients with clinically significant DED in a prospective, single-center, randomized, parallel-group, clinical trial. Subjects with DED were randomized to either a single TearCare treatment conducted at the clinic or 4 weeks of daily warm compress (WC) therapy. The TearCare procedure consisted of 12 minutes of thermal eyelid treatment immediately followed by manual expression of the meibomian glands. WC therapy consisted of once daily application of the compresses to the eyelids for 5 minutes. Subjects were followed until 6 months post-treatment. The primary effectiveness end point was defined as change from baseline to 4 weeks for TBUT. Twenty-four subjects were enrolled, and all subjects completed 6 months follow-up. At the 1-month follow-up, TearCare subjects demonstrated an improvement from baseline in mean (±SD) TBUT of 11.7 ±2.6 seconds compared with an average worsening of -0.3 ±1.1 seconds for subjects in the WC group. Significantly greater improvements in the change from baseline in meibomian gland scores, as well as corneal and conjunctival staining scores, were observed in the TearCare group. Subjects in the TearCare group also showed significantly greater improvement in dry eye symptoms as measured by 3 questionnaires. Both treatments were well-tolerated. The investigator concluded that the findings of this pilot study suggest that the TearCare System is an effective treatment option for patients with DED, with the effects on the signs and symptoms of DED persisting for at least 6 months. This study was limited by lack of masking to the intervention. A larger number of subjects enrolled at different centers is needed to enhance the evidence base for this technology.

Clinical Practice Guidelines

American Academy of Ophthalmology

The American Academy of Ophthalmology Preferred Practice Pattern Guidelines on Blepharitis (2018a) or dry eye syndrome (2018b) do not address wearable, open-eye eyelid treatment devices.

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Code	Description
0208T	Pure tone audiometry (threshold), automated; air only
0209T	Pure tone audiometry (threshold), automated; air and bone
0210T	Speech audiometry threshold, automated;
0211T	Speech audiometry threshold, automated; with speech recognition
0212T	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated

Automated speech audiometry that is either self-administered or administrated by non-audiologists is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

While automated audiometry that is either self-administered or administrated by non-audiologists has been studied, its efficacy has not been adequately validated to be equivalent to audiometry performed by an audiologist. Further studies are needed to support its routine use.

Wasman et al. (2022) conducted a systematic review of the current status of automation and machine learning approaches in hearing assessment using validated pure-tone audiometry with possible indicators of accuracy, reliability, and efficiency of these approaches. These automated methods are being developed for self-administered digital hearing assessments without the direct administration by professionals. This review is an extension of a 2013 systematic review (Mahomed, 2013). Fifty-six reports from 2012 to June 2021 were included. There were 27 select automated approaches that were identified. The authors

noted the following. Machine learning approaches require fewer trials than conventional threshold-seeking approaches, and personal digital devices make assessments more accessible. Validity can be improved using digital technologies for quality surveillance, including noise monitoring and detecting inconclusive results. In the past 10 years, an increasing number of automated approaches have reported similar accuracy, reliability, and time efficiency as manual hearing assessments. Limitations included commercialized automated approaches may have been developed without peer-reviewed reports, no gold standard for reporting audiometry validation studies, which confines a consistent comparison among methods and early users could lead to more optimistic findings. New developments, including machine learning approaches, offer features and versatility beyond manual audiometry. Additional peer-reviewed studies are needed to support their use in the future while taking the limitations into consideration (Mahomed, 2013 included below).

Colsman et al. (2020) examined the accuracy and reliability of a calibrated application (app) for pure-tone screening audiometry by self-assessment on a tablet computer: The Audimatch app installed on Apple iPad 4 in combination with Sennheiser HDA-280 headphones. In a repeated measures design audiometric thresholds collected by the app were compared to those obtained by standardized automated audiometry administered by a trained professional and additionally test-retest reliability was evaluated. A total of 68 subjects aged 19 to 65 years with normal hearing were tested in a sound-attenuating booth. A similar test revealed comparable hearing thresholds for the app compared with standardized automated audiometry. A test-retest reliability analysis within each method showed a high correlation coefficient for the app (Spearman rank correlation: rho = 0.829) and for the automated audiometer (rho = 0.792). The authors concluded that the results indicated that the self-assessment of audiometric thresholds via a calibrated mobile device represents a valid and reliable alternative for stationary assessment of hearing loss thresholds, supporting the potential use within the area of occupational health care. Study limitations includes the following: the sessions were performed in a sound-insulated booth and therefore the findings may not be generalizable to other environments where self-administered audiometry could be performed; the participant can self-administer the test, yet calibration with the app is required; special headphones are required; the sample was not completely a random selection and only participants with normal hearing were included; and the authors were involved in the development of the app, which could have introduced a bias in the interpretation of the findings. Future studies are needed to explore the validity of this app.

Brennan-Jones et al. (2018) conducted a study to compare remote interpretation of manual and automated audiometry. The results from 42 participants who underwent manual and automatic audiograms were interpreted by five audiologists. Audiograms were randomized and audiologists were blinded as to whether they were interpreting a manual or automated audiogram. Cohen's Kappa and Krippendorff's Alpha were used to calculate and quantify the intra- and inter-observer agreement, respectively, and McNemar's test was used to assess the audiologist-rated accuracy of audiograms. Audiologists were 2.8 times more likely to question the accuracy of an automated audiogram to a manual audiogram. The authors noted that there is a lack of agreement between audiologists when interpreting audiograms, whether recorded with automated or manual audiometry.

Pereira et al. (2018) examined the validity and efficiency of automated audiometry in school-aged children. Hearing thresholds for 0.5, 1, 2, 4, 6, and 8 kHz were collected in 32 children ages 6-12 years using standard audiometry and tablet-based automated audiometry in a soundproof booth. Results revealed that the majority (67%) of threshold differences between automated and standard were within the clinically acceptable range (10 dB). The threshold difference between the two tests showed that automated audiometry thresholds were higher by 12 dB in 6-year-olds, 7 dB in 7- to 9-year-olds, and 3 dB in 10- to 12-year-olds. Results suggest that the clinical use of at least some types of tablet-based automated audiometry may not be feasible in children 6 years of age but support the use of tablet-based automated audiometry in children from ages 7-12 years. Further study is needed to determine the long-term safety and efficacy of tablet-based automated audiometry in children.

Saliba et al. (2017) in a prospective study compared the accuracy of 2 previously validated mobile-based hearing tests in determining pure tone thresholds and screening for hearing loss to determine the accuracy of mobile audiometry in noisy environments through noise reduction strategies. A total of 33 adults with or without hearing loss were tested (mean age of 49.7 years; women, 42.4 %). Air conduction thresholds measured as pure tone average and at individual frequencies were assessed by conventional audiogram and by 2 audiometric applications (consumer and professional) on a tablet device. Mobile audiometry was performed in a quiet sound booth and in a noisy sound booth (50 dB of background noise) through active and passive noise reduction strategies. On average, 91.1 % (95 % CI: 89.1 % to 93.2 %) and 95.8 % (95 % CI: 93.5 % to 97.1 %) of the threshold values obtained in a quiet sound booth with the consumer and professional applications, respectively, were within 10 dB of the corresponding audiogram thresholds, as compared with 86.5 % (95 % CI: 82.6 % to 88.5 %) and 91.3 % (95 % CI: 88.5 % to 92.8 %) in a noisy sound booth through noise cancellation. When screening for at least moderate hearing loss (pure

tone average greater than 40 dB HL), the consumer application showed a sensitivity and specificity of 87.5 % and 95.9 %, respectively, and the professional application, 100 % and 95.9 %. Overall, patients preferred mobile audiometry over conventional audiograms. The authors concluded that mobile audiometry could correctly estimate pure tone thresholds and screen for moderate hearing loss. Adding noise reduction strategies in mobile audiometry could provide a portable effective solution for hearing assessments outside clinical settings where noise is a factor. Study limitations include the following: small sample size, the number of adults with audiometric hearing loss was limited which per the author could have affected sensitivity and specificity, each ear was counted separately which could have inflated sample size, also the earbuds used in mobile testing is different than commercial testing. Additional studies with larger samples are needed to validate the efficacy of mobile-based hearing.

Brennan-Jones et al. (2016) evaluated automated audiometry in adults with a variety of different characteristics using the KUDU wave automated audiometer. Comparative manual audiometry was performed in a sound-treated room. Automated audiometry was not performed in a sound treated room. A total of 42 adults were recruited. Absolute mean differences ranged between 5.12 to 9.68 dB (air-conduction) and 8.26 to 15 dB (bone-conduction). A total of 86.5 % of manual and automated 4FAs were within 10 dB (i.e., ±5 dB); 94.8 % were within 15 dB. There were significant ($p < 0.05$) differences between automated and manual audiometry at 250, 500, 1,000, and 2,000 Hz (air-conduction) and 500 and 1,000 Hz (bone-conduction). The effect of age (greater than or equal to 55 years) on accuracy ($p = 0.014$) was not significant on linear regression ($p > 0.05$; $r (2) = 0.11$). The presence of a hearing loss (better ear greater than or equal to 26 dB) did not significantly affect accuracy ($p = 0.604$; air-conduction), ($p = 0.218$; bone-conduction). The authors concluded that the findings provided clinical validation of the automated audiometry using KUDOwave, however variations in study design were significant and future research is recommended.

Mahomed et al. (2013) conducted a systemic review and meta-analysis on the validity of automated threshold audiometry. Databases included: MEDLINE, Scopus, and PubMed; a secondary search strategy was the review of references from identified reports. In total, 29 reports on automated audiometry (method of limits and the method of adjustment techniques) met the inclusion criteria and were included in this review. Accuracy results on the meta-analysis indicated overall average differences between manual and automated air conduction audiometry (0.4 dB, 6.1 SD) to be comparable with test-retest differences for manual (1.3 dB, 6.1 SD) and automated (0.3 dB, 6.9 SD) audiometry. No significant differences ($p > 0.01$; summarized data analysis of variance) were seen in any of the comparisons between test-retest reliability of manual and automated audiometry compared with differences between manual and automated audiometry. Validation data is still limited for automated bone conduction audiometry, automated audiometry in the pediatric and difficult to test populations and different types and degrees of hearing loss.

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Code	Description
0247U	Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth

Code	Description
81599	Unlisted multianalyte assay with algorithmic analysis (when used to report PreTrm)

The use of a serum-based proteomic biomarker based algorithmic analysis test (PreTRM®) for screening pregnant individuals to predict the risk of preterm labor is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

PreTRM it is a blood test to predict spontaneous preterm birth (sPTB) risk by measuring two proteins, insulin-like growth factor-binding protein 4 and sex hormone-binding globulins (IBP4 and SHGB) that are relatively over- or under-expressed and are predictive of premature birth (or delivery) (Sera Prognostics website).

Burchard and colleagues (2021) conducted replicated a second independent study to validate the findings of the Multicenter Assessment of a spontaneous Preterm Birth Risk Predictor (TREETOP) (Markenson et al.) and the Proteomic Assessment of Preterm Risk (PAPR) (Saade, et al.) studies mentioned below which assessed the ability of the ratio of IBP4 to SHBG to risk stratify preterm delivery and associated adverse outcomes. The authors assessed an actionable threshold learned in one study and applied to the second in a critical and rigorous manner to show that not only the likelihood of spontaneous preterm delivery is similarly significantly predicted, but also the associated and clinically adverse end points are well predicted and similarly elevated at or above the threshold. Both studies of the IBP4/SHBG proteomic biomarker showed the ratio's potential to predict the majority of preterm birth based on tested populations in excess of 1000 subjects, and for predicting associated newborn complications of prematurity as well. The primary objective of this research was to demonstrate that statistically significant thresholds of prediction of adverse pregnancy outcomes in PAPR are also significant in the independent TREETOP population. The authors indicated that an additional strength of this comparison of the PAPR and TREETOP studies is that while the subpopulations analyzed are both the same in the intended use population for the proteomic biomarker, they are notably different on several demographic and baseline characteristics (maternal age, BMI, education, race, prior sPTB, etc.). As well, the eligible PAPR and TREETOP subjects for this study were enrolled at 10 and 14 clinical sites, respectively. All of these factors would provide further confidence that despite these demographic differences and diversity in site enrollment, the same proteomic biomarker threshold identified pregnancies of increased risk of sPTB and associated adverse outcomes. The authors concluded that this comparison demonstrated consistency and accordance of the proteomic biomarker in two large studies for predicting preterm delivery in a large diverse segment of low-risk pregnant women tested at a time in the second trimester when most women are seen for their anatomic ultrasound. The authors noted that this provides confidence that pregnancies can be robustly risk-stratified by the proteomic biomarker.

The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin #234, Prediction and Prevention of Spontaneous Preterm Birth describes the risk factors, screening methods, and treatments for preventing spontaneous preterm birth in a review of the evidence supporting their roles in clinical practice. Several Level A and B recommendations are included. The bulletin does not provide recommendations on maternal serum analysis as several ongoing studies are evaluating the use of serum biomarkers for preterm birth risk assessment. (August 2021).

The multicenter, prospective TREETOP (The Multicenter Assessment of a Spontaneous Preterm Birth Risk Predictor) study investigated the performance of PreTRM in predicting preterm births occurring before the 32nd week of gestation (< 320/7). The study also assessed negative outcomes associated with these births, such as length of neonatal hospital stay and neonatal morbidity and mortality. The multicenter study enrolled 5,011 women across 18 sites, with a preplanned analysis performed on a randomly selected subgroup of 847 women. Results of the remaining study participants were blinded for future validation studies. In the subgroup, there were 9 preterm births and 838 non -cases at ≥ 320/7 weeks' gestation. The IBP4/SHBG ratio was predictive of birth < 320/7 weeks among all 847 women. Additionally, the test predicted increased length of neonatal hospital stay and increased severity of adverse neonatal outcomes. This study is limited by lack of control group and incomplete results. Further results are expected from the second phase of the study (Markenson et al., 2020). NCT02787213.

A Hayes report indicates there are insufficient studies to perform a health technology assessment of PreTRM (Hayes, 2019).

Saade et al. (2016) conducted the prospective Proteomic Assessment of Preterm Risk study to discover, verify and validate biomarkers for preterm birth. A total of 5,500 pregnant women between 17-28 weeks gestation were followed from 2011-2014 at 11 clinical sites in the United States. Of those, 5,235 remained in the study until their delivery and 4,825 were analyzed (410

were excluded due to being on progesterone therapy for preventing preterm birth). Of those 4,825 women, 4,292 carried their babies to term while 248 experienced spontaneous preterm birth (285 had medically indicated preterm births and were excluded.) Of these 248 sPTB subjects, 31 were excluded for pre -analytic reasons, leaving 217, 86 of which were used in discovery, 50 in verification, and 81 in validation. The discovery and verification process identified 2 serum proteins, insulin-like growth factor binding protein 4 (IBP4) and sex hormone-binding globulin (SHBG), as predictors of spontaneous preterm delivery. The study found that the test was able to predict whether a woman would deliver before 37 weeks with 75 percent sensitivity and 74 percent specificity, and an area under the receiver operating curve of .75. It was able to predict delivery before 35 weeks with 100 percent sensitivity and 83 percent specificity and an AUC of .93. These biomarkers may predict risk for preterm sPTB. However, the study had several limitations including small sample size and had insufficient number of women with prior preterm delivery, and less than one-third of participants had transvaginal ultrasound cervical length performed. Further studies are needed to determine the clinical application of this test and how it relates to the current techniques used to identify high risk for preterm labor.

There is insufficient evidence to support the use of serum-based proteomic testing to predict the risk of preterm delivery in asymptomatic pregnant women.

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Sera Prognostics website. Available at: https://www.pretrm.com/about-the-pretrm-test/. Accessed April 25, 2022.

Code	Description
0266T	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
0267T	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)
0268T	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
0269T	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
0270T	Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)
0271T	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
0272T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day)

Code	Description
0273T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming

Chronic baroreceptor stimulation of the carotid sinus is unproven and not medically necessary for treating hypertension, heart failure or other cardiovascular conditions due to insufficient evidence of safety and/or efficacy.

The Barostim neo™ is a second-generation device that replaces the Rheos® System (CVRx website). In December 2014, the FDA granted a unique and limited Humanitarian Device Exemption (HDE) for use of the Barostim neo™ legacy device for treatment of hypertension. The HDE applies to U.S. clinical trial patients who were implanted with the Rheos® Baroreflex Hypertension device, who achieved a significant decrease in blood pressure during their trial participation, and who now require a procedure to replace the device battery and/or repair the electrode lead. The FDA will allow the obsolete Rheos® Baroreflex Hypertension device to be replaced by the current Barostim neo™ legacy device. Additional information is available at:

- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=375580
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=388273

(Accessed March 31, 2022)

The Barostim neo™ received FDA premarket approval on August 16, 2019 (product code DSR) for treatment of heart failure. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P180050. (Accessed March 31, 2022)

Coverage for revision or removal of carotid sinus baroreflex activation devices may be addressed in the complication section of the benefit document. Refer to the member-specific benefit plan document.

Clinical Evidence

Baroreceptor reflex (baroreflex) activation therapy (BAT) devices stimulate pressure sensors in the neck that are intended to help regulate blood pressure and cardiac workload. BAT uses a pacemaker-like implantable pulse generator to deliver electrical signals to baroreceptors in the carotid arteries through electrodes placed in the carotid sinus (ECRI, 2013; updated 2018).

Hypertension

In a Clinical Evidence Assessment published by ECRI (2020), the evidence for the Barostim Neo™ System for treating resistant hypertension was inconclusive. One systematic review and three comparative studies that involved more than 101 participants were reviewed. The evidence was limited by small study sizes, single-center participation, and lack of randomization, blinding, and parallel control groups. Two of six ongoing clinical trials are randomized controlled trials (RCTs) comparing this device with standard of care; completion of these studies is expected in June 2022 and April 2028.

Wallbach et al. (2020) reported on a prospective, observational study of sustained effects of the Baroreflex activation therapy (BAT) Neo device on 24-hour ambulatory blood pressure (ABP). Office and 24-hour ABP were measured on 60 individuals with resistant hypertension (HTN) who were previously treated with the BAT Neo device. Blood pressure measurements were performed before BAT implantation, and at 6,12, and 24 months after implantation. Resistant HTN was defined as follows: (office BP 172 ±25/90 ±17 mmHg, 24-h ABP 150 ±16/80 ±12 mmHg, median of antihypertensive drugs 7 (IQR 6-8). “After 24 months, there was a significant reduction of - 25 ±33/- 9 ±18 mmHg (n = 50, both $p < 0.01$) in office BP and - 8 ±23/- 5 ±13 mmHg (n = 46, both $p = 0.02$) in 24-h ABP, while the number of antihypertensive medications was reduced to a median of 5 (4-6) drugs ($p < 0.01$). Patients with isolated systolic HTN (ISH) experienced a BP-lowering effect in office BP, but not in ABPM at month 24. Using unadjusted BP values, BAT seems to be more effective in combined hypertension (CH) than in ISH. After adjustment for baseline BP values, there was no significant difference in BP reduction between ISH and CH patients. Ambulatory SBP at baseline was the only independent correlate of BP response at month 24.” The authors concluded that BAT reduced office BP and improved relevant parameters of ABP which is associated with a high cardiovascular risk in patients with resistant HTN, whereas, after adjustment for baseline BP, BP reduction was not different in patients with CH compared with patients with ISH. However, they further stated that randomized controlled trials are needed to confirm the effects of BAT on 24-h ABP. This study is limited by lack of comparison group undergoing a different approach to resistant hypertension.

Spiering et al. (2017) conducted a prospective, first-in-human, proof-of-principle, open-label case series at 6 European centers to assess safety and efficacy of the MobiusHD endovascular baroreceptor amplification device (Vascular Dynamics, Mountain View, CA, USA) for the treatment of resistant hypertension. Known as the CALM-FIM_EUR study, 30 eligible subjects (office systolic blood pressure (SBP) ≥ 160 mm Hg despite taking at least 3 antihypertensive agents, including a diuretic) had the MobiusHD device implanted unilaterally in the internal carotid artery. The primary endpoint was the incidence of serious AEs at 6 months. Secondary endpoints included changes in office and 24 h ambulatory blood pressure. At 6 months, 5 serious AEs had occurred in four patients (13%): hypotension (n = 2), worsening hypertension (n = 1), intermittent claudication (n = 1) and wound infection (n = 1). Mean baseline 24 h ambulatory blood pressure was 166/100 mm Hg (17/14) at baseline and was reduced by 21/12 mm Hg (14-29/7-16) at 6 months. The authors concluded that the MobiusHD device substantially lowered blood pressure with an acceptable safety profile (NCT01911897). However, these findings are limited by lack of comparison group.

de Leeuw et al. (2017) assessed the long-term safety and efficacy of BAT by analyzing data from patients included in 1 of 3 trials that focused on treatment-resistant hypertension (US Rheos® Feasibility Trial, the DEBuT-HT Trial and the Rheos® Pivotal Trial). Collectively, 383 patients were available for analysis: 143 patients completed 5 years of follow-up and 48 patients completed 6 years of follow-up. In the entire cohort, systolic blood pressure fell from 179 ±24 mm Hg to 144 ±28 mm Hg, diastolic pressure dropped from 103 ±16 mm Hg to 85 ±18 mm Hg and heart rate fell from 74 ±15 beats per minute to 71 ±13 beats per minute. The effect of BAT was greater than average in patients with signs of heart failure and less than average in patients with isolated systolic hypertension. In 27% of patients, it was possible to reduce the number of medications from a median of 6 to a median of 3. After a follow-up of 6 years, the authors concluded that BAT maintains its efficacy for persistent reduction of blood pressure in patients with resistant hypertension without major safety issues. Limitations of this study include use of the first-generation Rheos® system, lack of randomization in 2 of 3 studies and lack of a control group during long-term follow-up.

Wallbach et al. (2016) conducted a prospective case series of 44 patients treated with BAT neo™ device for uncontrolled resistant hypertension. Ambulatory blood pressure monitoring (ABPM) was performed before BAT implantation and 6 months after the initiation of BAT. After 6 months, 24-hour ambulatory systolic (from 148 ±17 mm Hg to 140 ±23 mm Hg), diastolic (from 82 ±13 mm Hg to 77 ±15 mm Hg), day- and night-time systolic and diastolic blood pressure significantly decreased. Heart rate and pulse pressure remained unchanged. The authors concluded that this is the first study demonstrating a significant blood pressure reduction in ABPM in patients undergoing chronically stimulation of the carotid sinus using the BAT neo™ device and that BAT might be considered as a therapeutic option to reduce cardiovascular risk in patients with resistant hypertension. Randomized controlled trials are needed to evaluate BAT effects on ABPM in patients with resistant hypertension accurately. The findings of this study are limited by lack of comparison group.

Hoppe et al. (2012) evaluated the Barostim neo™, a second-generation BAT, in a case series of patients with resistant hypertension. Thirty patients with resting SBP ≥ 140 mm Hg despite treatment with ≥ 3 medications, including ≥ 1 diuretic, were included in the single-arm, open-label study. The authors reported results consistent with studies of the first-generation system and a safety profile comparable to a pacemaker. This study is limited by lack of control and small sample size.

The Rheos® Pivotal Trial evaluated BAT for resistant hypertension in a double-blind, randomized, prospective, multicenter, placebo-controlled Phase III clinical trial. Two hundred and sixty-five patients with resistant hypertension were implanted and subsequently randomized (2:1) 1 month after implantation. Subjects received either BAT (Group A) for the first 6 months or delayed BAT initiation following the 6-month visit (Group B). The 5 primary endpoints were: 1) acute systolic blood pressure (SBP) responder rate at 6 months; 2) sustained responder rate at 12 months; 3) procedure safety; 4) BAT safety; and 5) device safety. The trial showed significant benefit for the endpoints of sustained efficacy, BAT safety and device safety. However, it did not meet the endpoints for acute responders or procedural safety. The authors concluded that the weight of the overall evidence suggests that over the long-term, BAT can safely reduce SBP in patients with resistant hypertension. Future clinical trials will address the limitations of this study and further define the therapeutic benefit of BAT (Bisognano et al., 2011).

After completion of the randomized Rheos® Pivotal Trial, Bakris et al. (2012) conducted an open-label, nonrandomized follow-up study to assess the long-term safety and efficacy of BAT. Clinically significant responder status was assessed according to FDA-mandated criteria. Of 322 patients implanted, 76% (n = 245) qualified as clinically significant responders. An additional 10% were indeterminate. Among long-term responders receiving BAT, the mean blood pressure drop was 35/16 mm Hg. Medication

use was reduced by the end of the randomized phase and remained lower through the follow-up period. Among responders, 55% achieved targeted blood pressure reduction goals sustained through 22 to 53 months of follow-up.

A National Institute for Health and Care Excellence (NICE) guideline concluded that current evidence on the safety and efficacy of implanting a baroreceptor stimulation device for resistant hypertension is inadequate (2015).

The American College of Cardiology and American Heart Association joint Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults states that there is insufficient evidence to recommend the use of these devices in managing resistant hypertension (Whelton et al., 2018).

Recruiting has been completed for the interventional, multicenter 100-patient Nordic BAT study (NCT02572024), a randomized, double-blind, parallel-design clinical trial to examine the effect of baroreflex activation therapy (BAT) compared to continuous pharmacotherapy on blood pressure, as well as arterial and cardiac function and structure using non-invasive high technology methodology. This study has a primary completion date of November 2022, with a final completion date of April 2028. For more information, refer to www.clinicaltrials.gov. (Accessed March 31, 2022)

Recruiting has been completed for the 300-patient Calm-2 trial (NCT03179800), a prospective, multi-center randomized, sham-controlled, double-blinded study using the MobiusHD device in patients with drug-resistant hypertension. This study has a primary completion date of May 2025 with a final completion date of May 2025. For more information, refer to www.clinicaltrials.gov. (Accessed March 31, 2022)

Heart Failure

Heidenreich et al. (2022) presented a Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. The guideline states that "autonomic nervous system modulation is intriguing as a treatment for HFrEF because of the heightened sympathetic response and decreased parasympathetic response in HF. Trials of device stimulation of the vagus nerve, spinal cord, and baroreceptors have had mixed responses. An implantable device that electrically stimulates the baroreceptors of the carotid artery has been approved by the FDA for the improvement of symptoms in patients with advanced HF who are unsuited for treatment with other HF devices including CRT. In a prospective, multicenter, RCT with a total of 408 patients with current or recent NYHA class III HF, LVEF ≤35%, baroreceptor stimulation was associated with improvements in QOL, exercise capacity, and NT-proBNP levels." However, to date, "there are no mortality or hospitalization rates results available with this device. Although early trials of vagus nerve stimulation were positive, the largest and latest trial did not show a reduction in mortality and HF hospitalizations. Multisite LV pacing studies initially were promising. However, more recent data have not confirmed benefit, and the larger phase 2 trial was terminated early for low probability of benefit".

Hayes (2021) published an Evidence Analysis Research Brief for the Barostim Neo System for Treatment of Heart Failure. The report indicated that a review of the abstracts suggests that the quantity of published, peer-reviewed clinical data is insufficient to evaluate this technology for the treatment of heart failure.

ECRI (2020) published a Custom Product Brief for the Barostim Neo™ System for the treatment of heart failure (HF) indicating that the evidence is somewhat favorable based on a review of two ongoing RCTs involving 368 participants. These studies show that the BAT device is safe and more effective than standard of care for improving quality of life and functional status based on preliminary 6-month data. Both studies will provide up to 5—year data with an expected completion date of December 2021.

Zile et al. (2020) evaluated the safety and effectiveness of BAT in patients with heart failure with reduced ejection fraction (HFrEF) in the Baroreflex Activation Therapy for Heart Failure (BeAT-HF) clinical trial. This prospective, multi-center RCT involved 408 participants with HFrEF randomized into two study arms, one receiving BAT with optimal medical management or one receiving optimal medical management alone. There was a total of four patient cohorts. Effectiveness endpoints were the change from baseline to 6 months in 6-min hall walk distance (6MHW), Minnesota Living with HF Questionnaire quality-of-life (QOL) score, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. The safety endpoint included the major adverse neurological or cardiovascular system or procedure-related event rate (MANCE). The fourth cohort, Cohort D, which included the intended use population that reflected the Food and Drug Administration (FDA)-approved instructions for use (enrollment criteria plus NT-proBNP of less than 1,600 pg/ml), consisted of 245 participants followed-up for 6 months (120 in the BAT group and 125 in the control group). The authors concluded that BAT was safe and significantly improved QOL, exercise

capacity, and NT-proBNP. They noted that the study has several limitations including not examining morbidity and mortality or change in cardiovascular structure or function endpoints, the lack of blinding in this trial, and that there might be subject to placebo effects. The researchers indicated that further studies are needed to examine the impact of BAT on the frequency of hospitalization and mortality and identify patients with HFrEF most likely to gain lasting benefit from this type of intervention.

In 2016, Gronda et al. conducted a comparative investigation on effects of BAT on arterial stiffness in 18 NYHA Class III subjects with HF with reduced ejection fraction (HFrEF). Patients were equally divided into the BAT group and the group receiving medical management alone. Clinical parameters and MSNA were gathered as baseline and again at 3 months. The authors concluded that despite significant reductions in MSNA and some clinical improvements, BAT does not appear to chronically modify arterial stiffness within this HFrEF cohort. Additional study is required to determine if this result applies to the HFrEF population as a whole.

In a pooled analysis of 2 multicenter, prospective, randomized controlled trials, Abraham et al. (2015) assessed the safety and efficacy of carotid BAT in advanced HF. A total of 146 patients with NYHA functional class III HF and ejection fractions ≤ 35% on chronic stable guideline-directed medical therapy (GDMT) were randomly assigned to receive ongoing GDMT alone (n = 70) or ongoing GDMT plus BAT (n = 76) for 6 months. The major adverse neurological and cardiovascular event-free rate was 97.2%. Patients assigned to BAT, compared with control group patients, experienced improvements in functional status, exercise capacity, QOL score and N-terminal pro-brain natriuretic peptide. The treatment was also associated with a trend toward fewer hospitalizations for HF. Further study is needed to determine the long-term safety and efficacy of BAT in this patient population.

Zile et al. (2015) reported on the same study population as Abraham et al. (2015). However, this report compared outcomes in GDMT plus BAT group patients with (n = 24) and without (n = 47) a cardiac resynchronization therapy (CRT) device. The goal was to determine differences in treatment effect produced by BAT in the 2 groups. There were no statistically significant differences in safety and tolerability between the CRT group and the non-CRT group. There was a significantly greater response to BAT in the non-CRT group compared with the CRT group in some parameters. The difference was statistically significant in QOL score and 6-minute hall walk distance. There was no statistically significant difference between CRT and non-CRT groups in NYHA classification. Further study is needed to determine the long-term safety and efficacy of BAT.

Gronda et al. (2014) assessed the effects of BAT in clinical HF. In a single-center, open-label pilot study, 11 patients with NYHA class III HF, ejection fraction < 40%, optimized medical therapy and not eligible for CRT received BAT for 6 months. Efficacy was assessed with serial measurement of muscle sympathetic nerve activity (MSNA) and clinical measures of QOL and functional capacity. Serial MSNA exhibited significant reductions at 1-, 3- and 6-months following device activation. The reduction was incremental between 1 and 3 months, and stable between 3 and 6 months. At 6 months, MSNA was reduced by one-third versus baseline. Improvements were also seen in baroreflex sensitivity, ejection fraction, NYHA class and QOL. On an observational basis, hospitalization and emergency department visits for worsening HF were markedly reduced. The authors concluded that BAT was safe and provided chronic improvement in MSNA and clinical variables. Based on present understanding of HF pathophysiology, these results suggest that BAT may improve outcomes in HF by modulating autonomic balance. This study is limited by small patient population, limited follow-up, and lack of a control group. Prospective, randomized trials to test the hypothesis are warranted.

The American College of Cardiology/American Heart Association guidelines and the Heart Failure Society of America's report on the management of HF do not include recommendations for BAT, stating that trials of baroreceptors have had mixed responses, and there are no mortality or hospitalization rates results available with this device. (Heidenreich et al. 2022).

Two clinical trials are currently recruiting to study Barostim Therapy in Heart Failure.
Recruiting is currently underway for the CVRx Barostim Therapy in Heart Failure with Reduced Ejection Fraction (HFrEF) Registry (NCT04502316). The registry will include individuals who were recently implanted with the Barostim System for heart failure. Enrollment is expected to be up to 5,000 patients, from whom evaluations will be taken prior to device implant, at implant, and every six months after implant, up to 36 months. The purpose of the registry is to develop valid scientific evidence of the safety and efficacy of Barostim in this patient population. This study has an estimated completion date of June 2028. For more information, refer to www.clinicaltrials.gov. (Accessed March 31, 2022)

Recruiting is also currently underway for a study of Barostim Therapy In Heart Failure With Preserved Ejection Fraction (HFpEF) (NCT02876042). This registry will include individuals who were recently implanted with the Barostim System for heart failure. Enrollment is estimated to be 70 patients with resistant hypertension that also have evidence of heart failure with preserved

ejection fraction (HFpEF). Data will be obtained from standard of care measurements taken prior to implant, at enrollment/baseline, and at 3 and 6 months after the device. The purpose of the study is to evaluate the Barostim Neo System in this population. The study has an estimated completion date of July 2024. For more information, refer to www.clinicaltrials.gov. (Accessed March 31, 2022)

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Code	Description
0330T	Tear film imaging, unilateral or bilateral, with interpretation and report

Tear film imaging to monitor or assess tear film disorders is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Techniques that gather information from the tear film by processing reflected light or images from the tear are being investigated as representing the true state of the ocular surface. This includes techniques such as interferometry, meniscometry, high speed video topography, and optical coherence tomography (Dry Eye Workshop 2007). These tear film imaging techniques are being investigated to assist in better differentiating dry eye disorders and developing dry eye treatments.

Lee et al. (2020) evaluated the clinical accuracy and utility of the Antares topographer in the diagnosis of dry eye disease (DED). Thirty-three consecutive patients underwent analyses of their non-invasive first tear-film break-up time (NIF-BUT), tear meniscus height (TMH) and meibography with the Antares topographer. The meibography with the LipiView scan was conducted. Slit-lamp examinations were done for assessments of meibomian glands (MG) and fluorescein tear-film break-up time (FBUT). Schirmer 1 test was done. The Ocular Surface Disease Index (OSDI) scores were graded. Thirty-three eyes of 33 patients (mean age 61.5 ±10.6 years, range 37.5-76.4 years, 27.3% males) completed the study. According to the Antares measurements, the NIF-BUT of the patient population was 5.0 ±3.4 seconds on average (1.1-15.0 seconds), and the TMH was 0.2 ±0.1 mm at center (0.1-0.5 mm). The average OSDI score was 22.4 ±16.6 points (0.0-79.5 points). When correlations were calculated, significant correlations were found between the NIF-BUT from the Antares topographer and FBUT ($r = 0.538$, $p = .001$), and between MG dropout from the Antares topographer and that from the LipiView interferometer ($r = 0.446$, $p = 009$). Antares NIF BUT and FBUT were in agreement with one another (95% limits of agreement (LOA) -5.04 ±6.37, $p = .198$) as were the infrared images from the Antares topographer and those from the LipiView interferometer (95% LOA -0.25 ±0.35, $p = .073$). The authors concluded that the Antares topographer is useful in the diagnosis of DED. Among its outputs, the NIF-BUT and MG dropout most closely correlated with currently accepted modes of diagnosis. The authors indicated that concurrent clinical examinations are recommended for clinical follow-up. While this study reports correlations, it doesn't test diagnostic performance or clinical utility of tear film imaging.

Lee et al. (2019) compared the lipid layer thickness (LLT) using the LipiView ocular surface interferometer between the eye treated with glaucoma medication and untreated normal eye in the unilateral glaucoma patients and evaluated the effect of topical glaucoma medication on the LLT parameters in glaucoma eyes. The 30 participants in this cross-sectional comparative study were unilateral glaucoma patients treated with topical glaucoma medications for more than 12 months. Three LLT parameters (average, minimum, and maximum) obtained by the LipiView were compared between the glaucomatous eye and normal eye. The factors associated with LLT parameters in the eyes treated with glaucoma medication were investigated with multiple regression analysis. Lipid layer average, minimum, and maximum were 64.83 ±16.50, 51.63 ±16.73, and 82.53 ±20.62 in glaucomatous eyes, 77.26 ±17.81, 62.83 ±20.99, and 86.13 ±15.42 in normal eyes. Lipid layer average and minimum were significantly thinner than those in normal eyes ($p < 0.001$, $p < 0.001$, respectively). Longer duration of glaucoma eye drops and a greater number of glaucoma medications were associated with the lower LLT average ($\beta = -0.456$, $p < 0.001$, $\beta = -8.517$, $p = 0.003$, respectively), and increasing glaucoma medications have a significant correlation with lower LLT minimum in glaucoma eyes ($\beta = -8.814$, $p = 0.026$). The authors concluded that patients with long-term glaucoma medications need to be assessed for LLT parameters to objectively evaluate their ocular surface health. According to the authors, the findings of this study are subject to the following limitations. First, the sample size of patients with unilateral glaucoma was relatively small because the prevalence of unilateral glaucoma treated with topical glaucoma medication in the affected eye only is much less than the prevalence of bilateral glaucoma. Also, the present study did not compare the parameters in the LipiView interferometer with other measurements including tear break-up time, ocular surface disease index, or tear osmolarity for OSDI. According to the authors, further study is needed for evaluating the correlations between conventional measurements in OSDI and LipiView interferometers.

The American Academy of Ophthalmology Preferred Practice Pattern Guidelines on dry eye syndrome (2018) does not address tear film imaging.

Ji et al. (2017) investigated the clinical utility of automated values obtained by the Keratograph and LipiView when evaluating non-Sjögren dry eye syndrome (NSDES) with meibomian gland dysfunction (MGD). Sixty-four patients (64 eyes) diagnosed with NSDES with MGD were enrolled. All eyes were evaluated using the Ocular Surface Disease Index (OSDI), fluorescence staining score, tear film breakup time (TBUT), Schirmer test, and MGD grade. Noninvasive Keratograph average tear film breakup time (NIKBUTav), tear meniscus height (TMHk), meibomian gland (MG) dropout grade, and lipid layer thickness (LLT) using interferometry were measured. Among automated indexes, NIKBUTav and the MG dropout grade significantly correlated with the OSDI, as did all conventional indicators, except the Schirmer score. TMHk had significant correlation with the Schirmer score, the staining score, TBUT, and NIKBUTav, but not any MGD indicator, even the MG dropout grade. NIKBUTav showed significant correlations with all clinical parameters and other automated values, except the Schirmer score and LLT. The MG dropout grade highly correlated with all indexes except TMHk. LLT was significantly associated with TBUT, MGD grade, and MG dropout grade, although it was not related to patient symptoms. The authors concluded that automated noninvasive measurements using an advanced corneal topographer and LLT measured with an ocular surface interferometer can be alternatives to conventional methods to evaluate tear conditions on the ocular surface; the former device can provide information about conformational MG changes in NSDES with MGD. According to the authors, a limitation of this study was that they included dry eye limited to NSDES with MGD. Therefore, caution should be exercised when applying the present results to the general patient population with dry eye. While the study reports correlations, it doesn't specifically test diagnostic performance or clinical utility of tear film imaging.

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Code	Description
0331T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment;
0332T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment; with tomographic SPECT

Myocardial sympathetic innervation imaging with 123 Iodine meta-iodobenzylguanidine (^{123}I-MIBG) is unproven and not medically necessary as a prognostic marker in patients with heart failure due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

While myocardial sympathetic innervation imaging has been studied, the evidence is insufficient to support its routine use as proven in clinical practice.

Seo et al. (2022) utilized the data from Osaka Prefectural Trial: Acute Heart Failure Syndrome Registry (OPAR); a prospective, single-center, observational prospective cohort to study 148 individuals admitted with acute decompensated heart failure (ADHF) and nonischemic preserved left ventricular ejection fraction (HFpEF) who underwent cardiac iodine-123 labeled metaiodobenzylguanidine (^{123}I-MIBG) imaging at discharge. The author's goal was to uncover the prognostic value of cardiac sympathetic nerve dysfunction using ^{123}I-MIBG single-photon emission computed tomography (SPECT) imaging in those individuals with HFpEF. Methods utilized for the study include the cardiac ^{123}I-MIBG heart to mediastinum ratio (H/M), which calculated the delayed planar image (late H/M), and SPECT analysis of the delayed image conducted, with the tracer uptake in all 17 regions on the polar map, scored with a 5-point scale. Calculating the total defect score (TDS) was accomplished by adding the score of each of the 17 segments, with the primary endpoint being the association between TDS and cardiac events. The authors concluded that from a mean follow-up period of 2.4 +/- 1.6 years, 61 individuals suffered cardiac events. TDS and

cardiac events were significantly associated following the multivariate Cox adjustment (p < 0.0001). Those individuals with high TDS levels exhibited substantially greater risk for cardiac events than those with average or low TDS levels (63% vs 40% vs 20%, respectively; p < 0.0001; HR: 4.69; 95% CI: 2.29 to 9.61; and HR: 2.46; 95% CI: 1.14 to 5.29). C-statistic of TDS was 0.730 (95% CI: 0.651 to 0.799), which was considerably higher than previous H/M (0.607; 95% CI: 0.524 to 0.686; p = 0.0228). The authors conclude that cardiac ^{123}I-MIBG SPECT imaging offered valuable prognostic information for individuals with nonischemic ADHF with HFpEF. The study has several limitations that limit the technologies applicability to larger populations. The study was a single-center cohort with a small sample size and short follow-up period.

Seo et al. (2021) conducted a prospective study in OPAR to determine the prognostic significance of cardiac ^{123}I-MIBG imaging in individuals with reduced, mid-range and preserved left ventricular ejection fraction admitted for ADHF. The study participants were 349 individuals admitted for ADHF who received cardiac ^{123}I-MIBG imaging, echocardiography, and venous sampling before discharge. After the isotope injection, the ^{123}I-MIBG late H/M was measured on the anterior chest view images. The study's endpoint was cardiac events, defined as unplanned HF hospital admissions and cardiac death, which was measured during a follow-up period of 2.1 +/- 1.4 years. During the follow-up period, 128 individuals experienced cardiac events. Multivariable Cox analysis revealed significant association of late H/M with cardiac events in the overall cohort (p = 0.0038); and in the subgroup analysis of each LVEF subgroup (p = 0.0235 in HFrEF, p = 0.0119 in HFmEF and p = 0.0311 in HFpEF). Utilizing Kaplan-Meier analysis, outcomes indicated that individuals with low late H/M had greater risk of cardiac events in the overall cohort (49% vs. 25% p < 0.0001) and in each LVEF subgroup (HFrEF: 48% vs. 23% p = 0.0061, HFmrEF: 51% vs. 21% p = 0.0068 and HFpEF: 50% vs. 26% p = 0.0026). The authors concluded that cardiac sympathetic nerve dysfunction was associated with poor outcomes in ADHF patients regardless of HFrEF, HFmrEF, or HFpEF. Limitations of the study consist of a single-center cohort study with small sample size and a short follow-up period. Additionally, ^{123}I-MIBG uptake may have been affected by medication at discharge or during the follow-up period. Although the authors conveyed that serial ^{123}I-MIBG scintigraphy studies can be valuable for foreseeing cardiac events in HFrEF patients, the prognostic value of serial change of cardiac ^{123}I-MIBG studies remain to be clarified.

In follow up of the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure study (ADMIRE-HF), Agostini et al. (2019) published an evaluation of whether planar ^{123}I-MIBG myocardial scintigraphy was accurate in predicting risk of death in heart failure (HF) patients up to five years (median 62.7 months) after initial imaging. Using the heart/mediastinum (H/M) ratio on planar ^{123}I-MIBG scintigraphic images obtained at baseline (< 1.60 vs ≥ 1.60), 964 subjects were stratified according to their results. In subjects with H/M < 1.60, all-cause mortality was 38.4% compared to 20.9% in subjects with H/M ≥ 1.60. Cardiac mortality was 16.8% in subjects with H/M < 1.60 compared to 4.5% in subjects with H/M ≥ 1.60. Risk of arrhythmic events, sudden cardiac death, potentially life-threatening arrhythmias, all cause and cardiac death was substantially lower in subjects showing preserved sympathetic innervation of the myocardium (H/M ≥ 1.60). Within LVEF strata, trend toward a higher mortality, reaching significance only for LVEF 25 to ≤ 35%, for subjects with H/M < 1.60, was observed. The authors concluded that during this median follow-up of 62.7 months, patients with H/M ≥ 1.60 were at significantly lower risk of death and arrhythmic events independent of LVEF values. However, no clinical decisions were based on the ^{123}I-MIBG imaging results, therefore ADMIRE-HF and its follow up studies do not evaluate benefit derived from the ^{123}I-MIBG imaging stratification in terms of such key outcomes as mortality.

Shah et al. (2012) conducted a sub-analysis of the ADMIRE-HF study which explored whether ^{123}I-MIBG HMR provided any improvement in risk stratification over LVEF. The ADMIRE-HF LVEF values reported by the core laboratory (some core LVEF measurements were > 35 %) were stratified by a late HMR of 1.6, and the combined ADMIRE-HF endpoints were estimated in each group. A late HMR of < 1.6 conferred, a greater risk of death and arrhythmic events across all LVEF subgroups. Interestingly, among subjects with an LVEF > 40 %, a late HMR > 1.6 was not associated with any risk of death or an arrhythmic event over the follow-up period. In contrast, individuals with an LVEF > 40 % and a late HMR < 1.6 had a 7.5 %/100 person-years risk of death and arrhythmic events. While this was a post-hoc analysis, the observations raise the possibility that assessing global cardiac sympathetic innervation may ultimately aid in identifying individuals at an increased risk of arrhythmic death who would otherwise be categorized as low risk based upon relatively preserved LV function. The authors concluded that imaging cardiac sympathetic innervation provides prognostic information in patients with left ventricular dysfunction, and that numerous studies have documented that this information is independent of routine clinical and demographic parameters. Nevertheless, the clinical translation of these findings to routine patient care remains unclear. There appears to be sufficient preliminary data to move in the direction of pragmatic clinical trials which incorporate cardiac sympathetic imaging into algorithms with therapeutic implications.

Jacobson et al. (2010) conducted a large prospective study evaluating global I-MIBG uptake and clinical outcomes. The study was known as the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure study (ADMIRE-HF). In this study, planar ^{123}I-MIBG and SPECT perfusion imaging were performed in 961 patients with NYHA class II or III heart failure (HF) and LVEF ≤ 35 %. The majority of patients (66 %) had ischemic cardiomyopathy. Over a median follow-up of 17 months, the primary composite endpoint (heart failure progression, arrhythmic events and cardiac death) occurred more frequently among those with a global reduction in sympathetic innervation (prospectively defined as a late HMR < 1.6). Although the frequency of arrhythmic events was significantly higher among those with a HMR < 1.6, the vast majority were non-sustained VT. SCD, resuscitated sudden cardiac arrest, and appropriate ICD discharges (shock or anti-tachycardia pacing) were a small portion of the total composite endpoints (21%). Quantification of regional defects was attempted in a subgroup of patients but did not provide any additional value to global indices of ^{123}I-MIBG uptake in predicting prognosis.

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Code	Description
0335T	Insertion of sinus tarsi implant
0510T	Removal of sinus tarsi implant
0511T	Removal and reinsertion of sinus tarsi implant
S2117	Arthroereisis, subtalar

The use of a sinus tarsi implant is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy.

Clinical Evidence

Flexible flatfoot (Flexible Pes Planovalgus, Pes Planus) is the result of the loss of the medial logitudinal arch, abduction of the forefoot and subtalar aversion. It is common in children, and in adults may be due to trauma, overuse and inflammatory disorders. It may be asymptomatic or become painful and require intervention. Non-surgical interventions include rest, physical therapy, orthotics and anti-inflammatory medications. Surgery may be indicated when conservative treatment is not successful. Subtalar arthroereisis (SA) is a surgical procedure designed to correct the excessive movement of the joint by placing an implant in the sinus tarsi, or adjacent to it. The implants are commonly made of titanium or a resorbable poly-L-lactic acid (PLLA).

Smolle et al. (2022) conducted a systematic review of the published literature up to July 2021 on the clinical and radiographic outcomes in children aged 6-11 who had surgical treatment for flexible flatfoot (FFF), with a follow up of at least 4 years. Ten studies of surgical procedures were included, 8 of them were in regard to arthroereisis, with and without concomitant achilles tendon lengthening. In half of the studies, nonoperative treatment had not been successful (this was not explicitly stated in the other half). For clinical and functional outcomes, the results showed implant associated complication rate of 2.8% for screw loosening or breakage and wound healing problems of 1.6%. At last follow up, chronic pain was present in 2.8% of the patients. American Orthopaedic Foot & Ankle Society (AOFAS) scores improved 23 points from preoperative to latest follow up and was reported in 6 studies. Radiological outcomes were reported in 7 of the 8 studies and showed radiologically measured angles towards the values of a normal pediatric foot at final follow-up. The authors concluded that the quality of these studies is low.

Outcome parameters reported are inconsistent, few provide patient-reported outcome measures, and long-term results on definite bony corrections are still missing. Larger studies comparing different therapeutic approaches in symptomatic pediatric FFF are needed.

In a 2021 systematic review, Smith et al. assessed the outcomes of arthroereisis for the treatment of symptomatic paediatric flexible pes planus. 24 studies (18 case series and six comparative studies with overall moderate methodological quality) met the inclusion criteria and radiological, clinical and kinematic outcomes, as well as complications were reviewed. A total of 2550 feet of at least 1399 patients were operated on and all studies stated inclusion criteria of flexible pes planus with symptoms of pain or fatigue. Failure of conservative treatment was only a requirement in 13 studies. The results showed a variety of radiological, kinematic and clinical outcomes used across the 24 studies, with poor homogeneity among them. Three studies did not measure any radiological outcome, ten measured any type of kinematics and only eight assessed patient reported outcomes. The authors concluded that overall results appear encouraging. There is an overall lack of high-quality prospective studies, limited long term data and heterogeneity of outcome measures, and these need to be addressed in future research to truly evaluate if arthroereisis is an effective treatment for symptomatic paediatric flexible pes planus.

Baryeh et al. (2021) conducted a systematic review to examine the outcomes of adult flatfoot deformity (AFFD) when treated surgically with subtalar arthroereisis. Nine studies met the inclusion criteria and were reviewed for both clinical and radiological outcomes as well as reported complications. A total of 167 patients underwent 190 procedures. Six of the 9 studies used the American Orthopaedic Foot and Ankle Society (AOFAS) score, 3 used the visual analog scale (VAS), 1 used the SF-36, and 1 used the Visual analogue scale foot and ankle (VAS-FA). Radiological measurements included Meary's angle, TN, Kite angle, and T1MT. The results showed five papers used the AOFAS hindfoot score with one using the foot and ankle outcome score (FAOS) , one used the VAS-FA score and three used the VAS for reporting outcomes. In general, this systematic review suggests treatment with subtalar arthroereisis, either alone or as an adjunct, results in improvement of clinical and radiological outcome, however it is unclear if the improvement would have occurred regardless. Only one paper used subtalar arthroereisis as the sole intervention and among the remaining papers, there was heterogeneity among additional procedures used. Sinus tarsi pain is the most common complication and, in this review, resulted in removal of 29% of implants. This review is limited by all studies being case series conducted at single centers, as well as only 2 being prospectively designed. Additionally, the heterogeneity of the procedures used also adds to the difficulty in identifying whether the improvements in clinical and radiological parameters were due to the use of subtalar arthroereisis or as a result of the additional procedures. Additional high-quality studies are needed to establish the best use of subtalar arthroereisis in the management of AAFD.

In a 2020 ECRI clinical evidence assessment on the HyProCure Sinus Tarsi Stent (no data was available for the HyProCure II device) (GraMedica) for correcting foot deformities, it was concluded that based on the evidence from 3 small case series at very high risk of bias, results are inconclusive and need validation in multicenter prospective controlled trials that compare HyProCure II to conventional surgical reconstruction and conservative treatment with orthoses.

A 2020 Hayes health technology assessment (updated in 2021) regarding subtalar arthroereisis for the treatment of adult-acquired flatfoot deformity concluded that based on the results of seven studies with very low-quality evidence, SAS remains an evolving technique for this condition and there is a need for additional well-designed clinical studies to develop patient selection criteria and evaluate the long-term efficacy and safety.

A 2020 Hayes health technology assessment (updated in 2021) regarding subtalar arthroereisis for the treatment of pediatric flatfoot (FF) focused on this treatment for children with symptomatic flatfoot deformity that does not respond to conservative measures and negatively impacts daily activities of living (ADLs). 13 studies were included and 11 of those included children with idiopathic flexible flatfoot (FFF) and 2 included children with spastic FF associated with cerebral palsy (CP). An overall low-quality body of evidence suggests that SA is relatively safe and efficacious for treating idiopathic FFF in children with pain, decreased function, and other symptoms that are refractory to standard medical therapies. However, the majority of studies are retrospective, there are few comparative studies, and no well-designed controlled studies to draw firm conclusions regarding its efficacy and safety. For children with spastic FF, there is a paucity of evidence and the overall quality of the body of evidence is very low. Indications were consistent in studies of idiopathic or spastic FF, but overall substantial heterogeneity exists in surgical approaches, implant devices, and concomitant procedures. Clinical outcome measures varied from validated questionnaires and scales to patient-reported, subjective results (e.g., patient satisfaction with SA). There is a need for additional well-designed clinical studies to develop patient selection criteria and evaluate the long-term efficacy and safety.

In a 2020 retrospective comparative study (included in Smolle study above) Bernasconi et al. sought to show that subtalar arthroereisis for treating flexible flatfoot (FFF) provided significant radiographic correction of low longitudinal arch and forefoot abduction in pediatric patients. From 70 consecutive feet, 62 (31 patients) treated at 10.5 years of age were identified and compared to 48 controls (24 patients). Multiple measurements of preoperative and most recent postoperative follow-up radiographs were recorded by two observers and compared to assess for correction of the FFF. Ankle and hindfoot range of motion (ROM), the American Orthopedic Foot and Ankle Society Score (AOFAS) hindfoot score and the Visual Analogue Scale foot and ankle (VAS-FA) score were compared with controls without foot symptoms or deformity. Mean follow-up was 62 months. Radiographic measurements demonstrated significant improvement after surgery, but significance was not reached in talonavicular coverage angle and calcaneo-fifth metatarsal angle on dorsoplantar view. In the most recent follow-up, patients had less hindfoot inversion than controls, and lower AOFAS scores due to pain and alignment sub scores. Using the VAS-FA score, patients were found to demonstrate higher pain at rest and during activity, and felt limited when standing on one leg and running. This improvement remained after removal of the implant. The authors concluded that STA corrected the low longitudinal arch in symptomatic pediatric FFF, but did not correct forefoot abduction in relation to the hindfoot. Mid-term assessment revealed STA provided satisfactory ankle and hindfoot ROM, pain and function levels, but there are limitations when compared to the control. The complication rate in this study is not negligible and resulted in the unplanned removal of the implant in 24% of the patients. Limitations of this study include a retrospective design, and a limited patient sample size.

Suh et al. (2019) performed a systematic review to compare radiographic correction, clinical outcomes, complications, and re-operations between lateral column lengthening (LCL) and arthroereisis (AR) for treating symptomatic flatfoot in children. Twenty-one and 13 studies were included in the LCL and AR groups, respectively. The reviewers reported that the LCL group achieved more radiographic corrections and more improvements in the American Orthopedic Foot and Ankle Society (AOFAS) score than the AR group. Complications were more common in the LCL group, and re-operation rates were similar between the two groups.

Indino and colleagues (2018) conducted a retrospective cross-sectional study to evaluate the radiographic effectiveness of subtalar arthroereisis with endorthesis for pediatric flexible flatfoot in patients that have reached skeletal maturity. Sixty consecutive patients were eligible to participate, with 56 (112 feet) being enrolled. Outcome measures were collected pre-operatively and at the final follow-up with a minimum follow-up period of 18 months. The sequence of testing for the outcome measures was randomized among patients, with the mean follow up being 40 months. The study demonstrated not only that subtalar arthroereisis with endorthesis significantly improves the radiographic parameters measured, but also that the ultimate correction is kept in pediatric patients that have reached the skeletal maturity. The authors concluded that endorthesis was effective for improving radiographic parameters of the foot in pediatric flexible flatfoot giving satisfactory ultimate outcomes at the end of foot growth. Future studies that help quantify radiographic measurement in the standard weight-bearing anteroposterior and lateral foot and establish the Minimal detectable change (MDC) value cutoff score would be useful.

Despite the good clinical results of subtalar arthroereisis for the management of flexible flatfoot in children, it is mostly performed using a metallic screw which typically requires removal after 2-3 years. Giannini et al. (2017), included in Smolle study above, conducted a retrospective cohort study of a consecutive series of 44 patients treated with a bioabsorbable calcaneal screw. The surgical technique was simple, and no intraoperative complications were reported. The mean follow-up duration was 56 months, with more than 95% of the patients reporting excellent or good clinical results. The authors concluded that the using the absorbable screw was an effective solution for flexible flatfoot in pediatric patients, simple, reliable and minimally invasive, with a high patient satisfaction level by eliminating a second surgical procedure for implant removal.

Numerous implant systems have received FDA approval through the 510(k) process. Refer to the following website for more information (use product code HWC): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed April 12, 2022)

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Code	Description
0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery (ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral
0339T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery (ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral

Transcatheter renal sympathetic denervation (unilateral or bilateral) for resistant hypertension is unproven due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

In a systematic review and meta-analysis of blinded randomized, placebo-controlled trials, Ahmad et al. (2021) sought to compare the effect of renal denervation (RD) in individuals taking medication for hypertension and those not taking medication. Seven eligible trials were identified including a total of 1,368 individuals. Review of the data showed that RD significantly reduced ambulatory systolic (mean difference 3.61 mm Hg; 95% CI: 4.89 to −2.33 mm Hg; $p < 0.0001$), office systolic (5.86 mm Hg; 95% CI: 7.77 to 3.94 mm Hg; $p < 0.0001$), and office diastolic (3.63 mm Hg; 95% CI: 4.77 to 2.50; $p < 0.0001$) blood pressure (BP). Weighted mean follow-up duration was 4.5 months. The researchers indicate that the review of these studies found consistent evidence that RD can reduce ambulatory and office BP, although the reduction appears to be modest (approximately 4/2 mm Hg). The reduction appeared to be similar between individuals who were taking antihypertension medications and those who were not, but there was no indication whether the reduction would persist over time. The authors concluded that RD could be a useful strategy for individuals with hypertension, especially if they are unwilling to add antihypertensive medications, however larger scale, high-quality studies are needed to help determine safety and potential long-term effect of RD. Evidence addressing the effect of the therapy on end organ damage or patient-centered outcome would also be useful. Study by Azizi et al. (2021) discussed below was included in this systematic review.

In an effort to evaluate the safety and efficacy of endovascular ultrasound RD in patients with resistant hypertension, Azizi et al. (2021) conducted a randomized, single-blind international sham-controlled clinical trial which took place at 28 facilities in the

United States and 25 facilities in Europe (RADIANCE-HTN). Individuals aged 18-75 with office-measured BP of at least 140/90 despite the use of at least 3 antihypertensives (including diuretic) were included. Of 989 total originally enrolled, 136 participants met all inclusion criteria and were randomly assigned to either RD (n = 69) or sham (n = 67) procedure. Both the participants and those making assessments were masked to randomization. Participating individuals were switched to a daily, fixed-dose, single-pill including an angiotensin receptor blocker, a calcium channel blocker and a thiazide diuretic, which continued for 4 weeks. Change in daytime ambulatory systolic BP at 2 months in the intention-to-treat group was the primary endpoint of the study, along with safety. With measured adherence to combination medication similar in both groups (82% in RD group vs 82% in sham group), the RD group showed a reduced ambulatory systolic BP compared to the sham procedure. Median between-group difference was -4.5 mm Hg and among participants with complete ambulatory BP data the difference was -5.8 mm Hg. No difference in safety outcomes was noted between the two groups. The authors concluded that ultrasound RD resulted in reduced BP after 2 months in participants with resistant hypertension compared to sham procedure. They suggest that if studies continue to demonstrate the safety and BP-lowering effects of RD, it may become an option (potentially as an alternative to addition of further antihypertensive medication) for treatment of individuals with resistant hypertension.

In a 2021 Emerging Evidence Review, Hayes reported on the current status of the evidence for the Paradise renal denervation system (RDS) for hypertension. Paradise RDS uses ultrasound energy delivered via catheter to perform targeted denervation to renal sympathetic nerves. Paradise was granted Breakthrough Device Designation by the FDA in December 2020 and is currently in pivotal clinical trials for stage 2 and treatment-resistant hypertension. The highest quality evidence for this technology thus far comes from the ongoing RADIANCE-HTN trial and the ACHIEVE study. The authors notes that although published evidence has demonstrated that ultrasound RD with the Paradise system decreases BP in individuals with resistant hypertension, the decrease has been < 10 mm Hg and most patients still required antihypertensive medications. They concluded that it is uncertain whether treatment with this device will be determined to be clinically meaningful and useful for individuals with stage 2 or resistant hypertension.

Pisano et al. (2021) published a Cochrane systematic review of randomized controlled trials (RCT) evaluating short- and long-term effects of RD in individuals with resistant hypertension. Clinical outcomes included cardiovascular events (fatal and non-fatal), hospital admissions, quality of life, all-cause mortality, BP control, cardiovascular and metabolic profile, left ventricular hypertrophy, kidney function and potential adverse effects of RD treatment. Selection criteria included RCT comparing RD to standard therapy or sham treatment. After excluding studies not meeting criteria, 15 studies with 1416 participants were evaluated. Many of the studies had unclear or high risk of bias for blinding/allocation concealment. The review found low-certainty evidence that RD had little or no effect on risk of myocardial infarction, ischemic stroke, unstable angina, or hospitalization. Moderate-certainty evidence suggested that RD could reduce 24-hour ambulatory blood pressure monitoring (ABPM) systolic BP, diastolic BP and office diastolic BP. RD had little or no effect on office systolic BP. Moderate-certainty evidence also suggested that this procedure may not reduce serum creatinine or increase estimated glomerular filtration rate or creatinine clearance. In summary, the authors concluded that for individuals with resistant hypertension, the evidence is insufficient to support the clinical use of the RD procedure for improving cardiovascular outcomes and renal function, however there is moderate-certainty evidence that it may improve 24-hour ABPM and diastolic office measured BP. Additional high-quality clinical trials which seek to measure patient-centered outcomes and include longer follow-up periods, larger sample sizes and more standardized procedures are required in order to clarify clinical utility of RD for resistant hypertension. Studies by Desch, et al. (2015), Bhatt, et al. (2014) and Esler, et al. (2012), included in previous versions of this policy were included in this review.

Schmieder et al. (2021) published a position statement on behalf of the European Society of Hypertension regarding the use of RD for lowering BP, suggesting a structured pathway for clinical use of RD including standardized shared decision-making to select the most appropriate treatment option for individuals with hypertension. This recommendation was made based on results of recent sham-controlled clinical trials, however the authors point out the knowledge gaps related to this procedure that continue to exist, including predictors of BP response to RD, predictors of efficacy, direct comparison of different ablative techniques, long term efficacy and safety, safety in patients with decreased glomerular filtration rates, impact related to hypertensive comorbidities, cost-effectiveness and patient perspective and preference. In addition, the authors stress the importance of establishing a structured and transparent way to qualify facilities to perform RN.

Silverwatch et al. (2021) published a systematic review and network meta-analysis of RCT comparing the efficacy and safety of existing RD interventions for uncontrolled hypertension (UH) and resistant hypertension (RH) to determine their effects on several intermediate and clinical outcomes. Twenty RCT's were included with 2,152 patients (mean ages 48-64 years-old) with RH and/or UH and follow-up time ranging from two to six months. Network meta-analysis (NMA) and frequentist framework

were used to evaluate RD interventions such as radiofrequency (RF) in the main renal artery (MRA) and branches, RF in MRA, RF in MRA plus antihypertensive therapy (AHT), ultrasound (US) in MRA, sham, and AHT. The data findings were RF in MRA, and branches was the best intervention to reduce 24-h ambulatory, and daytime and nighttime SBP and DBP compared to other interventions, only 24-h ambulatory SBP and DBP were significantly reduced in comparison. RF in MRA plus AHT was the best intervention to lower office SBP and DBP compared to other interventions, but neither was significant. The leading RD interventions were similar after analysis in six-month follow-up and RH only trials. The authors concluded scarce data and uncommonly described outcomes in the existing trials led to no significant difference of RD on clinical outcomes. Therefore, more clinical outcome data is needed for future trials to further the safety and efficacy of RD interventions. The studies by Desch, et al. (2015), Bhatt, et al. (2014), included in the previous versions of this policy are included in this systematic review and are no longer discussed in detail below. In addition, this systematic review is included in the 2021 Hayes Evolving Evidence Review above.

A systematic review and meta-analysis regarding the state of renal sympathetic denervation (RSD) for management of patients with hypertension was published by Syed et al. in 2021. Eight studies, with a total of 1363 patients, were included. Mean age was 56 years of age ±2.6 years, and 29% of patients included were women. Data was pooled from RCT and comparison of RSD in the management of hypertension to sham procedures was performed. Median maximum follow-up was 6-month range (3-12 months). Data showed greater reduction in ambulatory systolic blood pressure (ASBP), ambulatory diastolic blood pressure (ADBP), office systolic blood pressure (OSBP) and office diastolic blood pressure (ODBP) with RSD. The authors concluded that the use of RSD for management of hypertension demonstrated reduced ambulatory and office BP compared to sham procedure(s), however, additional high-quality RCT of RSD are needed to assess impact on clinical outcomes and confirm safely and reproducibility. The studies by Desch, et al. (2015), Bhatt, et al. (2014) Esler, et al. (2012), included in the previous versions of this policy are included in this systematic review and are no longer discussed in detail below.

Lambert et al. (2012) evaluated the effects of RD on health-related quality of life (QOL) measures. Using the Medical Outcomes Study 36-Item Short-Form Health Survey and Beck Depression Inventory-II, (BDI-11) QOL was examined before and three months after RD in patients with uncontrolled BP. For baseline comparisons, matched data were extracted from the Australian Diabetes, Obesity, and Lifestyle database. Before RD, patients with resistant hypertension (n = 62) scored significantly worse in 5 of the eight 36-Item Short-Form Health Survey domains and the Mental Component Summary score. Three months after denervation (n = 40), clinic BP was reduced (change in systolic and diastolic BP, -16 ±4 and -6 ±2 mm Hg, respectively; $p < 0.01$). The Mental Component Summary score improved (47.6 ±1.1 versus 52 ±1; $p = 0.001$) as a result of increases in the vitality, social function, role emotion, and mental health domains. The BDI scores were also improved, particularly with regard to symptoms of sadness ($p = 0.01$), tiredness ($p < 0.001$), and libido($p < 0.01$). The magnitude of BP reduction or BP level achieved at 3 months bore no association to the change in QOL. RD did not have detrimental effect on any elements of the 36-Item Short-Form Health Survey. These results indicate that patients with severe hypertension resistant to therapy present with a marked reduction in subjective QOL. In this pre- and post-hypothesis generating study, several aspects of QOL were improved after RD; however, this was not directly associated with the magnitude of BP reduction. Study limitations included lack of comparison group.

Brandt et al. (2012) investigated the effect of catheter-based RSD on left ventricular hypertrophy (LVH) and systolic and diastolic function in a cohort study of patients with resistant hypertension. Forty-six patients underwent bilateral RD, and 18 patients served as controls. Transthoracic echocardiography was performed at baseline, and after 1 month and 6 months. Besides reduction of systolic and diastolic BP (-22.5/-7.2 mm Hg at 1 month and -27.8/-8.8 mm Hg at 6 months, $p < 0.001$ at each time point), RD significantly reduced mean interventricular septum thickness from 14.1 ±1.9 mm to 13.4 ±2.1 mm and 12.5 ±1.4 mm ($p = 0.007$), and LV mass index from 53.9 ±15.6 g/m(2.7) (112.4 ±33.9 g/m(2)) to 47.0 ±14.2 g/m(2.7) (103.6 ±30.5 g/m(2)) and 44.7 ±14.9 g/m(2.7) (94.9 ±29.8 g/m(2)) ($p < 0.001$) at 1 month and 6 months, respectively. The mitral valve lateral E/E' decreased after RD from 9.9 ±4.0 to 7.9 ±2.2 at 1 month and 7.4 ±2.7 at 6 months ($p < 0.001$), indicating reduction of LV filling pressures. No significant changes were observed in control patients. Study authors suggest that RD significantly reduces LV mass and improves diastolic function, which might have important prognostic implications in patients with resistant hypertension at high cardiovascular risk.

In May of 2012, the National Institute for Health and Clinical Excellence (NICE) published guidance for percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. The guideline stated that while the current evidence is limited due to the number of patients, there is evidence of short/medium term efficacy. However, the evidence for long term efficacy and safety is inadequate As of May 2022, NICE has indicated that this guidance is currently being updated and will be published soon.

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Code	Description
0351T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative
0352T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred
0353T	Optical coherence tomography of breast, surgical cavity; real-time intraoperative
0354T	Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred

Intraoperative optical coherence tomography is unproven and not medically necessary for the following due to insufficient evidence of safety and/or efficacy:

- assessment of lymph nodes or tumor margins in breast conserving surgery
- as guidance for real-time assessment of surgical margins for solid breast tumors

Clinical Evidence

The National Comprehensive Cancer Network does not mention optical coherence tomography in their clinical practice guideline on breast cancer (April 2022).

Heidkamp et al. (2021) conducted a systematic review and meta-analysis on 134 studies evaluating the use of novel imaging techniques for intraoperative margin assessment in human subjects, with histopathology as the reference standard. This overview of 16 techniques, which included optical coherence tomography (OCT), assessed technical properties, feasibility in clinical practice and diagnostic accuracy. Most studies (73% n = 66) were in the early stages of research and development. The majority (n = 100; 75%) of techniques were applied in open surgical procedures and most techniques (n = 108) assessed margins on the specimen resected. Only one fourth of all studies (n = 33) reported diagnostic accuracy on margin assessment

with sensitivities ranging from 21% to 100% and specificities from 37% to 100%. Per the authors, the field of novel techniques (including OCT) for intraoperative margin assessment is highly evolving and in early developmental stages; the results suggested that none of the techniques studied were superior nor had high feasibility or diagnostic accuracy. The researchers concluded that this review does not support the recommendation of any of these techniques as showing promise for clinical practice. A comparison of all techniques within one framework could assist in the selection of imaging techniques for intraoperative margin assessment that meet specific needs and may subsequently guide research and development of promising techniques.

A systematic review by Butler-Henderson et al. (2014) assessed current intra-operative methods for assessing margin status. Comparison between the studies included pathology status, accuracy of tumor margin assessment, the time impact on the procedure, and the rate of second operations. Pathology methods, such as frozen section and imprint cytology performed well, but added an average of 20 to 30 minutes to operating time. Although ultrasound probe allows accurate, timely examination of the margins, its role is limited in ductal carcinoma in-situ, and multi-focal cancer. The authors concluded that further research is needed in other intra-operative margin assessment techniques, such as optical coherence tomography, mammography, and radiofrequency spectroscopy.

Patel et al. (2013) used optical coherence tomography and dye-enhanced wide-field polarization imaging for rapid demarcation of end face cancer margins for cross-sectional evaluation of ductal carcinoma specimens. Because both modalities provided diagnostic information on cancer margins, the authors concluded that combined optical coherence tomography and wide-field polarization imaging shows promise for intra-operative detection of ductal breast carcinoma. Because accurate and rapid assessment of tumor margins during breast cancer resection surgery is critical, a more objective measure is needed.

Sullivan et al. (2011) studied the potential of a one-dimensional fractal box-counting method to classify cancer in optical coherence tomography. They computed the fractal dimensions along the depth axis of 44 ultra-high-resolution optical coherence images of human breast tissue from 4 cancer patients. They found that the fractal dimension of stroma is much higher than that of cancer. The authors concluded that the use of fractal analysis with optical coherence tomography could potentially provide automated identification of tumor margins during breast-sparing surgery. This study is limited by the small study population.

Reference(s)

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Code	Description
0358T	Bioelectrical impedance analysis whole body composition assessment, with interpretation and report

Bioelectrical impedance analysis whole body composition assessment is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Bioelectrical impedance analysis (BIA) is a commonly used method for estimating body composition, and in particular body fat. Since the advent of the first commercially available devices in the mid-1980s the method has become popular owing to its ease of use, portability of the equipment and its relatively low cost compared to some of the other methods of body composition analysis. BIA actually determines the electrical impedance, or opposition to the flow of an electric current through body tissues which can then be used to calculate an estimate of total body water (TBW). TBW can be used to estimate fat-free body mass and, by difference with body weight, body fat.

Campa et al. (2022) conducted a systematic review to compare the accuracy of and Bioelectrical Impedance Vector Analysis (BIVA) vs. reference methods for the assessment of body composition in athletes. Forty-two studies published between 1988 and 2021 were included. Twenty-three studies had an overall good rating in terms of quality, while 13 were rated as fair and 6 as poor, resulting in a low to moderate risk of bias. The results showed that fat mass was inconsistently determined using BIA vs. the reference methods, regardless of the BIA-technology. When using the foot to hand technology with predictive equations, there was consistency between BIA and the reference methods measurements of fat-free mass, total body, intra and extra cellular water. However, an underestimation in fat-free mass and body fluids was found when using generalized predictive equations. The authors concluded that BIA and BIVA can be used for assessing body composition in athletes, provided that other reference methods such as foot-to-hand technology, predictive equations, and BIVA references are used.

A systematic review was conducted by Sheean et al. (2020) for the American Society for Parenteral and Enteral Nutrition to evaluate the best available evidence regarding the validity of relevant body composition methods (e.g., dual energy X-ray absorptiometry [DXA], ultrasound [US], and BIA in clinical populations. Based on a limited number of studies and expert opinion, DXA is recommended for the assessment of fat mass in patients with a variety of disease states; however, the validity of DXA for lean mass assessment in any clinical population remains unknown. The ASPEN clinical guideline found that no recommendations can be made to support the use of BIA in the clinical setting, as data to support its validity in any specific patient population are limited in scope or by the proprietary nature of manufacture-specific BIA regression models to procure body composition data, respectively.

A systematic review aimed to investigate if multi-frequency bioelectric impedance (MF-BI) is a valid tool to determine body composition in patients with obesity was performed by Becroft et al. (2019). Sixteen studies were eligible for inclusion. Sample sizes ranged from 15 to 157, with BMI 26-48 kg/m2. MF-BI underestimated fat mass (FM) in 11 studies and overestimated fat-free mass (FFM) in nine studies in comparison with reference methods. Correlations of absolute values from MF-BI and reference methods for FM and FFM were high, however, agreement was lower at an individual level. When adjustments for BMI were made to machine algorithms, measurement accuracy improved. The authors concluded that MF-BI is reliable for use at a group level. Multiple variables contributed a lack of consistency among studies included, highlighting the need for more robust studies that control variables to establish clear validity assessment.

A 2019 ECRI report on body composition analyzers for diagnosis and management of obesity found that BIA clinical validity and utility for assessing obesity in individuals with BMI > 25 kg/m2 is unclear. Diagnostic cohort studies of varying size and quality reported only moderate agreement between BIA and reference body composition analysis methods. BIA methods varied across studies. Clinical guidelines consider BIA to be of unproven validity or impractical for obesity screening (ECRI, 2019).

Fonseca et al. (2018) performed a study to investigate the validity of an eight-contact electrode BIA system within a household scale for assessing whole body composition in patients with COPD. Seventeen patients with COPD underwent DXA and an eight-contact electrode BIA system for body composition assessment. There was a strong inter-method correlation for fat mass, fat-free mass, and lean mass, but the correlation was moderate for bone mineral content. In the agreement analysis, the values between DXA and the BIA system differed by only 0.15 kg, 0.26 kg, -0.13 kg, and -0.55 kg for fat-free mass, lean mass, bone mineral content, and fat mass, respectively. The eight-contact electrode BIA system showed to be a valid tool in the assessment of whole-body composition in the sample of patients with COPD. The small sample size limits the conclusions of this study.

The aim of a study by Thivel et al. (2018) was to assess the sensitivity of BIA in tracking body composition changes in adolescents with various degrees of obesity. Whole-body and segmental body composition were assessed by BIA and DXA among 196 obese adolescents, before and after a 3-month weight loss program. Except for the measurement of FFM (kg), the percentage of variation between M0 and M3 for FM% and FMkg are significantly correlated and show significant concordance between DXA and BIA. FMkg and FM% changes between M0 and M3 are similarly tracked by DXA and BIA. The authors found inconsistent and low correlations and concordances between the two devices when tracking FM% changes whatever the degree of weight and FM variations. The accuracy of body composition assessment using BIA decreases with increasing obesity, and its reliability to track changes is reduced with high initial or variations of body weight, FM, FFM and BMI.

Brantlov et al. (2017) conducted a systematic review to study the degree to which bioelectrical impedance analysis (BIA) papers conducted in healthy pediatric populations (aged 0-17 years) were standardized. Internationally recognized electronic databases and hand searching of the reference lists was conducted to identify relevant papers. The review was limited to lead-type BIA devices for whole-body, segmental- and focal impedance measurements. In total, 71 papers published between 1988

and 2016 were included. To evaluate the degree of standardization of the papers, a recently published review detailing critical factors that may impact on BIA measurements in children was used as a model for structuring and extracting data. The results showed a general lack of BIA standardization, or its reporting, which hinders comparison of data between studies and could potentially lead to erroneous measurements. The authors concluded that if the BIA technique is accepted clinically for routine use in pediatric populations, but that there is a need for an increased focus on the importance of improved standardization and its reporting in future studies.

Haverkort et al. (2015) conducted a systematic review to explore the variability of empirical prediction equations used in BIA estimations and to evaluate the validity of BIA estimations in adult surgical and oncological patients. Studies developing new empirical prediction equations and studies evaluating the validity of BIA estimations compared with a reference method were included. Only studies using BIA devices measuring the entire body were included. To illustrate variability between equations, fixed normal reference values of resistance values were entered into the existing empirical prediction equations of the included studies. The validity was expressed by the difference in means between BIA estimates and the reference method, and relative difference in %. Substantial variability between equations for groups was found for total body water (TBW) and fat free mass (FFM). BIA mainly under-estimated TBW (range relative difference -18.8 % to + 7.2 %) and FFM (range relative differences -15.2 % to + 3.8 %). Estimates of the FM demonstrated large variability (range relative difference -15.7 % to + 43.1 %). The authors concluded that application of equations validated in healthy subjects to predict body composition performs less well in oncologic and surgical patients. They suggested that BIA estimations can only be useful when performed longitudinally and under the same standard conditions.

Johnstone et al. (2014) conducted a study utilizing three groups of six obese men to evaluate the accuracy of bioelectrical impedance spectroscopy (BIS) in measuring the following: fat mass (FM), total body water (TBW) and extracellular water (ECW) changes induced by different degrees of caloric deficit in obese men. Each group of men were instructed to participate in either (i) a total fast (for 6 days); (ii) a VLCD (2.5 MJ/day for 3 weeks); or (iii) LCD (5.2 MJ/day for 6 weeks). FM was measured using a 4-compartment (4-C) model. TBW and ECW were determined by dilution methods. TBW, ECW and FM were also assessed with BIS. Body weight loss in the fasting group was 6.0 ±1.3 kg over 6 days; the VLCD group lost 9.2 ±1.2 kg over 21 days and the LCD group lost 12.6 ±2.4 kg over 42 days. BIS underestimated FM changes (bias = -3.3 ±3.8 kg) and overestimated changes in TBW and ECW by +1.8 ±4.8 kg and + 2.3 ±6.4 kg, respectively. The measurement error was consistently larger in the fasting group and the magnitude of the bias is greater with greater weight loss.

Widen et al. (2014) attempted to provide validation of bioelectric impedance analysis. The purpose of the study was to measure the total body water and percent body fat before and 12 months after bariatric surgery. The findings showed that the T0 to T12 median (IQR) change in deuterium TBW and 3C %fat was -6.4 L (6.4 L) and -14.8 % (13.4 %), respectively. There were no statistically significant differences between deuterium and BIA determined TBW [median (IQR) difference: T0 -0.1 L (7.1 L), $p = 0.75$; T12 0.2 L (5.7 L), $p = 0.35$; △ 0.35 L (6.3 L), $p = 1.0$]. Compared with 3C, BIA underestimated %fat at T0 and T12 [T0 -3.3 (5.6), $p < 0.001$; T12 -1.7 (5.2), $p = 0.04$] but not change [0.7 (8.2), $p = 0.38$]. Except for %fat change, Bland-Altman plots indicated no proportional bias. However, 95 % limits of agreement were wide (TBW 15-22 L, %fat 19-20 %). According to the authors, BIA may be appropriate for evaluating group level response among severely obese adults. The authors state that clinically meaningful differences in the accuracy of BIA between individuals exist.

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Code	Description
0394T	High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed
0395T	High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed

High dose rate electronic brachytherapy is unproven and not medically necessary for treating all indications due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Electronic brachytherapy is a form of brachytherapy that delivers relatively high doses of radiation within or in very close proximity to cancer tissue using miniaturized x-ray sources instead of a radionucleotide source.

An American Brachytherapy Society consensus statement states the following: In light of a randomized trial in breast showing higher rates of recurrence and the lack of prospective data with mature follow up with other sites, as well as concerns regarding dosimetry, it is not recommended that electronic brachytherapy be utilized for accelerated partial breast irradiation, non-melanomatous skin cancers, or vaginal cuff brachytherapy outside prospective clinical trials at this time (Tom et al., 2019).

Breast Cancer

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer do not specifically address electronic brachytherapy (NCCN, 2021).

An ECRI product brief found the evidence inconclusive for electronic brachytherapy (Axxent) as an adjuvant treatment for breast cancer. Randomized controlled trials comparing electronic brachytherapy with external beam radiation therapy and conventional brachytherapy are needed (ECRI, 2019a).

A National Institute for Health and Care Excellence (NICE) report concluded that there is a lack of robust evidence evaluating the Axxent electronic brachytherapy system for treating early-stage breast cancer. Key uncertainties around the evidence are that the available studies include patients for whom the technology is not recommended by the manufacturer, and there is a lack of long-term follow-up evidence (NICE, 2016).

Electronic brachytherapy is one of many techniques under investigation for accelerated partial breast irradiation (APBI). Dooley et al. (2011) describe patient, tumor and surgical characteristics from a prospective, nonrandomized, multicenter study of electronic brachytherapy to deliver radiation to the tumor bed post-lumpectomy in eligible patients with breast cancer. Forty-four patients were treated with APBI using the Axxent electronic brachytherapy system following lumpectomy. The prescription dose of 34 Gy in 10 fractions over 5 days was delivered in 42 of 44 patients. The authors concluded that early-stage breast cancer can be treated with breast conserving surgery and APBI using electronic brachytherapy. Treatment was well tolerated, and these early outcomes were similar to the early outcomes with iridium-based balloon brachytherapy. This study is limited by small numbers and lack of randomization or comparison of outcomes to established radiation therapy techniques.

Mehta et al. (2010) completed a phase IV prospective, non-randomized trial of 44 patients to evaluate the safety and device effectiveness of the Axxent electronic brachytherapy system. The study evaluated 44 patients. The subjects were over 50 years of age, had completely resected invasive ductal carcinoma or ductal carcinoma in situ and negative microscopic margins of equal to or greater than 1 mm. The treatment was completed with a balloon applicator with treatments twice per day for 5 days. Treatment was successfully completed in 42/44 patients. All 44 patients were followed up at one month, 43/44 followed up to 6

months and 36 of the 44 patients completed follow up at 1 year. No tumor recurrences were reported up to 1 year. The infection rate was high at 11%. Cosmetic evaluation was rated as good or excellent (minimal or no identifiable effects of radiation). The authors concluded that the electronic brachytherapy system performed as expected with similar acute toxicity profiles to other high-rate approaches in patients with resected, early breast cancer with no serious acute toxicities or serious AEs. This study is limited by small numbers, short-term follow-up and lack of randomization or comparison of outcomes to established radiation therapy techniques.

Skin Cancer

NCCN guidelines on basal cell and squamous cell skin cancers state that there are insufficient long-term safety and efficacy data to support the routine use of electronic surface brachytherapy (NCCN, 2022a; NCCN 2022b).

An American Brachytherapy Society consensus statement regarding the use of brachytherapy in the treatment of keratinocyte carcinoma (KC, previously nonmelanoma skin cancer) states that studies of electronic brachytherapy are emerging, although limited long-term data or comparative data are available. Radionuclide-based brachytherapy represents a well-established technique; however, the current recommendation is that electronic brachytherapy be used for KC on prospective clinical trial or registry because of a lack of mature data (Shah et al., 2020).

An ECRI clinical evidence assessment found the evidence inconclusive for electronic brachytherapy (Axxent) as a treatment for nonmelanoma skin cancer. Low-quality evidence showed no differences in outcomes between electronic brachytherapy (Axxent) and Mohs surgery, but the studies were at very high risk of bias. Randomized controlled trials comparing Axxent with Mohs surgery or other brachytherapy systems are needed to validate findings and assess long-term outcomes (ECRI, 2019b).

American Academy of Dermatology guidelines of care for the management of primary cutaneous melanoma state that there is no data to support the use of electronic surface brachytherapy for treating cutaneous melanoma (Swetter et al., 2019).

American Academy of Dermatology guidelines of care for the management of nonmelanoma skin cancers state that there is insufficient evidence to make a recommendation on the use of electronic surface brachytherapy in the treatment of basal cell carcinoma or cutaneous squamous cell carcinoma. Long-term safety and effectiveness data are lacking (Kim et al., 2018a; Kim et al., 2018b).

In a comparative effectiveness review on treatments for basal cell and squamous cell carcinoma of the skin, the Agency for Healthcare Research and Quality (AHRQ) concluded that there is no clear evidence to support the benefits of brachytherapy for these indications (Drucker et al., 2017).

An American Academy of Dermatology position statement on electronic surface brachytherapy (2016) presents several guiding principles, including the following:

- Based on current evidence, surgical management remains the most effective treatment for basal cell and squamous cell carcinomas, providing the highest cure rates.
- Additional research is needed on electronic surface brachytherapy, particularly on long term outcomes.
- Electronic surface brachytherapy may be considered as a secondary option for the treatment of basal cell and squamous cell carcinomas, for use in special circumstances and after the benefits and risks of treatment alternatives have been discussed with the patient.

Ballester-Sánchez et al. (2016) assessed outcomes from two consecutive prospective, single-center, non-randomized, pilot studies using different radiation doses of electronic brachytherapy with the Esteya® system for treating superficial and nodular basal cell carcinoma. Twenty patients were treated in each study. Group 1 was treated with 36.6 Gy in 6 fractions of 6.1 Gy, and Group 2 with 42 Gy in 6 fractions of 7 Gy. Cure rate, acute toxicity and late toxicity related to cosmesis were analyzed. Group 1 achieved a 90% clinical cure rate at 1 year. Group 2 achieved a 95% clinical cure rate at 1 year. The differences in acute toxicity and cosmetic results between the two treatment groups were not statistically significant. The authors noted that the role of electronic brachytherapy in the treatment of basal cell carcinoma is still to be defined. Both studies were limited by small numbers, short-term follow-up and lack of randomization or comparison of outcomes to established surgical treatment (e.g., Mohs surgery).

Delishaj et al. (2015) retrospectively evaluated 57 lesions in 39 elderly patients affected with nonmelanoma skin cancer (NMSC) treated with high-dose rate (HDR) brachytherapy using a Valencia applicator to estimate tumor control, toxicity and cosmetic

outcomes. All lesions had a diameter ≤ 25 mm (median: 12.5 mm) and a depth ≤ 4 mm. Twelve lesions were treated as a supplementary therapy after surgery treatment. The total dose was chosen based on the lesion dimensions, age, and performance status. The dose prescription was delivered as two/three fractions a week, with a minimum interval of 48 hours between fractions. After 12 months median follow-up, 55 lesions (96.5%) completely regressed and only two lesions persisted. No recurrences were observed, and the treatment was very well tolerated with no Grade 3 or higher acute or late toxicities. The authors concluded that this treatment was safe and effective in elderly patients. The limitation of this study compared with studies of more established treatments for NMSC was the relatively short follow-up and small number of patients due to the age of the patients (mean age 84 years) as well as comorbidities.

Bhatnagar (2013) reported clinical outcomes at 1 year or more after HDR electronic brachytherapy using surface applicators for the treatment of NMSC. A total of 122 patients with 171 NMSC lesions were treated with electronic brachytherapy to a dose of 40Gy in eight fractions, delivered twice weekly. At follow-up, patients were assessed for acute and late toxicities, cosmesis and local control. No recurrences were reported with a mean follow-up of 10 months. Follow-up data at 1 year or more were available for 46 lesions in 42 patients. Hypopigmentation (all Grade 1) was present in 5 (10.9%) of 46 lesions at 1 year. Other late effects at 1 year included dry desquamation, alopecia and rash dermatitis, which occurred in 1 (2.2%), 1 (2.2%) and 3 (6.5%) of 46 lesions, respectively. Cosmesis was excellent for 39 (92.9%) and good for 3 (7.1%) of the 42 evaluable lesions. This study is limited by lack of randomization and control and short-term follow-up.

Bhatnagar and Loper (2010) reported their initial experience with HDR brachytherapy for treating NMSC. Thirty-seven patients with 44 cutaneous malignancies were treated. Lesion locations included the nose (16), ear (5), scalp (5), face (14) and an extremity (4). Median follow-up was 4.1 months. No severe toxicities occurred. Cosmesis ratings were good to excellent for 100% of the lesions at follow-up. This study is limited by its retrospective design, small patient numbers and short-term follow-up.

Other Indications

Clinical evidence evaluating the safety and efficacy of high dose rate electronic brachytherapy for treating other indications is sparse and limited at this time.

A 2021 ECRI clinical evidence assessment regarding the Axxent Electronic Brachytherapy System (iCAD, Inc.), focused on its safety and effectiveness in treating gynecological cancers and how it compares with conventional brachytherapy. Seven case series were assessed, all of which were at high risk of bias, due to 2 or more of the following: small study size, retrospective design, single-center focus, and lack of parallel controls. Additionally, some studies enrolled patients with various types and stages of gynecologic cancers or used external beam radiation therapy (EBRT) in addition to electronic brachytherapy (EBT), or 192Ir high-dose rate (HDR) brachytherapy before EBT treatment, both of which limits evidence interpretation. One study enrolled patients both with and without previous chemotherapy, further confounding results. Furthermore, two studies may have had patient overlap, but reported on different outcomes of interest. It was concluded that the evidence is inconclusive and does not demonstrate that electronic brachytherapy with the Axxent system improves outcomes in women with gynecological cancers better than conventional brachytherapy and large trials that assess its effectiveness in each type of cancer are needed.

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Code	Description
0397T	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)
43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy
43252	Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy
88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session

Confocal laser endosmicroscopy (CLE), also known as confocal fluorescent endomicroscopy and optical endomicroscopy is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Optical endomicroscopy also referred to as confocal endomicroscopy (CEM) or optical biopsy is an endoscopic procedure that is being used to provide high-resolution images of the mucosal layer of the gastrointestinal (GI) tract. This technique can be performed with probe-based or needle-based systems that pass through the accessory channel of an endoscope or with integrated endoscopic systems. Endomicroscopy can potentially expand the imaging capabilities of flexible endoscopy by obtaining optical biopsies (method that uses the interaction of light and tissue to make a diagnosis rather than using tissue excision). CEM has been used in patients suspected of colon cancer, gastric cancer, celiac disease, pancreaticobiliary disease, Barrett's esophagus (BE) and for the identification of Helicobacter pylori infection.

Park et al. (2019) conducted a randomized controlled trial assessing probe confocal laser endomicroscopy (pCLE) and if this new emerging procedure could increase the yield of endoscopic biopsy for gastric cancer compared with white light endoscopy (WLE). There was a total of 30 gastric cancers and 61 undifferentiated-type gastric cancers were examined in the pilot and confirmatory studies, separately. All lesions in the pCLE and WLE groups were initially evaluated through WLE. In the pCLE group, lesions were further examined through pCLE. In the pilot study, five and three biopsy specimens were obtained for

histopathological examination and tumor marker analysis, respectively. In the confirmatory study, six biopsy specimens for histopathological evaluation were obtained. The proportion of cancer cells in biopsy samples of poorly differentiated adenocarcinoma or signet ring cell carcinoma was higher in the pCLE group than in the WLE group in both the pilot and confirmatory studies (pilot: median proportion, 65% vs 30%, p = 0.010; confirmatory: mean ± standard deviation, 49.5 ±29.3 vs 29.3 ±13.7, p = 0.002). The expression ratio of tumor markers including carcinoembryonic antigen, GW112, HOX transcript antisense RNA, and H19 tended to be higher in the pCLE group than in the WLE group. Although the proportion of cancer cells in biopsy samples was higher in the pCLE-targeted biopsy than in the WLE-targeted biopsy, the unsuccessful examination in two patients with small early gastric cancer, which had a very small amount of cancer, may demonstrate a limitation. Other limitations included different biopsy samples were used for histopathological examination of tumor markers. There may be a learning curve for the pCLE examination and lack of data on patients' outcomes limiting the conclusions that can be drawn on the clinical utility of this technology. Results will need to be validated with further studies on this new emerging technique.

Xiong et al.(2017) A systematic literature review and meta-analysis were performed to assess the accuracy of within-patient comparisons of narrow band imaging (NBI) and (CLE) for diagnosis of high-grade dysplasia (HGD)/ / esophageal adenocarcinoma (EAC) in patients with Barrett's Esophagus (BE). Five studies involving 251 patients, reported within-patient comparisons of NBI and CLE, were eligible for meta-analysis. Compared with NBI, pooled additional detection rate of CLE for per-lesion detection of neoplasia in patients with BE was 19.3% (95% CI: 0.05—0.33, I2 = 74.6%). The pooled sensitivity of NBI was 62.8% (95% CI: 0.56—0.69, I2 = 94.6%), which was lower (not significantly) than that of CLE (72.3%, 95% CI: 0.66—0.78, I2 = 89.3%). The pooled specificity of NBI and CLE were similar [85.3% (95% CI: 0.84—0.87, I2 = 92.1%) vs 83.8% (95% CI: 0.82—0.85, I2 = 96.8%)]. This systematic review and meta-analysis have shown that when compared with NBI, CLE significantly increased the per-lesion detection rate of esophageal neoplasia, HGD and EAC, in Barrett's esophagus. Whether CLE is superior to NBI in neoplasia detection at per-patient level and in terms of patient outcomes needs to be further investigated.

In a 2016 systematic review and meta-analysis, the position of the American Society for Gastrointestinal Endoscopy (ASGE) is that chromoendoscopy, including confocal laser endomicroscopy (CLE) has demonstrated efficacy for surveillance of patients with nondysplastic BE. Because most of the studies evaluated were performed by practitioners at large centers with limited data regarding experience by specialists in the general community settings, they endorse this technology when performed by endoscopists proficient in these techniques. Other advanced imaging modalities hold promise for BE surveillance, but further studies are needed.

A systematic review and meta-analysis was conducted by Fugazza et al. (2016), analyzing the current literature on CLE and evaluating the applicability and diagnostic yield of CLE in patients with GI and pancreatobiliary diseases. Both prospective and retrospective studies were eligible, identifying 102 studies for inclusion conducted in 16 different countries between 2004 and 2015 (n = 6943). The meta-analysis demonstrated that combining CLE with endoscopic retrograde cholangiopancreatography (ERCP) yields high sensitivity (90%) in the assessment of biliary strictures, demonstrating it as a useful tool for differentiating benign from malignant biliary strictures in individuals with biliary neoplasia. CLE for the surveillance of BE does not appear to be sensitive enough to replace current standard of care such as the Seattle biopsy protocol. For the stomach and duodenum, CLE demonstrated high sensitivity, specificity, accuracy, and positive and negative predictive values in comparison with both histopathology and other endoscopic techniques (e.g., white light endoscopy, narrow band imaging, and chromoendoscopy). However, these data were used with caution based on a limited number of publications. CLE is associated with a pooled sensitivity and specificity of 83% and 90%, respectively, in the detection of colorectal neoplasms and malignant foci in polypoid lesions. Graft-versus-host disease, infectious colitis and irritable bowel syndrome have been less extensively studied, but outcomes are promising. Limitations to the studies reviewed included the total evidence per organ was limited and often too low to draw definitive conclusions, as well as high heterogeneity, and that studies were primarily conducted in specialized centers. In spite of these limitations, the authors concluded that CLE has unique advantages and can provide real-time histological examination during diagnostic and therapeutic procedures. Further clinical trials are needed to assess the applicability and implementation of CLE in routine clinical practice, as currently very few such studies exist.
In a small prospective study evaluating lesions of the larynx (30 lesions in 19 patients), Vollger et al. concluded that when used in conjunction with optical coherence tomography, CLE seems helpful for discrimination of noninvasive lesions, although it tends to overrate the severity of the changes (2016).

In a systematic review and meta-analysis, Su et al. (2013) assessed the effectiveness of CLE for discriminating colorectal neoplasms from non-neoplasms. The secondary aim of the review was to compare the efficacy of endomicroscopy and chromoendoscopy for diagnosing colorectal neoplasms. Pooled sensitivity and specificity were compared using univariate regression analysis according to prespecified subgroups. Pooled relative risk was computed to compare the accuracy of

endomicroscopy and chromoendoscopy. Fifteen studies (published between 2000 and 2012) involving 719 patients and 2290 specimens were included in the analysis. The pooled sensitivity of all studies was 0.94, and pooled specificity was 0.95. Real-time CLE yielded higher sensitivity and specificity than blinded CLE. For real-time CLE, endoscopy-based systems had better sensitivity and specificity than probe-based systems. CLE yielded equivalent accuracy compared with magnifying virtual chromoendoscopy and magnifying pigment chromoendoscopy. The authors concluded that CLE is comparable to colonoscopic histopathology in diagnosing colorectal neoplasms, and that CLE is better when used in conjunction with conventional endoscopy. According to the authors, this review was limited by the relatively high heterogeneity presented across the 15 enrolled studies. The authors stated that there is a need for prospective randomized studies to obtain unbiased results on the effectiveness of CLE along with standardization of the procedure and a comparison between this strategy and conventional colonoscopy.

In a prospective, multicenter, RCT, Wallace et al. (2012) assessed if use of (pCLE) in addition to high-definition white light (HDWL) could aid in determination of residual BE. After an initial attempt at ablation, patients were followed-up either with HDWL endoscopy or HDWL plus pCLE, with treatment of residual metaplasia or neoplasia based on endoscopic findings and pCLE used to avoid overtreatment. The study was closed after the interim analysis due to low conditional power resulting from lack of difference between groups as well as higher-than-expected residual BE in both arms. After enrollment was halted, all patients who had been randomized were followed to study completion. Among the 119 patients with follow-up, there was no difference in the proportion of patients achieving optimal outcomes in the two groups. Other outcomes were similar in the 2 groups. The authors concluded that this study yields no evidence that the addition of pCLE to HDWL imaging for detection of residual BE or neoplasia can provide improved treatment.

Clinical Practice Guidelines

American Society for Gastrointestinal Endoscopy (ASGE)

The 2019 ASGE guideline on screening and surveillance in patients with Barrett's esophagus (BE) and is based on systematic reviews of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. In patients with BE undergoing surveillance, the authors suggest against routine use of CLE compared with WLE with Seattle protocol biopsy sampling (conditional recommendation, low quality of evidence).

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Code	Description
0398T	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed

Magnetic resonance image guided high intensity focused ultrasound (MRgFUS) intracranial stereotactic ablation is unproven and not medically necessary for treating movement disorders due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Magnetic resonance guided focused ultrasound therapy (MRgFUS) (ExAblate®; InSightec Ltd.) is a noninvasive treatment that integrates magnetic resonance imaging (MRI) with high-intensity focused ultrasound for the precise planning and control of the localized delivery of high-frequency sound waves to destroy lesions in tissue or bone. On July 11, 2016, the Food and Drug Administration (FDA) approved ExAblate Neuro for use in patients with essential tremor who have not responded to medication. The FDA approved an expansion of the indication of ExAblate Neuro to include the treatment of patients with tremor-dominant Parkinson's disease (PD) on December 16, 2018. Despite FDA approval, findings from ongoing clinical trials will need to be completed to determine whether any patient populations may benefit from this therapy. A double-blind randomized controlled trial of transcranial ExAblate and sham transcranial ExAblate evaluating patients with severe, medication refractory essential tremor is scheduled to be completed in December 2021. For more information, refer to ClinicalTrials.gov Identifier NCT01827904.

Essential Tremor

An updated 2021 Hayes report for Magnetic Resonance–Guided Focused Ultrasound (MRgFUS) Unilateral Thalamotomy for Essential Tremor indicates that there is new evidence regarding efficacy. According to the Hayes, the impact of newly published studies is unlikely to change their 2019 position that evidence is insufficient to draw conclusions regarding benefit of MRgFUS for essential tremor (Hayes, 2019; updated April 2021).

ECRI published a report for ExAblate Neuro for Treating Essential Tremor (ECRI, 2020a). According to ECRI, the evidence is somewhat favorable based on low-strength evidence from a small, double-blind, multicenter, randomized controlled trial (Elias et al., 2016); 2 retrospective comparative studies (Kim et al., 2107, Huss et al., 2015); 2 retrospective analyses of 5 unpublished case series; and 1 additional case series. The 2 retrospective comparison studies suggest benefits may be comparable to those achieved with deep brain stimulation (DBS) and radiofrequency ablation (RFA), but randomized controlled trials (RCTs) are needed to confirm results on comparative effectiveness. According to ECRI, the RCT is at risk of bias due to small sample size. All studies except the RCT are at high risk of bias due to 3 or more of the following: retrospective design, single-center focus, small sample size, and lack of randomization, controls, and blinding.

Giordano et al. (2020) performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to compare unilateral MRgFUS thalamotomy to unilateral and bilateral DBS in the treatment of essential tremor (ET) in terms of tremor severity and quality of life improvement. Forty-five eligible articles, published between 1990 and 2019, were retrieved. 1202 patients were treated with DBS and 477 were treated with MRgFUS thalamotomy. Postoperative tremor improvement was greater following DBS than MRgFUS thalamotomy ($p < 0.001$). A subgroup analysis was carried out stratifying by treatment laterality: bilateral DBS was significantly superior to both MRgFUS and unilateral DBS ($p < 0.001$), but no significant difference was recorded between MRgFUS and unilateral DBS ($p < 0.198$). Postoperative quality of life improvement was significantly greater following MRgFUS thalamotomy than DBS ($p < 0.001$). Complications were differently distributed among the two groups ($p < 0.001$). Persistent complications were significantly more common in the MRgFUS group ($p = 0.042$). While bilateral DBS proves superior to unilateral MRgFUS thalamotomy in the treatment of ET, a subgroup analysis suggests that treatment laterality is the most significant determinant of tremor improvement, thus highlighting the importance of future investigations on bilateral staged MRgFUS thalamotomy.

Halpern et al. (2019) published the 3-year results of the of the open-label extension study by Chang et al. (2018). The study assessed the effectiveness, durability, and safety of transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) thalamotomy for patients with medication refractory ET. Overall, the 3-year attrition from the treated patient cohort was 31%, with a loss of 23 patients. Scores at 36 months were compared with baseline and at 6 months after treatment to assess for

efficacy and durability. Adverse events were also reported. Measured scores remained improved from baseline to 36 months (all p < 0.0001). Range of improvement from baseline was 38%-50% in hand tremor, 43%-56% in disability, 50%-75% in postural tremor, and 27%-42% in quality of life. When compared to scores at 6 months, median scores increased for hand tremor (95% confidence interval [CI] 0-2, p = 0.0098) and disability (95% CI 1-4, p = 0.0001). During the third follow-up year, all previously noted adverse events remained mild or moderate, none worsened, two resolved, and no new adverse events occurred. The investigators concluded that results at 3 years after unilateral tcMRgFUS thalamotomy for ET show continued benefit, and no progressive or delayed complications. Patients may experience mild degradation in some treatment metrics by 3 years, though improvement from baseline remains significant. Author noted limitations included the high dropout rate and the patient analysis differed from the cohorts present in the original RCT and the two-year follow-up. This study provides Class IV evidence that for patients with severe ET, unilateral tcMRgFUS thalamotomy provides durable benefit after 3 years.

Altinel et al. (2019) conducted a systematic review and meta-analysis evaluating randomized controlled trials of DBS and lesion surgery (LS) in the treatment of tremor. PubMed, Embase, and the Cochrane database were searched to include RCTs with either LS, deep brain stimulation, or controls. The outcomes were the change in tremor score, quality of life, cognitive function, and neuropsychiatric function. Fifteen trials, including 1508 patients, met eligibility criteria. No significant difference in change of tremor scale (SMD -0.07, 95% confidence interval [CI]: -0.38 to 0.24), quality of life (SMD -0.21, 95% CI: -0.69 to 0.27), cognitive function (SMD 0.06, 95% CI: -0.27 to 0.39), or neuropsychiatric function (SMD -0.15, 95% CI: -0.49 to 0.19) were observed between LS and stimulation surgery. Heterogeneity across studies was observed during indirect comparison of quality of life. The investigators identified a possible effect modifier: improvement in quality of life correlated with duration of disease (p = 0.035). The focused-ultrasound LS was associated with a 0.70 SMD increase (p = 0.014) in quality of life versus DBS in an exploratory subgroup analysis by separating 2 studies with focused-ultrasound LS from other LS studies. The investigators concluded that although the main analysis showed that LS and DBS were equally effective in the treatment of patients with tremor, an exploratory subgroup analysis indicated an improvement in quality of life with noninvasive focused-ultrasound surgery. The investigators stated that focused ultrasound LS could be considered as a potential choice for tremor control, based on currently available evidence. However, additional evidence from randomized trials comparing stimulation with the focused-ultrasound approach is needed given the lack of direct comparison between the two in the literature and therefore in this meta-analysis. Authors Bond et al., 2017 and Elias et al., 2016 are included in this meta-analysis.

The International Parkinson and Movement Disorder Society commissioned a task force on tremor to review clinical studies of treatments for essential tremor. A systematic review of current pharmacological and surgical treatments for essential tremor was conducted using standardized criteria defined a priori by the International Parkinson and Movement Disorder Society. Sixty-four studies of pharmacological and surgical interventions were included in the review. MRI-guided focused ultrasound thalamotomy was, for the first time, assessed and was considered to be possibly useful. This conclusion was based on a single RCT (Elias et al., 2016) with a follow-up limited to 12 months. According to the investigators, there is a need to improve study design in essential tremor and overcome the limitation of small sample sizes, cross-over studies, short-term follow-up studies, and use of non - validated clinical scales (Ferreira et al., 2019).

The American Society of Stereotactic and Functional Neurosurgery (ASSFN), which acts as the joint section representing the field of stereotactic and functional neurosurgery on behalf of the Congress of Neurological Surgeons and the American Association of Neurological Surgeons, provided expert consensus opinion on evidence-based best practices for the use and implementation of MRgFUS for ET. The ASSFN concluded that MRgFUS is an effective and safe treatment option for medically refractory ET. According to the ASSFN, Long term follow-up studies should continue to be pursued in larger cohorts of subjects. Investigations into precise targeting and dosing as well as temperature limits and correlations with outcomes should be evaluated (Pouratian et al., 2019).

A systematic literature review was conducted by Langford et al. (2018) to identify and analyze evidence supporting the use of the emerging MRgFUS compared to alternative stimulatory and ablative interventions (ablative interventions included radiofrequency thalamotomy, unilateral DBS, and stereotactic radiosurgery) for treating medication-refractory essential tremor. Because of the lack of comparative evidence found, a feasibility assessment was performed to determine possible comparisons between interventions. The systematic literature review identified 1,559 records, and screening provided 46 relevant articles. The matching-adjusted indirect comparison and simulated treatment comparison results demonstrated no evidence of a difference in efficacy (measured by Clinical Rating Scale for Tremor Total) and health-related quality of life (measured by Clinical Rating Scale for Tremor Part C) outcomes between MRgFUS and unilateral DBS in the short term (≤12 months). According to the authors, this study provides preliminary evidence that MRgFUS could elicit similar short-term tremor and health-related quality of life -related benefits to DBS, the current standard of care. The authors indicated that the limited

high-quality evidence available from the systematic literature review (i.e., lack of large-scale, comparative studies) and the inconsistencies in reporting of Clinical Rating Scale for Tremor (CRST) maximum achievable scores in the literature meant comparisons were only possible for two interventions (MRgFUS and DBS) and two outcomes (CRST Total and Part C scores). Data availability allowed analyses only at the 1-, 3-, 6-, and 12-month time points, meaning conclusions on efficacy were limited to the short-term effect of these interventions. Further analyses are required to determine the comparative efficacy between these two interventions on a long-term basis with direct comparison. The study is limited by indirect comparison.

Mohammed et al. (2018) conducted a meta-analysis to analyze the overall outcomes and complications of MRgFUS in the treatment of ET. The change in the CRST score after treatment was analyzed. The improvement in disability was assessed with the Quality of Life in Essential Tremor Questionnaire (QUEST) score. Nine studies with 160 patients who had ET were included in the meta-analysis. The ventral intermediate nucleus was the target in 8 of the studies. The cerebellothalamic tract was targeted in 1 study. There was 1 randomized controlled trial, 6 studies were retrospective, and 2 were prospective. On meta-analysis with the random-effects model, the pooled percentage improvements in the CRST Total, CRST Part A, CRST Part C, and QUEST scores were 62.2%, 62.4%, 69.1%, and 46.5%, respectively. Dizziness was the most common in-procedure complication, occurring in 45.5%, followed by nausea and vomiting in 26.85% (pooled percentage). At 3 months, ataxia was the most common complication, occurring in 32.8%, followed by paresthesia's in 25.1% of the patients. At 12 months posttreatment, the ataxia had significantly recovered, and paresthesia's became the most common persisting complication, at 15.3%. The authors concluded that MRgFUS therapy for ET significantly improves the CRST scores and improves the QOL in patients with ET, with an acceptable complication rate. According to the authors, there are several limitations of this meta-analysis. Most of the included studies were retrospective case series; only 1 RCT (Elias et al., 2016) was included. Thus, the possibility of bias is high. Other limitations include a short follow-up period and a small patient population. According to the authors, randomized trials comparing deep brain stimulation (the current standard surgical treatment for medication-refractory ET) to MRgFUS are the needed. Authors Elias et al., 2016; Kim et al., 2107; and Huss et al., 2015 are included in this meta-analysis.

Chang et al. (2018) reported on the results at a 2- year follow-up after MRgFUS thalamotomy for ET. A total of 76 patients with moderate-to-severe ET, who had not responded to at least two trials of medical therapy, were enrolled in the original randomized study of unilateral thalamotomy (Elias et al., 2016) and evaluated using the clinical rating scale for tremor. Sixty-seven of the patients continued in the open-label extension phase of the study with monitoring for 2 years. Nine patients were excluded by two years, for example because of alternative therapy such as deep brain stimulation (n = 3) or inadequate thermal lesioning (n = 1). However, all patients in each follow-up period were analyzed. Mean hand tremor score at baseline improved by 55% at 6 months. The improvement in tremor score from baseline was durable at 1 year (53%, 8.9 ±4.8, 70 patients) and at 2 years (56%, 8.8 ±5.0, 67 patients). Similarly, the disability score at baseline improved by 64% at 6 months. This improvement was also sustained at 1 year and at 2 years. Paresthesia's and gait disturbances were the most common adverse effects at 1 year-each observed in 10 patients with an additional 5 patients experiencing neurological adverse effects. None of the AEs worsened over the period of follow up and 2 of these resolved. There were no new delayed complications at 2 years. The authors stated that tremor suppression after MRgFUS thalamotomy for ET is stably maintained at 2 years and latent or delayed complications do not develop after treatment. The authors indicated that there are some important limitations of this study. Nine patients, many of whom had unsuccessful treatment or suboptimal benefit, crossed over to an alternative treatment, dropped out, or were lost to follow-up. The exclusion of non-responders from the analysis introduces a bias and an overestimate of the benefit in those patients that remained in the study. According to the authors, additional follow-up will be required to determine the incidence of recurrence and the efficacy of MRgFUS over the long term. The authors also stated that further work is required to optimize patient selection, improve clinical results, and avoid adverse effects.

A Health Quality Ontario (HQO) evidence-based guideline indicated that MRgFUS thalamotomy provides a treatment option for people with essential tremor who are ineligible for invasive neurosurgery and offers a noninvasive option for all people with essential tremor considering neurosurgery. The health technology assessment found no significant differences in tremor severity, disability, or quality of life (QOL) with MRgFUS compared with DBS and no significant difference in tremor severity compared with radiofrequency thalamotomy (very low certainty of the evidence). MRgFUS was found to be significantly more effective than a sham procedure (high certainty of the evidence). Significant improvements in tremor severity, disability, and QOL were noted in non-comparative studies (low certainty of evidence) (HQO, 2018).

The National Institute for Health and Care Excellence (NICE) evidence-based guideline for unilateral MRgFUS thalamotomy concluded that MRgFUS thalamotomy for treatment-resistant ET raises no major safety concerns, but evidence of efficacy was limited in quantity. NICE recommends that this procedure should not be used unless there are special arrangements for

oversight. NICE suggests that future research include the identification of patient selection criteria and long-term follow-up data (NICE, 2018).

Elias et al. (2016) conducted a double-blind, sham-controlled randomized trial to evaluate the efficacy of MRgFUS thalamotomy for the treatment of essential tremor. Trial selection criteria included patients with moderate or severe postural or intention tremor of the hand (≥ 2 on the Clinical Rating Scale for Tremor) and refractory to at least two trials of medical therapy, including at least one first-line agent (propranolol or primidone). A total of 74 patients were randomized to unilateral focused ultrasound thalamotomy or sham treatment. Hand-tremor scores improved more after focused ultrasound thalamotomy (from 18.1 points at baseline to 9.6 at 3 months) than after the sham procedure (from 16.0 to 15.8 points); the between group difference in the mean change was 8.3 points (95% confidence interval [CI], 5.9 to 10.7; $p < 0.001$). The improvement in the thalamotomy group was maintained at 12 months (change from baseline, 7.2 points; 95% CI, 6.1 to 8.3). Secondary outcome measures assessing disability and quality of life also improved with active treatment (the blinded thalamotomy cohort) as compared with the sham procedure ($p < 0.001$ for both comparisons). Adverse events in the thalamotomy group included gait disturbance in 36% of patients and paresthesia's or numbness in 38%; these adverse events persisted at 12 months in 9% and 14% of patients, respectively. The investigators concluded that MRI-guided focused ultrasound thalamotomy reduced hand tremor in patients with essential tremor. Side effects included sensory and gait disturbances. This RCT was included in the systematic reviews above.

In 2011, the American Academy of Neurology (AAN) published a guideline on treating essential tremors. This guideline does not mention the use of magnetic resonance guided focused ultrasound therapy as a treatment option (Zesiewicz et al., 2011, reaffirmed on April 30, 2014).

Parkinson Disease

Ge et al. (2021) performed a meta-analysis of randomized clinical trials (RCTs) to evaluate the application of magnetic resonance-guided focused ultrasound (MRgFUS) for individuals with Parkinson's disease (PD). The safety and efficacy in the treatment of PD was evaluated for qualified RCTs comparing a focused ultrasound surgery (FUS) group to a sham procedure group utilizing databases of Medline, EMBASE, and Cochrane library. Recovered from the exploration was 777 possible records for inclusion. However, 166 records were duplicates, 552 omitted due to irrelevant content, leaving 2 RCTs to complete the meta-analysis. With the 2 studies, the blinded phase lasted 4 months in one experiment and up to 3 months in the other. Of the 2 RCTs included, one review concentrated on individuals with asymmetric motor symptoms in PD and the other on those with tremor-dominant subtypes of PD. Individuals in both reviews had failed symptom control of motor signs with medication or were unable to tolerate side effects of medication dose adjustments. The FUS group exhibited noteworthy improvement in limb tremor on the treated side, and capability to complete activities of daily living (ADLs) compared to the sham group, however no substantial group differences in any other indicators were reported. Adverse events such as dizziness was common in the treatment group, with no group differences in the residual adverse events. The authors suggest useful effects of MRgFUS in individuals with PD however propose larger multicenter studies to select the most fitting target and surgical device setup parameters. Furthermore, the review implies the need for improvement in reducing adverse events such as mild hemiplegia.

Lennon & Hasson (2021) completed a systematic review utilizing data bases PubMed, CINAHL, PsycINFO, and Cochrane Library from January 2016 to January 2020. The authors reviewed clinical trials comprehensively assessing pre- and post-operative neurocognitive functioning in PD patients undergoing MRgFUS through Guidelines for Preferred Reporting Items for Systematic Review and Meta-Analysis. Limited literature was discovered for tremor-dominant Parkinson's disease (TDPD); therefore, the search was expanded to PD with severe dyskinesia. The review resulted in 22 abstracts for inclusion, however, after removal of duplicates, and full text review, only 2 studies were chosen. The 2 studies were utilized due to their inclusion of comprehensive neuropsychological evaluations of individuals with PD undergoing MRgFUS thalamotomy or pallidotomy. Results showed minimal cognitive decline following MRgFUS for individuals with PD from baseline at 3 and 6 months follow up, with exceptions in verbal fluency and inhibition. Limitations to the review were small sample size and lack of diversity. The authors conclude significant methodological gaps, with few studies to date having administered comprehensive neuropsychological batteries to establish MRgFUS risks of adverse neurocognitive functioning in PD. Additionally, the first systematic review concentrated on non-motor neurocognitive outcomes of MRgFUS in PD which essentially accentuates the limitations in the capability to report on these conclusions. The small number of clinical trials, obtainable articles on these trials, and overall studies do not permit robust conclusions. Furthermore, the authors suggest studies that extend beyond brief screeners when assessing PD populations susceptible to decline would be beneficial. Lastly, a consensus on a comprehensive battery to better serve replicability and the capability to engage in useful meta-analyses is needed.

Lin et al. (2021) compared the efficacy of DBS and MRI-guided focused ultrasound (MRIgFUS) in parkinsonian tremor. The literature was searched for articles published between January 1990 and October 2020 using three databases: PubMed, Embase and Cochrane Library (The Cochrane Database of Systematic Reviews). A total of 24 studies were included in the analysis, comprising data from 784 participants. The findings revealed similar efficacy of DBS and MRIgFUS in parkinsonian tremor suppression. Compared with internal globus pallidus (GPi)-MRIgFUS, GPi-DBS -1.84 (-6.44, 2.86), pedunculopontine nucleus (PPN)_DBS -3.28 (-9.28, 2.78), PPN and caudal zona incerta (cZI)-DBS 0.40 (-6.16, 6.87), subthalamic nucleus (STN)_DBS 0.89 (-3.48, 5.30), STN and cZI-DBS 1.99 (-4.74, 8.65), ventral intermediate nucleus (VIM)_DBS 1.75 (-2.87, 6.48), VIM_FUS 0.72 (-5.27, 6.43), cZI-DBS 0.27 (-4.75, 5.36) were not significantly different. Compared with VIM-MRIgFUS, GPi-DBS -2.55(-6.94, 2.21), GPi-FUS -0.72 (-6.43, 5.27), PPN_DBS -4.01(-9.97, 2.11), PPN and cZI-DBS -0.32 (-6.73, 6.36), STN_DBS 0.16 (-3.98, 4.6), STN and cZI-DBS 1.31(-5.18,7.87), VIM-DBS 1.00(-3.41, 5.84) and cZI-DBS -0.43 (-5.07, 4.68) were no significantly difference. With respect to the results for the treatment of motor symptoms, GPi-DBS, GPi-MRIgFUS, STN-DBS and cZI-DBS were significantly more efficacious than baseline (GPi-DBS 15.24 (5.79, 24.82), GPi-MRIgFUS 13.46 (2.46, 25.10), STN-DBS 19.62 (12.19, 27.16), cZI-DBS 14.18 (1.73, 26.89). The results from the surface under the cumulative ranking results showed that STN-DBS ranked first, followed by combined PPN and cZI-DBS, and PPN-DBS ranked last. MRIgFUS, an efficacious intervention for improving parkinsonian tremor, has not demonstrated to be inferior to DBS in parkinsonian tremor suppression. Hence, clinicians should distinguish individual patients' symptoms to ensure that the appropriate intervention and therapeutic approach are applied.

Xu et al. (2021) conducted a systematic review to investigate the safety and efficacy of MRgFUS for PD by systematically reviewing related literature. Eleven studies containing 80 patients were included. Nine studies were observational studies with no controls. Two publications included a randomized and controlled phase and appear to report on the same sample of patients. Most studies included tremor-dominant PD. Ten studies reported decline of Unified Parkinson's Disease Rating Scale (UPDRS)-III scores after MRgFUS, and five reported a statistically significant decline. Nine studies evaluated the quality of life (QOL). Significant improvement of QOL was reported by four studies using the 39-item Parkinson's disease questionnaire. Four studies investigated the impact of MRgFUS on non-motor symptoms. Most tests indicated that MRgFUS had no significant effect on neuropsychological outcomes. Most adverse events were mild and transient. The two publications reporting on a RCT mostly failed to show significant difference between the active and sham interventions at three months, possibly due to small sample size, and lacked longer term outcomes in the randomized phase of the study. The investigators concluded that MRgFUS is a potential treatment for PD with satisfying efficacy and safety. However, studies in this field are still limited. According to the investigators, more studies with strict design, comparison groups, larger sample size, and longer follow-up are needed to further investigate its efficacy and safety for PD.

Martinez et al. (2020) conducted a randomized trial on focused ultrasound subthalamotomy for PD by randomly assigning individuals in a 2:1 ratio. Individuals with markedly asymmetric PD whose motor signs were uncontrolled by medication or those disqualified for deep-brain stimulation surgery received the focused ultrasound subthalamotomy on the opposite side of main motor sign or received a sham procedure. The characteristics of the patients were similar in the two groups at baseline. Efficacy and principal safety results were measured at 4 months. Efficacy outcomes in the between-group variances from baseline to 4 months was assessed with the Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) for the affected side in the off-medication state. The trial consisted of 40 individuals, 27 assigned to focused ultrasound subthalamotomy and 13 in the sham procedure. The average MDS-UPDRS III score for the most affected side indicated improvement from 19.9 at baseline to 9.9 at 4 months in the active-treatment group. The control group resulted in MDS-UPDRS score of 17.1 from 18.7 at 4 months ensuing a between-group difference of 8.1 points. Adverse events in the non-medicated, active-treatment individuals were recorded with results as follows: Dyskinesia was noted in 6 individuals; with symptoms persisting at 3 months follow-up, and dyskinesia found in 6 individuals who were on medication; with persistent symptoms at 1 month follow-up. Weakness was recorded in 5 individuals on the treated side and continued in 2 individuals at 4 months follow up. Speech disturbances were documented in 15 individuals and continued in 3 individuals at 4 months. Facial weakness was logged in 3 individuals and persisted in 1 individual at 4 months. Gait disturbance was noted in 13 individuals which persisted in 2 individuals at 4 months. In the active-treatment group, 6 individuals were recorded to have the same deficits present at 12 months follow up. Limitations include small sample size. The authors conclude focused ultrasound subthalamotmy in one hemisphere improved motor features of PD in selected individuals with asymmetric signs. However, adverse events included speech and gait disturbances, weakness on treated side, and dyskinesia. Longer-term and larger trials are needed to determine the role of focused ultrasound subthalamotmy in the management of Parkinson’s disease and its effects compared with other available treatments.

ECRI published a report for ExAblate Neuro for Treating Tremor-dominant Parkinson Disease (ECRI, 2020b). According to ECRI, the evidence is inconclusive because of too few data. One small RCT and 3 small case series suggest that MRgFUS can safely reduce tremor and improve quality of life in Parkinson Disease patients. These studies are too small and at too high a risk of bias to be conclusive.

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Code	Description
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
K1030	External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only

Cardiac contractility modulation, using an implantable device, is unproven and not medically necessary for treating chronic heart failure due to insufficient, quality evidence of safety and/or efficacy. Future robust RCTs are warranted.

Clinical Evidence

Cardiac contractility modulation (CCM) signals are nonexcitatory electrical signals delivered during the cardiac absolute refractory period (between beats) that enhance the strength of cardiac muscular contraction. CCM signals are provided by a pacemaker-like device that is implanted under the skin of the upper chest, along with electrical leads that are placed in the heart's right ventricle through the veins. After the procedure, the physician programs the delivery of CCM® therapy for each patient and activates the device. The implanted device then sends precisely calibrated and timed electrical pulses to the heart muscle. In contrast to a pacemaker or a defibrillator, the system is designed to modulate the strength of contraction of the heart muscle rather than the rhythm (Impulse Dynamics website).

The Optimizer™ implantable CCM system received FDA premarket approval (P180036) on March 21, 2019. Based on this FDA approval, the device 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%. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180036. (Accessed March 23, 2022)

An ECRI clinical evidence assessment (2021) compared the Optimizer Smart System use with that of optimal medical therapy (OMT) in patients with heart failure (HF). The systematic review included four high-quality randomized controlled trials (RCT) and one study that was used as a comparison group to RCT. ECRI found the evidence to be somewhat favorable that the Optimizer is more effective than OMT for improving functional status and quality of life in patients with moderate to severe, chronic HF. The assessment found it was unclear whether Optimizer reduced mortality rates or HF-related hospitalization rates due to a high a risk of bias in two of the studies which had a single-center focus and/or lack of randomization and blinding. Longer term follow up comparing Optimizer with OMT with a focus on mortality and HF-related hospitalization is recommended.

Fastner et al. (2021) conducted an observational study comparing long-term therapeutic effects of CCM therapy in patients with ischemic (ICM) versus non-ischemic cardiomyopathy (NICM). The functional parameters compared include left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), Kidney Disease Improving Global Outcomes (KDIGO) chronic kidney disease stage, and changes in NYHA class. Observed mortality rates at one and three years were compared to those predicted by the MAGGIC heart failure risk score and observed mortality rates were compared between groups for the entire follow-up period. Between 2002 and 2019, 174 consecutive patients with chronic heart failure and CCM device implantation were included in the analysis. LVEF was significantly higher in NICM patients after three years of CCM therapy (35 ±9 vs. 30 ±9%; p = 0.0211), and after five years, also TAPSE of NICM patients was significantly higher (21 ±5 vs. 18 ±5%; p = 0.0437). There were no differences in other effectiveness parameters. Over the entire follow-up period, 35% of all patients died; only in ICM patients, mortality was lower than predicted at three years (35 vs. 43%, p = 0.0395). The authors concluded that regarding improvement of biventricular systolic function, patients with NICM appeared to benefit principally from CCM therapy. Limitations include the retrospective and observational nature of the study, and lack of control group receiving a different intervention.

Giallauria et al. (2020) conducted an individual data meta-analysis of all prospective RCTs of CCM versus control that measured functional capacity and/or quality of life questionnaires in patients with HF plus data from one single arm study. Peak oxygen consumption, six min walk test distance and quality of life measured by Minnesota Living with Heart Failure Questionnaire (MLWHFQ). Five trials were identified, four RCTs (n = 801) for all endpoints of interest and one single arm study. The analysis of individual participant data revealed that compared with control, CCM significantly improved benefits in measures of functional capacity and HF-related quality of life. Limitations include relatively young and predominantly male cohorts, individuals with permanent atrial fibrillation were excluded, and the studies analyzed differed in design limiting the ability to define representative results across different individual subgroups. The authors recommend larger, well-conducted RCTs using parallel double-blind designs in order to determine the effect of CCM on mortality and morbidity outcomes before CCM can be widely recommended. Studies in less compromised HF patients, more women and older individuals are also encouraged. (Kadish et al., (2011), Borggrefe et al., (2008), and Neelagaru et al., (2006), which were previously cited in this policy, were included in this meta-analysis).

A Hayes (2019) health technology assessment reviewed the use of CCM with the Optimizer Smart System as an adjunct to OMT in patients with NYHA functional class III heart failure. Four fair quality RCTs, five poor-quality studies and one very poor-quality cohort study were identified that evaluated the safety and efficacy of CCM using the Optimizer Smart System for management of HF and were included in the review. The studies compared OMT alone with CCM therapy plus OMT. The review found there was a low-quality body of evidence suggesting that CCM with the Optimizer Smart System as an adjunct to OMT may improve outcomes related to cardiopulmonary stress tests, functional class severity and quality of life. The clinical significance of these findings and whether the effect is significantly better than with OMT alone remains uncertain. In patients with HF and an ejection fraction of ≤ 25%, limited evidence suggests that CCM therapy may be less effective. Additional well-designed comparative studies are recommended to determine whether CCM with the Optimizer Smart System is safe and more effective than OMT alone. The authors conclude that the technology has potential but unproven benefit.
Kloppe et al. (2016) conducted a single center pilot evaluation study involving 19 medically refractory symptomatic patients with heart failure and reduced left ventricular function who underwent implantation of an Optimizer system. Patients were randomized into one of two treatment groups: 5 h/day CCM treatment or 12 h/day CCM treatment. Subjects and evaluating physicians were blinded to the study group. Subjects returned to the hospital after 12 and 24 weeks. Efficacy evaluations included changes from baseline to 24 weeks in Minnesota Living with Heart Failure Questionnaire score (MLWHFQ), maximal oxygen consumption in the cardio-pulmonary stress test (peak VO2), NYHA classification, 6-min walk distance (6MWD), and ejection fraction (EF). At the end of 24 weeks, clinical improvement was observed in the entire cohort in all efficacy measures. There were no significant differences, either clinically or statistically, between the groups receiving CCM for 5 h/day versus 12

h/day. Given the small sample size, further studies are warranted. Additionally, the design of the study does not allow comparison of CCM to other approaches.

The 2021 European Society of Cardiology guideline for the diagnosis and treatment of heart failure notes that CCM was associated with a small improvement in exercise tolerance and quality of life for patients with NYHA class III-IV HF, with an LVEF ≥ 25% to ≤ 45% and QRS duration < 130ms. However, the evidence was considered insufficient to support specific guideline recommendations for a reduction in mortality or hospitalization. The guideline recommended larger RCTs for CCM therapy (McDonagh et al., 2022).

A National Institute for Health and Care Excellence (NICE) guideline concluded that current evidence on CCM for HF raises no major safety concerns. However, the guideline found inadequate evidence on the quantity and quality of efficacy and states this procedure should only be used in the context of research. The guideline recommends further RCTs addressing details of patient selection, duration and timing of stimulation, and duration of effect of stimulation. Additionally, outcomes should include oxygen consumption, ejection fraction, New York Heart Association classification, and patient-reported outcomes, including quality of life (2019).

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Code	Description
0440T	Ablation, percutaneous, cryoablation, includes imaging guidance; upper extremity distal/peripheral nerve
0441T	Ablation, percutaneous, cryoablation, includes imaging guidance; lower extremity distal/peripheral nerve
0442T	Ablation, percutaneous, cryoablation, includes imaging guidance; nerve plexus or other truncal nerve (e.g., brachial plexus, pudendal nerve)

Percutaneous cryoablation of upper/lower extremity distal/peripheral nerve(s), of nerve plexuses or of other truncal nerves for the treatment of chronic pain is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy.

Clinical Evidence

Grigsby et al. (2021) recently published the results of a pilot study evaluating the safety and efficacy of percutaneous cryoneurolysis for the treatment of occipital neuralgia (ON) related pain. A total of 26 patients (mean age 49.1 years) participated in this prospective, multicenter, nonrandomized cohort study which assessed the degree and duration of the effect of cryotherapy for pain reduction in individuals with either unilateral or bilateral ON. Results were measured by assessing level of pain due to ON based on an 11-point numeric scale at baseline and day 7. Ongoing treatment effect was measured at day 30 and day 56 by patient inquiry with "effect", "no effect" or "no longer effective" as possible responses. Overall, a clinically important improvement of symptoms (≥ 2 points in numeric rating scale) was reported by 64% of participants at day 7, with similar results lasting through day 30. Pain reduction continued for 50% of participants at day 30 and for 35% of participants at day 56. No adverse events were reported. The authors concluded that cryoneurolysis provided substantial relief from pain related to ON ≤ 30 days after treatment with no safety issues, however several limitations to this study were noted. The study was uncontrolled and unblinded in design, so cryoneurolysis was unable to be compared with other ON treatments, and the lack of a control group introduced potential for bias. In addition, the study had a very small population size and did not include outcome measures assessing impact of treatment with cryoneurolysis on quality of life. The researchers recommend more-rigorous clinical trials including a larger population, comparator group(s) and better characterization of participants at baseline to establish efficacy and safety.

In a 2021 Evolving Evidence Review, Hayes reported on the state of the evidence regarding the FDA-approved iovera system for treatment of chronic knee pain due to osteoarthritis (OA). One fair quality randomized sham-controlled clinical trial and one systematic review was identified. Although no serious treatment-related adverse events were reported, the randomized sham-controlled trial suggested short-term improvement in pain and function; by 6 months post-treatment advantages diminished. The systematic review included only one study addressing the use of iovera for knee pain due to OA (the randomized sham-controlled trial mentioned above). Other studies included addressed iovera as an adjunct to total knee arthroplasty. No clinical practice guidelines or position statements provided recommendations or support for the iovera system for treatment of knee pain due to OA. Hayes indicates that further high-quality studies are required to compare iovera with standard care or potential alternatives for treating knee pain from OA and evaluate clinical benefit from repeat iovera treatments.

Radnovich et al. (2017, included in the 2021 Hayes Evolving Evidence Review) conducted a randomized, double-blind, sham-controlled, multicenter trial to evaluate the efficacy and safety/tolerability of cryoneurolysis for reduction of pain and symptoms associated with OA. Patients were randomized 2:1 to cryoneurolysis targeting the infrapatellar branch of the saphenous nerve (IPBSN) or sham treatment. The primary endpoint was the change from baseline to Day 30 in the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain score adjusted by the baseline score and site. Secondary endpoints, including visual analogue scale (VAS) pain score and total WOMAC score, were tested in a pre-defined order. The intent-to-treat (ITT) population consisted of 180 patients (n = 121 active treatment, n = 59 sham treatment). Compared to the sham group, patients who received active treatment had a statistically significant greater change from baseline in the WOMAC pain subscale score at Day 30 ($p = 0.0004$), Day 60 ($p = 0.0176$), and Day 90 ($p = 0.0061$). Patients deemed WOMAC pain responders at Day 120 continued to experience a statistically significant treatment effect at Day 150. Most expected side effects were mild in severity and resolved within 30 days. The authors concluded that cryoneurolysis of the IPBSN resulted in statistically significant decreased knee pain and improved symptoms compared to sham treatment for up to 150 days and appeared safe and well tolerated. The study is limited by a follow-up of six months only.

Prologo et al. (2017) conducted a prospective pilot study to evaluate percutaneous image-guided nerve cryoablation for treatment of refractory phantom limb pain (PLP). Twenty-one patients underwent image-guided percutaneous cryoneurolysis procedures. Visual analog scale (VAS) scores were documented at baseline and 7, 45, and 6 months after the procedure. Responses to a modified Roland Morris Disability Questionnaire were documented at baseline and 7- and 45-days post-procedure as well. Technical success rate of the procedures was 100%. There were 6 (29%) minor procedure-related complications. Disability scores decreased from a baseline mean of 11.3 to 3.3 at 45-day follow-up. Pain intensity scores decreased from a baseline mean of 6.2 to 2.0 at 6 months. Limitations of this study include its exploratory nature (single-arm pilot cohort with no use of control, randomization, or blinding). Results will be used to design a larger, parallel-armed, RCT.

Yoon et al. (2016) evaluated the safety and efficacy of cryoneurolysis in 22 individuals with refractory peripheral neuropathic pain through a prospective study performed from July 2011 to July 2013. All percutaneous ablations were performed using a PerCryo 17R device (Endocare/Healthtronics, Austin, Texas) with ultrasound imaging guidance. Pain levels were recorded using a VAS score before and at 1, 3, 6, 9, and 12 months after the procedure. A Wilcoxon rank-sum test showed a statically

significant decrease between pre- and postprocedural pain scores, and no complications were reported. The authors concluded that US-guided cryoneurolysis of the peripheral nerve is safe and may be effective in controlling chronic refractory neuropathy, providing moderately long-term pain relief. Future studies with greater sample sizes would be able to quantify the amount of pain relief provided by the initial treatment versus each subsequent treatment with cryotherapy.

Prologo et al. (2015) evaluated the safety and efficacy of percutaneous CT-guided cryoablation of the pudendal nerve for the treatment of refractory pudendal neuralgia, selecting 11 patients following established diagnostic criteria. Using the Brief Pain Inventory questionnaires prior to treatment, the average level of pain on a scale from 0 (no pain) to 10 (worst pain imaginable) was 7.6, with pain described as "burning" (80%), "pulling" (37.5%), "crushing" (50%), "pressure" (84.5%), "throbbing" (50%), "knife-like" (52%), and "other" (60%). At 24 hours, 45 days, and 6 months post-treatment, pain intensity dropped to 2.6, 3.5, and 3.1, respectively. There were no procedure-related complications. The authors concluded that CT-guided percutaneous cryoablation may represent a safe and efficacious option for selected patients with refractory pudendal neuralgia. Study limitations include the lack of controls and small sample size.

Reference(s)

Hayes, Inc. Evolving Evidence Review. The iovera (Pacira Biosciences Inc.) system for knee osteoarthritis. Lansdale, PA: Hayes Inc., August 2021.

Grigsby E, Radnovich R, Nalamachu S. Efficacy and safety of cryoneurolysis for treatment of chronic head pain secondary to occipital neuralgia: a pilot study. Local Reg Anesth. 2021 Sep 17;14:125-132.

Prologo JD, Gilliland CA, Miller M, et al. Percutaneous image-guided cryoablation for the treatment of phantom limb pain in amputees: a pilot study. J Vasc Interv Radiol. 2017 Jan;28(1):24-34. e4.

Prologo JD, Lin RC, Williams R, et al. Percutaneous CT-guided cryoablation for the treatment of refractory pudendal neuralgia. Skeletal Radiol. 2015 May; 44(5):709-14.

Radnovich R, Scott D, Patel AT, et al. Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial. Osteoarthritis Cartilage. 2017;25(8):1247-1256.

Yoon JH, Grechushkin V, Chaudhry A, et al. Cryoneurolysis in patients with refractory chronic peripheral neuropathic pain. J Vasc Interv Radiol. 2016 Feb;27(2):239-43.

Code	Description
0444T	Initial placement of a drug-eluting ocular insert under one or more eyelids, including fitting, training, and insertion, unilateral or bilateral
0445T	Subsequent placement of a drug-eluting ocular insert under one or more eyelids, including re-training, and removal of existing insert, unilateral or bilateral

The placement of drug eluting ocular inserts under the eyelid(s) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Drug-eluting ocular inserts are thin, drug-impregnated, solid or semisolid consistency devices that are designed to be placed non-invasively under the eyelid to release medication over several weeks or months. There are few published studies addressing the use of these drug-eluting ocular inserts. Therefore, it is not possible to conclude whether these inserts have a beneficial effect on health outcomes.

Rubião et al. (2021) conducted a phase II controlled study of individuals with primary open-angle glaucoma (POAG) and ocular hypertension (OH), comparing the safety and efficacy of bimatoprost ocular inserts to bimatoprost eye drops. Thirteen OH patients, and sixteen POAG patients with Intraocular pressure (IOP) greater than 21 and less than or equal to 30mmHg, and a control group of five normal patients with IOP less than or equal to 14 mmHg were included in the study. Participants were between the ages of 40 and 75 years of age. For all participants, a chitosan-based insert of bimatoprost was placed in the upper conjunctival fornix of the right eye. In the left eye, every night for three weeks, one drop of Lumigan TM eye drops was used. “IOP reduction was similar during three weeks of follow-up (19.5 ±2.2 mmHg and 16.9 ±3.1 mmHg), insert, and eye drop, respectively; p = 0.165). The percentage of IOP reduction in the third week was 30% for insert and 35% for eye drops (p = 0.165). No intolerance or discomfort with the insert was reported. Among the research participants, 58% preferred the use of the insert while 25% preferred eye drops, and 17% reported no preference.” The authors concluded that both methods showed

similar efficacy during follow-up, which might suggest a possible change in the daily therapeutic regimen for treatment of these two conditions. A limitation of this study is small sample size, which may not have been large enough to detect clinically significant differences (type 2 error), and short follow-up period.

Brandt et al. (2016) conducted a parallel-arm, multicenter, double-masked, randomized, controlled trial of 130 patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). Eligible patients were randomized 1:1 to receive a bimatoprost ocular insert plus artificial tears twice daily or a placebo insert plus timolol (0.5% solution) twice daily for 6 months after a screening washout period. Diurnal IOP measurements (at 0, 2, and 8 hours) were obtained at baseline; weeks 2, 6, and 12; and months 4, 5, and 6. A mean reduction from baseline IOP of -3.2 to -6.4 mmHg was observed for the bimatoprost group compared with -4.2 to -6.4 mmHg for the timolol group over 6 months. The study met the non-inferiority definition at 2 of 9 time points but was underpowered for the observed treatment effect. Adverse events (AEs) were consistent with bimatoprost or timolol exposure; no unexpected ocular AEs were observed. Primary retention rate of the insert was 88.5% of patients at 6 months. The authors concluded that clinically relevant reduction in mean intraocular pressure (IOP) was observed over 6 months with a bimatoprost ocular insert and seems to be safe and well tolerated. According to the authors, longer-term studies of a high-risk (low-adherence) population will be required to demonstrate the full usefulness of this ocular drug-delivery system in preserving visual fields.,

Torrón et al. (2013) compared the efficacy and safety of an ocular insert versus conventional mydriasis in cataract surgery. Seventy patients who were undergoing cataract surgery were included in the study. Thirty-five patients (Group 1) received instillation of mydriatic drops (tropicamide 1%, phenylephrine 10%, and cyclopentolate 1%) prior to surgery, and 35 patients (Group 2) had a Mydriasert insert (Théa Pharma) (0.28 mg of tropicamide and 5.4 mg of phenylephrine hydrochloride) placed in the inferior fornix of the eye. Pupil size before and after surgery, blood pressure, and heart rate were measured. Before surgery, pupil diameter was 9.44 ±1.17 mm in Group 1 and 9.05 ±1.54 in Group 2. Twenty-four hours after surgery, pupil diameter was 5.20 ±1.54 mm in Group 1 and 3.33 ±1.15 in Group 2. The authors concluded that the effect of the Mydriasert insert was similar to conventional mydriatic agents. The authors indicated that pupil size was restored to normal faster when using the Mydriasert insert compared with conventional mydriatic agents for pupil dilation. Study limitations included a small sample size that may not have allowed detection of clinically significant differences and lack of clinical outcome data.

In their preferred practice pattern document for primary open-angle glaucoma, the American Academy of Ophthalmology (AAO) does not specifically mention the use of ocular inserts for the treatment of glaucoma. (March 14, 2022)

Reference(s)

American Academy of Ophthalmology. Primary open-angle glaucoma preferred practice pattern. March 14, 2022. Available at: https://www.guidelinecentral.com/guideline/309953.

Brandt JD, Sall K, DuBiner H, et al. Six-month intraocular pressure reduction with a topical Bimatoprost ocular insert: results of a phase II randomized controlled study. Ophthalmology. 2016 Aug;123(8):1685-94.

Rubião F, Araújo ACF, Sancio JB, et al. Topical bimatoprost insert for primary open-angle glaucoma and ocular hypertension treatment - A phase II controlled study. Curr Drug Deliv. 2021;18(7):1022-1026. doi: 10.2174/1567201818666210101112256. PMID: 33388018.

Torrón C, Calvo P, Ruiz-Moreno O, et al. Use of a new ocular insert versus conventional mydriasis in cataract surgery. Biomed Res Int. 2013; 2013:849349.

Code	Description
0469T	Retinal polarization scan, ocular screening with on-site automated results, bilateral

Retinal birefringence scanning/retinal polarization scanning is unproven and not medically necessary for the detection of eye misalignment or strabismus due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Retinal birefringence scanners (RBS), such as the Rebion blinq™ binocular birefringent ocular alignment screener, are handheld devices that measure the changes in the polarization of light returning from the eye to detect eye misalignment or strabismus during a brief scan of the eye.

The U.S. Food and Drug Administration (FDA) awarded the Pediatric Vision Scanner, now being marketed as blinq™, market clearance through the “de novo” pathway in June 2016. For more information, refer to the following website: https://www.accessdata.fda.gov/cdrh_docs/reviews/den130051.pdf. (Accessed March 21, 2022).

The AAPOS uniform guidelines for instrument-based pediatric vision screen validation 2021, Arnold et al. regarding instruments such as blinq, only state that “a novel instrument-based device using bilateral birefringent foveal scanning recently became commercially available and shows promise for screening for amblyopia per se”.

Bosque et al. (2021) reported results of a prospective test validation study evaluating the accuracy of the blinq pediatric vision scanner for the detection of amblyopia and strabismus. Testing was performed by individuals masked to the diagnosis. Following testing, pediatric ophthalmologists performed complete examinations and were masked to the screening result. The study included 193 subjects, (53 previously treated, 140 treatment-naïve subjects), “including 65 (46%) with amblyopia or strabismus, 11 (8%) with risk factors/suspected binocular vision deficit without amblyopia/strabismus, and 64 (46%) controls. Sensitivity was 100%, with all 66 patients with referral-warranted ocular disease referred. Five patients with intermittent strabismus receiving pass results were deemed "acceptable pass" when considering patient risk factors and amblyogenic potential. Specificity was 91%, with 7 incorrect referrals. Subanalysis of children aged 2-8 years (n = 92) provided similar results (sensitivity 100%; specificity 89%).” The authors concluded very high sensitivity and specificity for detecting referral-warranted unilateral amblyopia and strabismus was detected with the blinq scanner. The authors further stated that “Implementation of the device in vision screening programs could lead to improved rates of disease detection and reduction in false referrals. The study is limited by the use of non-standard calculations of adjusted sensitivity and specificity.

A cross-sectional study by Arnold (2020) evaluated the blinq™ binocular birefringent ocular alignment screener and the 2WIN with Corneal Reflex (CR) function (Adaptica, Padova, Italy) according to the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) Uniform Guidelines. In this study, 100 adults and children were enrolled from a high-risk ophthalmology practice. Each participant was screened with the blinq screener with validation by AAPOS 2003 guidelines for amblyopia risk factors (which had a prescreening probability of 66%). Then, the blinq was compared to the Adaptica 2WIN with CR with validation by AAPOS 2003 guidelines and additional screenings to identify participants with diminished binocularity. By AAPOS 2003 guidelines, blinq had a sensitivity of 75%, specificity of 68% and positive predictive value of 81% compared to 2WIN with CR which had a sensitivity of 91%, specificity of 68% and PPV of 84%. Adding cases with presumed limited binocularity, blinq had a sensitivity of 64%, specificity of 71% and PPV of 85% while 2WIN with CR function had sensitivity 87%, specificity 82% and PPV 93%. The authors concluded that the blinq pediatric vision scanner performed well in identifying refractive amblyopia and strabismus risk factors when compared to the AAPOS 2003 guidelines. Strengths of the study include the use of AAPOS Uniform guidelines and that older patients were able to confirm binocular status. Weaknesses include that the study did not include an average community pediatric population, it was single center and that there was a relatively small number of participants. Additionally, the sensitivity of the device was inferior to that of Adaptica 2WIN with CR. Clinical trials registry: NCT04195711.

In a comparative study, Jost et al. (2014) evaluated the diagnostic accuracy of the Pediatric Vision Scanner (PVS) in identifying strabismus and amblyopia and compared PVS to the SureSight Autorefractor, a widely used automated pediatric screening device. Three hundred consecutive preschool children (aged 2-6 years) were screened. A masked comprehensive pediatric ophthalmic examination provided the gold standard for determining sensitivity and specificity for each screening device. The primary outcome was sensitivity and specificity of the PVS device for detecting strabismus and amblyopia. Secondary outcomes included the positive and negative likelihood ratios of the PVS for identifying the targeted conditions. In addition, sensitivity, specificity and positive and negative likelihood ratios of the SureSight Autorefractor for the targeted conditions were assessed in the same cohort of children. The sensitivity and specificity of the PVS to detect strabismus and amblyopia was significantly higher than that of the SureSight Autorefractor. This study was performed in a clinical setting with a cohort of children referred for suspected visual impairments resulting in higher incidences than what would be seen in the general population.

Loudon, et al. (2011) performed a prospective study to investigate whether the PVS could detect anisometropic amblyopia as well as strabismus. The authors also followed patients during treatment to determine whether the improvements gained from treatment would be reflected in improved vision test results. A total of 154 patients and 48 controls between the ages of 2 and 18 years participated in the study with 21 children followed longitudinally to detect changes in their binocularity (BIN) scores. The control group consisted of subjects with no strabismus, amblyopia, or anisometropia. The authors concluded that PVS identified children with amblyopia or strabismus with high sensitivity and specificity, while successful treatment restored normal

BIN scores in amblyopic patients without strabismus. Study limitations again include small size, single center, and engagement of patients with known risk factors; it was also noted in this study that there was a lack of racial diversity with 74% of the participants identified as Caucasian.

Nassif et al. (2006) evaluated the clinical performance of the PVD in children in a pediatric ophthalmology office setting. Seventy-seven children between 2 and 18 years of age received gold-standard orthoptic examinations and were classified as at risk for amblyopia if strabismus or anisometropia was present. Binocularity as determined by the PVS was greater than 65% for all controls and less than 20% for all subjects with constant strabismus. Binocularity ranged from 0% to 52% in subjects with variable strabismus. All subjects with anisometropia and no strabismus had binocularity scores less than 10%. The PVS identified strabismus, when present, in all subjects and identified 3 subjects with anisometropia. The PVS shows potential to address a lack of screening instrumentation appropriate for use with preschool-aged children.

A 3-year, prospective clinical trial evaluating the PVS in a community pediatric setting was completed in January 2019 with results submitted to ClinicalTrials.gov on April 7, 2020 and were last updated on July 1, 2020; however, the results of the study have not yet been published. (NCT02536963)

Reference(s)

Arnold RW. Comparative AAPOS Validation of the birefringent amblyopia screener with isolated small-angle strabismus. Clin Ophthalmol. 2020; 14:325–329. Published 2020 Jan 31. doi:10.2147/OPTH.S242335.

Arnold RW, Donahue SP, Silbert DI, Longmuir SQ, Bradford GE, Peterseim MMW, Hutchinson AK, O'Neil JW, de Alba Campomanes AG, Pineles SL; AAPOS Vision Screening and Research Committees. AAPOS uniform guidelines for instrument-based pediatric vision screen validation 2021. J AAPOS. 2022 Feb;26(1):1.e1-1.e6. doi: 10.1016/j.jaapos.2021.09.009. Epub 2022 Jan 20. PMID: 35066152.

Bosque LE, Yamarino CR, Salcedo N, et al. Evaluation of the blinq vision scanner for detection of amblyopia and strabismus. J AAPOS. 2021 Aug;25(4):214.e1-214.e7. doi: 10.1016/j.jaapos.2021.02.011. Epub 2021 Jul 9. PMID: 34246763.

Jost RM, Yanni SE, Beauchamp CL, et al. Beyond screening for risk factors: objective detection of strabismus and amblyopia. JAMA Ophthalmol. 2014 Jul;132(7):814-20.

Loudon SE, Rook CA, Nassif DS, et al. Rapid, high-accuracy detection of strabismus and amblyopia using the pediatric vision scanner. Invest Ophthalmol Vis Sci. 2011 Jul 7;52(8):5043-8.

Nassif DS, Piskun NV, Hunter DG. The Pediatric Vision Screener III: detection of strabismus in children. Arch Ophthalmol. 2006;124(4):509-513.

US Food and Drug Administration (FDA). De novo summary: Pediatric vision scanner. https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130051.pdf. Published December 13, 2013. Accessed April 28, 2022.

Code	Description
0479T	Fractional ablative laser fenestration of burn and traumatic scars for functional improvement; first 100 cm2 or part thereof, or 1% of body surface area of infants and children
0480T	Fractional ablative laser fenestration of burn and traumatic scars for functional improvement; each additional 100 cm2, or each additional 1% of body surface area of infants and children, or part thereof (List separately in addition to code for primary procedure)

Fractional carbon dioxide laser treatment is unproven and not medically necessary for burn scars or traumatic scars due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Fractional laser resurfacing has been described as a promising treatment for scars. While there is a large body of evidence addressing cosmetic outcomes, and other scar characteristics, the evidence for the impact on functional outcomes is limited. It has not been widely adopted in pediatric burn care given the limited outcomes in the literature and no established guidelines for this population (Patel 2019).

In a 2021 systematic review, Buhalog et al. evaluated the existing literature regarding ablative fractional lasers for the treatment of hypertrophic scars. Twenty-three retrospective cohort randomized controlled trials, quasi-randomized controlled trials, observational prospective cohort, or case series with five or more subjects with hypertrophic scars incurred from burns and

related trauma were included. 859 patients were included and underwent a total of 2433 laser treatments. The majority of the studies utilized the Vancouver Scar Scale (VSS) as a primary outcome measure. The Patient and Observer Scar Assessment Scale (POSAS) was the next most common. Other objective outcome measures included ultrasound for scar height/thickness, instruments to assess scar pliability and color, quartiles of overall improvement, histologic evaluation of collagen and elastin architecture and content, immunohistochemistry for growth factors and other mediators, and range of motion. Subjective outcome tools used included quality of life indices, scales of pruritus, and patient willingness to pay for treatment. The results showed that of the studies that reported the overall VSS and POSAS, there was statistically significant improvement of all outcomes measured with these tools. Furthermore, 22 of the 23 studies documented statistically significant and meaningful improvements in nearly all outcome measures. Laser treatments were well tolerated in general, with minor adverse effects such as skin discoloration, pain and swelling, blistering, erythema, infection, and ulceration typically resolved by final follow up visit. The authors concluded that ablative fractional lasers are emerging as an alternative scar management treatment between conservative measures and surgical management. Treatment is well tolerated and has a relatively low incidence of minor adverse events. Future studies should prioritize standardized protocols including assessments of function and quality of life. This study is limited by the significant heterogeneity and high risk of bias of the included studies.

In 2021, Miletta et al. reported the results of a multicenter, site-controlled, prospective open-label study to determine the objective and subjective changes in mature, stable hypertrophic burn scars treated with a fractional ablative carbon dioxide (CO_2) laser, at least one year post burn injury, in 29 subjects aged 11 years and older (12 children and 10 adults). Objective and patient-reported outcome measures were documented at baseline, at each monthly laser treatment, and 6 months after treatment. Objective measurements assessed included mechanical skin torque to measure viscoelastic properties, ultrasonic imaging to measure scar thickness, and reflectometry to measure erythema and pigmentation. Subjective measures included health-related quality of life, patient and investigator scar assessment scales, and blinded scoring of before and after photographs. Each subject received 3 monthly treatment sessions with an ablative fractionated CO2 laser. Of the 29 participants, 26 received at least 1 fractional CO_2 laser treatment and 22 received 3 treatments. The results showed statistically significant objective improvements in elastic stretch, elastic recovery, extensibility, and thickness. Patient and physician-reported scar appearance and pain/pruritus were also significantly improved, these improvements were sustained at 6-month follow up. The authors concluded that fractional ablative laser treatment provides significant, sustained improvement of elasticity, thickness, appearance, and symptoms of mature hypertrophic burn scars in children and adults. These including contractured scars for which patients reported increased freedom of movement. This study is limited by the small number or participants and lack of long-term follow up. Future clinical studies should address the potential combination of laser with other treatments, dose-response data, and other determinants of individual response to treatment.

Peng et al. (2021) conducted a meta-analysis of twenty articles comprised of randomized controlled trials, cohort, case-control, and comparative studies, to assess the efficacy and safety of fractional CO_2 for the treatment of burn scars. The results showed significant improvements in the VSS, as well as the patient and observer scores of the POSAS. Scar thickness as measured by ultrasound was significantly reduced, as was pigmentation, elasticity, vascularity, pliability, and height of scar. Scar firmness as measured by cutometer was however not reduced. Only 5 studies reporting adverse side effects that included hypo/hyperpigmentation, discoloration, erythema, infection, bleeding and swelling, and none were severe. The authors concluded that treatment with fractional CO_2 significantly improves the appearance and morphology of burn scars evaluated using the VSS and POSAS by both patients and the physician, as well as ultrasound evaluated scar thickness. Limitations of this study include substantial heterogeneity of the studies, which included multiple countries, range of follow up and different treatment session protocols which limit generalizability. Additionally, most of the included studies had a small number of participants. Furthermore, the influence of other variables such as burn size and severity, hypertrophic scarring, and laser delivery parameters were not assessed. Well designed, larger studies are needed to validate these findings.

Osterhoff et al. (2021) conducted a systematic review regarding the outcomes of erythema, pigmentation, height, and pliability of the different laser systems on hypertrophic scarring (HR) and keloid. Thirteen studies with 16 study arms reporting outcomes on scar characteristics were identified. Three studies reported outcomes on characteristics with CO 2 laser system in fractional setting. In erythema a mean 56% improvement was seen, above the overall mean of 37%. Regarding pigmentation, a mean reduction of 36% was reported above the overall mean of 8%. Height was improved by 46%, where the overall mean was 37%. A mean 59% improvement was reported in pliability, above the 47% overall mean. Reduced pliability corresponds with complaints of contractures, and a clinically relevant improvement was seen in most study arms, with a slight advantage to CO 2 10,600 nm laser system. This systematic review suggests that the ablative fractional laser systems (CO 2 10,600 nm and the Er:YAG 2940 nm) yielded the most improvement across all scar characteristics. Most studies scored the scars by only utilizing observed subjective clinical improvement. Future randomized controlled trials and prospective studies with a methodologically

strong design, well- defined scar characteristics, standardized, and validated outcome measurements are needed to confirm this conclusion.

Zhang et al. (2019) conducted a meta-analysis to evaluate the effectiveness of fractional carbon dioxide (CO2) laser for the treatment of burn scars. Fourteen studies were included and all except one retrospective study were prospective in design and were single arm evaluations. There was no significant publication bias identified. The results showed significant improvements in Vancouver Scar Scale (VSS), Patient and Observer Scar Assessment Scale (POSAS), and Scar Assessment Scale (SAS) scores after treatment especially with regards to pigmentation, vascularity, pliability, and height of scar. Pain and pruritis also improved with this treatment. However, scar thickness decreased statistically non-significantly and no improvement could be observed in scar firmness or elasticity, although lesser data were available to evaluate scar thickness, firmness and elasticity. This meta-analysis finds that 1 to 4 sessions of treatment of burn scars with fractional CO2 laser is associated with significantly improved outcomes.

Patel et. al (2019, included in Buhalog systematic review) conducted a prospective cohort study of pediatric burn patients undergoing carbon dioxide ablative fractional laser (CO2-AFL) treatment of hypertrophic, symptomatic burn scars at a tertiary care regional burn center during a 2-year period. 49 patients with burn severity of full thickness (63.6%) and deep partial thickness (47.7%) were treated with a total of 180 laser sessions. Observer-rated POSAS scores revealed statistically significant improvements in pigment, thickness, relief, pliability, and surface area after one treatment with continued improvement until the last laser session. Patient-rated POSAS revealed statistically significant improvements in color, stiffness, thickness, and irregularity after laser treatments. Total POSAS improved from 89.6 ±17.5 to 76.6 ±16.8 ($p < .0001$) after one treatment with further improvement to 69.2 ±14.9 ($p < .0001$) at the final laser session. The authors concluded that CO2-AFL therapy improves hypertrophic burn scars on both patient- and observer-rated scales confirming statistical and clinical significance to both providers and families. These findings demonstrate that CO2-AFL can improve hypertrophic burn scars in pediatric patients providing a lower risk alternative to invasive therapies and a more immediate, efficacious alternative to more conservative scar treatments.

In 2020, an international panel of 26 dermatologists and plastic and reconstructive surgeons from 13 different countries and a variety of practice backgrounds was self-assembled to develop evidence-based consensus recommendations regarding laser treatment for traumatic scars and contractures. They intended to highlight the potential of laser techniques and offer recommendation and promote wider patient access guided by future high-quality research. The panel recommendations for texture, pliability, thickness, and contractures state the single most effective laser type is ablative fractional laser and it is groundbreaking treatment, and one of the most important developments in scar treatment in decades, with additional research needed to determine optimal beam profile. It was concluded that lasers are a first-line therapy in the management of traumatic scars and contractures, and patients without access to these treatments may not be receiving the best available care after injury. Updated international treatment guidelines and reimbursement schemes, additional high-quality research, and patient access should reflect this status (Seago et al., 2020, included in Buhalog systematic review).

Reference(s)

Buhalog B, Moustafa F, Arkin L, et al. Ablative fractional laser treatment of hypertrophic burn and traumatic scars: a systematic review of the literature. Arch Dermatol Res. 2021 Jul;313(5):301-317.

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Code	Description
0485T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; unilateral
0486T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; bilateral

Optical coherence tomography (OCT) for assessing and managing middle ear disorders is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Conventional diagnostic techniques for middle ear disorders include use of standard or pneumatic otoscopy, and typanometry to evaluate the surface of the tympanic membrane. Optical coherence tomography (OCT) is a non-invasive, real-time imaging technology that uses a low-intensity light source to produce 2- and 3- dimensional structural images of the middle ear with micron-scale resolution. The image produced by the reflected light is analyzed and can be used to differentiate air from fluid, as well as characterize fluid properties due to scattering of the imaging signal from particles in the fluid (Precaido et al. 2020). There is a lack of high-quality published studies that demonstrate the clinical utility of OCT on improved patient outcomes.

Preciado et al. (2020) conducted a cross-sectional study to evaluate clinical usability and image readability by clinical personnel in the detection and differentiation of middle ear effusions (MMEs) using an OCT otoscope. Seventy pediatric patients aged seven and older undergoing tympanostomy tube placement were preoperatively imaged using an OCT otoscope. Readable images were collected in 65 ears from 45 participants. Bilateral imaging was attempted when possible. Images were sorted into 3 groups: no fluid, serous fluid and nonserous fluid (purulent or mucoid). The groups assigned to read OCT images included otolaryngologists, pediatricians, physician extenders and non-medical professionals. Blinded reader analysis of OCT images for identifying presence and type of fluid was then compared with intraoperative findings to determine the sensitivity, specificity, accuracy, positive/negative predictive values, and inter/intrareader agreement of OCT otoscopy. The results showed reader detection of MEEs had a 90.6% accuracy, 90.9% sensitivity, 90.2% specificity, 94.5% positive predictive value, 84.2% negative predictive value, and intra/interreader agreement of 92.9% and 87.1% respectively, with no statistically significant differences between those with and without OCT experience. The authors concluded that OCT has potential to be a viable diagnostic tool in the hands of many users, regardless of experience with the technology and is at least as accurate as other diagnostic tools in terms of accuracy and specificity. This study is limited by the small number of participants, lack of standardization and does not address the clinical utility of OCT.

Monroy et al. (2018) conducted a prospective case series study to assess otitis media-associated biofilm structures affixed to the mucosal surface of the TM, both in vivo and in surgically recovered in vitro samples. Forty pediatric patients that were scheduled for tympanostomy tube placement surgery were imaged intraoperatively under general anesthesia. Following myringotomy, a portable OCT imaging system was used to assess for the presence of any biofilm affixed to the mucosal surface of the TM. OCT was achieved for 38 patients. Samples of suspected microbial infection-related structures were collected through the myringotomy incision. The sampled site was reimaged with OCT to confirm collection from the original image site. In vitro analysis was done based on confocal laser scanning microscope (CLSM) images of fluorescence in situ hybridization-tagged samples, and polymerase chain reaction (PCR) provided microbiological characterization and verification of biofilm activity. Thirty-four samples were collected from 38 subjects. CLSM images provided evidence of clustered bacteria in 32 of 33 samples. PCR detected the presence of active bacterial DNA signatures in 20 of 31 samples. The results showed that PCR and CLSM analysis of fluorescence in situ hybridization-stained samples validates the presence of active bacteria that have formed into a middle ear biofilm that extends across the mucosal layer of the TM. The authors concluded that OCT can rapidly and noninvasively identify middle ear biofilms in subjects with severe and persistent cases of otitis media. This study is limited by a small number of participants, no control group, and a high risk of bias. The clinical utility of this method to diagnose OM has not been established, and large well-designed studies are required to validate these findings.
Park et al. (2018) conducted a prospective study to examine the tympanic membranes (TMs) of 120 patients with middle ear conditions using a handheld optical coherence tomography-based otoscope (860 nm central wave length, 15 μm axial resolution, 15 μm lateral resolution, and 7 mm scanning range using relay lens). Both OCT and oto-endoscope images were compared according to the clinical characteristics such as perforation, retraction, and postoperative healing process. The objective grade about the thickness of perforation margins and the accurate information about the extent of TM retraction that was not distinguishable by oto-endoscopic exam could be identified using this system. The postoperative healing process of TMs could be also followed using the OCT device. The authors concluded that their findings suggest that the handheld OCT device would be another useful application.

Using OCT, Monroy et al. (2017) observed 6 pediatric patients diagnosed with chronic or recurrent otitis media before and following standard-of-care surgical treatment who completed a six month period follow up out of 25 participants initially included. At each time point, the tympanic membrane (at the light reflex region) and directly adjacent middle-ear cavity were observed in vivo with a handheld OCT probe and portable system. Imaging results were compared with clinical outcomes to correlate the clearance of symptoms in relation to changes in the image-based features of infection. OCT images of most all participants showed the presence of additional infection-related biofilm structures during their initial consultation visit and similarly for subjects imaged intraoperatively before myringotomy. Subjects with successful treatment (no recurrence of infectious symptoms) had no additional structures visible in OCT images during the postoperative visit. OCT image findings suggest surgical intervention consisting of myringotomy and tympanostomy tube placement provides a means to clear the middle ear of infection-related components, including middle-ear fluid and biofilms. Furthermore, OCT was demonstrated as a rapid diagnostic tool to prospectively monitor patients in both outpatient and surgical settings. This study is limited by the small number of participants, lack of standardization and does not address the clinical utility of OCT.

Cho et al. (2015) report on the application of OCT for the diagnosis and evaluation of otitis media (OM). They evaluated 39 patients who were diagnosed with OM via standard otoendoscopic examination and audiological tests between July and October 2012. Six volunteers with normal TM on otoendoscopy were also included, with OCT images used as a control. Of the 39 patients, OCT images were acquired from 16 patients (41.0%). The most common cause of failure to acquire an image was a narrow or curved external auditory canal (n = 5). Other causes were the presence of obstacles, such as profuse otorrhea (n = 3), cholesteatoma material (n = 4), and cerumen (n = 7), and poor compliance (n = 4). OCT could not be obtained for the three patients with chronic OM with cholesteatomas. Despite the benefits such as noninvasiveness, lack of radiation, high resolution and ability to use outpatient, the authors report some limitations, such as, difficulty securing a light pathway for the OCT device, and the diagnostic efficiency of otoendoscopy. The authors concluded that their evaluation suggests that a handheld OCT otoscope can be applied clinically to otology, and that OCT has the potential to facilitate diagnosis of OM; however, further clinical trials are necessary.

In a study by Monroy et al. (2015), OCT was used to determine TM thickness, and the presence and thickness of any middle-ear biofilm located behind the TM in 34 pediatric patients. Participants were placed into 3 subgroups: normal, acute OM and chronic OM based on the clinical presentation as diagnosed by otoscope. Average TM thickness values were calculated from three representative locations for each cross-sectional OCT image. The data analysis was based on the optic scattering properties of the tissue, which has a direct correlation to the stage of infection. The results showed an increased thickness in the participants in the acute infection group. In chronic OM, the optic scattering appeared to return to a thickness that is similar to normal when a biofilm was present. The authors concluded that OCT offers the potential to differentiate normal, acute, and chronic otitis media (OM) infections in pediatric subjects. This study is limited by a small number of participants. These findings and clinical utility of the device should be validated with larger well designed studies.

Nguyen et al. (2013) investigated the acoustic effects of bacterial biofilms, confirmed using OCT in adult ears. Biofilms have been linked to chronic OM and OM with effusion in the middle ear. Non-invasive OCT images were collected to visualize the 2D cross-sectional structure of the middle ear, verifying the presence of a biofilm behind the TM of 5 ears. Wideband measurements of acoustic reflectance and impedance (0.2 to 6 [kHz]) were used to study the acoustic properties of ears with confirmed bacterial biofilms. Compared to known acoustic properties of normal middle ears, each of the ears with a bacterial biofilm had an elevated power reflectance in the 1 to 3 [kHz] range, corresponding to an abnormally small resistance. The authors note that their preliminary study indicates that acoustic reflectance and impedance measurements may have utility for assessment of the presence and acoustic impact of biofilms in the middle ear; however, future study of a wide range of OM-related conditions, with definitive biofilm and non-biofilm classifications, is needed.

Professional society guidelines for OCT and the middle ear were not identified.

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Code	Description
0640T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); image acquisition, interpretation and report, each flap or wound
0641T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); image acquisition only interpretation and report, each flap or wound
0642T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); interpretation and report only, each flap or wound

Contact or non-contact near-infrared spectroscopy (NIRS) is unproven and not medically necessary for assessing tissue oxygenation in tissue flaps or wounds due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Near-infrared spectroscopy (NIRS) is a noninvasive technique using wavelengths to measure tissue oxygenation. NIRS has been proposed to be used as indication of wound healing.

Lindelauf et al. (2022) conducted a systematic review evaluating the use of near infrared spectroscopy (NIRS) versus hyperspectral Imaging (HSI) to detect flap failure in reconstructive surgery compared to standard monitoring such as clinical assessment and a handheld doppler. PubMed and Embase were searched in August 2021 with studies selected by two independent reviewers. Five HSI and sixteen NIRS studies totaling 3,662 flap procedures carried out in 1,970 patients using NIRS and 90 patients using HSI were included. The flap survival of HSI was 92.5% and NIRS 99.2% with statistically significant differences observed in flap survival, flaps returned to OR, and partial flap loss rate. The literature concludes NIRS and HSI are reliable, accurate and user-friendly, however according to recent available literature, no concrete conclusions can be made regarding non-invasive monitoring techniques superiority.

Hill et al. (2020) conducted a cohort study to evaluate the capacity of NIR spectroscopy to detect clinically relevant differences in flap perfusion intraoperatively. Patients undergoing oncologic resection of breast cancer, sarcomas, and cutaneous tumors requiring flap reconstruction (local, regional, or free) between January 2018 and January 2019 were analyzed in this study. Clinicians were blinded to device tissue oxygen saturation (StO2) measurements taken intraoperatively after closure and at follow-up appointments in the first 30 days. Measurements were categorized as (1) control areas not affected by the procedure, (2) areas at risk, and (3) areas of necrosis. These areas were retrospectively demarcated by 2 blinded assessors on follow-up images and transposed onto anatomically correlated intraoperative StO2 measurements. Forty-two patients were enrolled, and 51 images were included in the analysis. Oncologic procedures were predominantly breast (22), post-extirpative melanoma (13), and sarcoma (3) reconstructions. Flap reconstruction involved 30 regional skin flaps, 3 pedicled flaps, and 3 free flaps. Nine patients (20.9%) and 11 surgical sites developed skin flap necrosis (SFN). Mean intraoperative StO2 measurements for control areas, areas at risk, and areas of SFN were 74.9%, 71.1%, and 58.3%, respectively. Relative to control areas, mean intraoperative StO2 measurements were lower by 17.5% ($p = 0.01$) in ultimate areas of SFN and in areas at risk by 5.8% ($p = 0.003$). Relative to areas at risk, mean StO2 measurements from areas of ultimate SFN were lower by 8.3% ($p = 0.04$). The investigators indicated that these preliminary data suggest that measuring skin flap tissue oxygenation intraoperatively, with NIR spectroscopy, can differentiate objective variations in perfusion that are associated with clinical outcomes. According to the investigators, the relatively small sample size made analysis of the sensitivity and specificity of this device limited and not applicable in a clinical context.

Lin et al. (2020) evaluated the use wearable NIRS to determine the effect of Buerger exercises on diabetic foot ulcer (DFU) healing. Fifty consecutive patients were enrolled in a 1-year prospective observational study of DFUs. The patients were divided into groups by their arterial statuses: group A (no peripheral arterial disease [PAD]), group B (PAD without angioplasty), and group C (PAD with angioplasty). Tissue perfusion was assessed through wireless wearable NIRS to determine the effects of Buerger exercises on wound healing. The patients in group C were older, were more likely to have had an amputation, and had more severe wounds than did the patients in other groups. At the end of the survey, 19 patients (38%) had unhealed DFUs. The NIRS revealed that most non healed patients in groups B and C shared higher resting hemoglobin levels and tissue blood volume and lower tissue oxygen concentration, which indicated inflammation accompanied by higher blood flow and oxygen consumption. Notably, the non-healed patients in group C showed paradoxically reduced hemoglobin and tissue blood volume after the exercises. The investigators concluded that although DFUs remain a challenge to treat, NIRS may prove valuable in predicting wound healing by identifying risk factors for poor wound prognosis, such as reduced hemoglobin and tissue blood volume after exercise. The investigators indicated that further research is needed to establish NIRS' ability to predict wound outcomes as a treatment guide. According to the investigators, the major limitation of this investigation is that it is a nonrandomized study with a small number of patients.

Serena et al. (2020) conducted a study to compare measurement of tissue oxygenation of NIRS with transcutaneous oxygen measurement (TCOM) in patients with acute and hard-to-heal wounds. The Shapiro-Wilk test was used to evaluate the normality of the data. The level of agreement between NIRS and TCOM was determined using Bland-Altman analysis. The relationship between TCOM and NIRS was examined using Pearson correlation. A total of 24 observations were obtained from 10 patients using TCOM and NIRS. The weighted mean partial pressure of oxygen (pO2) in the study population was 39.54mmHg (8.96 standard deviation). Bland-Altman analysis showed that mean difference was positive (18.75), suggesting an overestimation of oxygen measurements using TCOM compared with NIRS. The oxygen levels measured by TCOM and NIRS showed a strong correlation ($r = 0.74$). The investigators indicated that the wound and hyperbaric community would benefit from a simplified procedure for measuring tissue oxygenation. According to the investigators, these findings suggest a strong trend toward correlation between NIRS and TCOM. The major limitation of this study is that it is a nonrandomized study with a small sample size. Further studies in larger populations are needed.

In a systematic review, Mortensen et al. (2019) evaluated diagnostic modalities used for acute compartment syndrome (ACS). Fifty-one pre-clinical and clinical articles were included in this study, reporting on 38 noninvasive and 35 invasive modalities. Near-infrared spectroscopy and direct intercompartmental pressure measurement were the most common diagnostic modalities. According to the authors, all modalities lacked a reliable threshold. The authors indicated that future studies on diagnostic modalities should include continuous assessment tools to better identify the earliest signs of ACS and thereby establish a reliable threshold.

Shuler et al. (2018) evaluated NIRS as a continuous, non-invasive monitor for acute compartment syndrome (ACS). NIRS sensors were placed on 86 patients with, and 23 without (controls), severe leg injury. NIRS values were recorded for up to 48 hours. Longitudinal data were analyzed using summary and graphical methods, bivariate comparisons, and multivariable multilevel modelling. Mean NIRS values in the anterior, lateral, superficial posterior, and deep posterior compartments were between 72% and 78% in injured legs, between 69% and 72% in uninjured legs, and between 71% and 73% in bilaterally uninjured legs. In patients without ACS, the values were typically > 3% higher in injured compartments. All seven limbs with ACS had at least one compartment where NIRS values were 3% or more below a reference uninjured control compartment. Missing data were encountered in many instances. The authors concluded that NIRS oximetry might be used to aid the assessment and management of patients with ACS. However, additional interventional studies are required to validate the use of NIRS for ACS monitoring.

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Mortensen SJ, Vora MM, Mohamadi A, et al. Diagnostic modalities for acute compartment syndrome of the extremities: a systematic review. JAMA Surg. 2019 Jul 1;154(7):655-665.

Serena TE, Yaakov R, Serena L, et al. Comparing near infrared spectroscopy and transcutaneous oxygen measurement in hard-to-heal wounds: a pilot study. J Wound Care. 2020 Jun 1;29(Sup6):S4-S9.

Shuler MS, Roskosky M, Kinsey T, et al. Continual near-infrared spectroscopy monitoring in the injured lower limb and acute compartment syndrome: an FDA-IDE trial. Bone Joint J. 2018 Jun 1;100-B (6):787-797.

Code	Description
0506T	Macular pigment optical density measurement by heterochromatic flicker photometry, unilateral or bilateral, with interpretation and report

Heterochromatic flicker photometry for evaluation of age-related macular degeneration is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Najjar et al. (2016) studied ocular lens density and transmittance measurements of 43 subjects, obtained by an improved psychophysical scotopic heterochromatic flicker photometry (sHFP) technique. This was compared to the results obtained by three other measures: a psychophysical threshold technique, a Scheimpflug imaging technique, and a clinical assessment using a validated subjective scale. Ocular lens densities were compared for all methods by using linear regression analysis. The sHFP technique showed that transmittance decreased with age over the entire visual spectrum. Lens density obtained from sHFP highly correlated with the values obtained with the other approaches. sHFP also showed the lowest variability and the best fit with a quadratic trend of lens density increase as a function of age, compared to other objective measures. The authors concluded that the HFP technique offers a practical, reliable, and accurate method to measure lens density in vivo and predict lens transmittance over the visible spectrum. This study is limited by population size.

Reference(s)

Najjar RP, Teikari P, Cornut PL, et al. Heterochromatic flicker photometry for objective lens density quantification. Invest Ophthalmol Vis Sci. 2016 Mar;57(3):1063-71.

Code	Description
0507T	Near-infrared dual imaging (i.e., simultaneous reflective and trans-illuminated light) of meibomian glands, unilateral or bilateral, with interpretation and report

The use of near-infrared dual imaging of meibomian glands is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Near Infrared Dual Imaging (e.g., LipiScan Dynamic Meibomian Imager)

There is a lack of evidence regarding the effectiveness of near-infrared dual imaging in the diagnosis and management of patients with meibomian gland dysfunction or blepharitis. Furthermore, professional society guidelines are lacking regarding near-infrared dual imaging of meibomian glands.

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

Finis et al. (2015) conducted an evaluation of meibomian gland dysfunction (MGD) and local distribution of meibomian gland atrophy by non-contact infrared meibography. A retrospective analysis of 128 patients (92 women and 36 men, 57 ±17 years) from a dry eye clinic was performed. Infrared meibography was performed using the Keratograph 5 M (Oculus, Wetzlar, Germany) and evaluated with a scoring system introduced by Arita et al. The results showed a significant inverse correlation between Meibomian gland atrophy measured by meibography and expressible Meibomian glands ($r = -0.197$, $p = 0.003$) as well as between meiboscore and TBUT ($r = -0.1615$, $p = 0.012$). There also was a significant correlation between the total meiboscore and the age ($r = 0.33$, $p < 0.0001$). The authors found a strong and highly significant correlation between the total meiboscore and the individual meiboscore of the upper eyelid ($r = 0.905$, $p < 0.0001$) and the lower eyelid ($r = 0.892$, $p < 0.0001$). There was no significant difference of Meibomian gland atrophy between the individual thirds of the upper eyelid, but for the lower eyelid, a higher degree of Meibomian gland atrophy was found in the nasal third compared with the middle and the temporal third (Dunn's post hoc test, $p < 0.0001$). The authors concluded that meibomian gland atrophy seems to be not constant over the tarsal plate, but the examination of the lower tarsus might be sufficient in most of the cases. The correlation of the meiboscore with functional dry eye parameters suggest that in patients with detectable Meibomian gland atrophy there is also an impaired Meibomian gland function. However, meibography seems not to be sufficient as a single test for the diagnosis of MGD. Larger, prospective studies are needed to confirm these results and further evaluate the potential of meibography in the diagnosis of MGD.

Reference(s)

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Johnson&Johnson website. Lipican Dynamic Mibomian Imager. Available at https://www.jnjvisionpro.com/products/lipiscan%E2%84%A2-dynamic-meibomian-imager. Accessed May16, 2022.

Code	Description
0508T	Pulse-echo ultrasound bone density measurement resulting in indicator of axial bone mineral density, tibia

The use of pulse-echo ultrasound bone density measurement is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Currently, the diagnosis of osteoporosis is based on the measurement of bone mineral density (BMD), using axial dual energy X-ray absorptiometry (DXA) of the hip and/or the lumbar spine. Bindex® a pocket-sized tool for osteoporosis screening and diagnostics is used for measuring the cortical thickness of the tibia or radius. The results, combined with other patient data, are used to estimate the hip region's bone mineral density van den Berg et al. (2020) conducted a cross-sectional pilot study using pulse-echo ultrasonometry (P-EU) in 209 women with a recently sustained non-vertebral fracture (NVF) to identify those without osteoporosis and/or subclinical vertebral fracture (VF). All of the patients received dual X-ray absorptiometry (DXA) and P-UE. The results of the study showed that 83 women had osteoporosis (40%) and 17 women at least one VF (8%). "Applying the manufacturer's recommended P-EU threshold (DI 0.844 g/cm2) being their proposed cut-off for not having hip osteoporosis resulted in 77 negative tests (37%, 31% true negative and 6% false negative tests). A density index (DI) of 0.896 g/cm2 resulted in 40 negative tests (19.3%) (38 true negative (18.3%) and 2 false negative tests (1.0%)." "The most conservative P-EU threshold resulted in 18.3% true negative tests verified by DXA/VFA against 1% false negative test results." The authors concluded that a substantial proportion of women with recent non-vertebral fractures were identified by the application of P-EU. Thus, these women would not need a DXA referral because no osteoporosis and/or subclinical vertebral fractures were found.

Nazari-Farsani et al. (2020) conducted a cohort study of postmenopausal women with primary hip osteoarthritis that underwent total hip arthroplasty with implantation of a parallel-sided femoral stem. The sixty-five participants were women between the ages of 60 and 85-year-old who were part of a single-center, double-blinded, placebo-controlled, randomized clinical trial. Preoperatively, subjects had multisite DXA measurement of bone mineral density (BMD) and pulse-echo ultrasonometry of the cortical-bone thickness using the Bindex mobile device. Measurements were conducted by two physiotherapists. Five successful repeated measurements in each location were taken and averaged. Patients then underwent a total hip replacement. The patients were randomly assigned to receive antiresorptive denosumab treatment (a subcutaneous injection of 60 mg every 6 months) or placebo for 1 year, which started 4 weeks before surgery. The authors found the measurement of

cortical-bone thickness was challenging as the pulse-echo ultrasonometry (Bindex) only gave a rough estimate of bone thickness. Limitations of the trial included a study design that doesn't inform the use of this technology as a substitute to DXA for osteoporosis screening, a relatively small sample size along, with inclusion limited to postmenopausal women.

In this study by Karjalainen et al. (2018), a pulse-echo ultrasound (US) method was investigated for osteoporosis screening. A total of 1091 Caucasian women (aged 50-80 years) were recruited for the study and measured with US in the tibia and radius. This method measures cortical thickness and provides an estimate of Bone Mineral Density (BMD) and Density Index (DI). BMD assessment of the hip was available for 988 women. A total of 888 women had one or more risk factors for osteoporosis, and 100 women were classified healthy. Previously determined thresholds for the DI were evaluated for assessment of efficacy of the technique to detect hip BMD at osteoporotic range (T-score at or below -2.5). In the osteoporosis group, the application of thresholds for the DI showed that approximately 32% of the subjects would require an additional dual-energy x-ray absorptiometry (DXA) measurement. The multi-site US measurement-based DI showed 93.7% sensitivity and 81.6% specificity, whereas the corresponding values for single-site US measurement-based DI were 84.7 and 82.0%, respectively. The US measurements showed a high negative predictive value 97.7 to 99.2% in every age decade examined (ages 50-59, 60-69, 70-79 years). The authors concluded the data demonstrated a strategy of combining ultrasound measurement with added DXA measurements can be useful for identifying subjects at risk for a low bone mineral density in the osteoporotic range.

The aim of a study by Schousboe et al. (2016) was to estimate whether or not pulse-echo ultrasonometry could discriminate between those who had from those who had not one or more radiographically confirmed clinical fracture within the previous five years. The study included 555 Caucasian females between ages 50 and 89 years old. Subjects were examined using ultrasound measurements of cortical bone thickness and DI (Bindex®, Bone Index Finland Ltd., Kuopio, Finland) and BMD of the femoral neck and total hip (Hologic Discovery, Hologic Inc., MA, USA). Ninety-five individuals had 102 radiographically documented fractures within the five years prior to the study date. All but 9 of these individuals also self-reported having had a prior fracture when asked on their study date. The majority of these were in the distal radius/wrist, lumbar spine, or thoracic spine. Measures of cortical thickness of the tibia were as strongly associated with radiographically confirmed fracture in the electronic health record as was femoral neck BMD, and the author results compared favorably to the discrimination of prior fractures that had been shown with other ultrasound and peripheral bone mass measurement devices. Pulse-echo ultrasonometry shows promise as a tool for fracture risk assessment, but future prospective and randomized control studies are warranted.

In a study by Karjalainen et al. (2016), a total of 572 Caucasian women (age 20 to 91 years) were examined using a new US method to diagnose osteoporosis. The participants were examined using pulse-echo US measurements in the tibia and radius. Areal BMD measurements at the femoral neck (BMD (neck)) and total hip (BMD (total)) were determined by using axial DXA for women older than 50 years of age (n = 445, age = 68.8 ±8.5 years). The osteoporosis thresholds for the DI were determined according to the International Society for Clinical Densitometry (ISCD). Finally, the FRAX questionnaire was completed by 425 participants. The results demonstrate a significant correlation between the ultrasound and DXA measurements at the proximal femur. The thresholds presented here with the application to current osteoporosis management pathways show promise for the technique to significantly decrease the amount of DXA referrals and increase diagnostic coverage; however, these results need to be confirmed in future studies.

A National Institute for Health and Care Excellence (NICE) innovation briefing concluded that there are key uncertainties around the evidence along with no prospective studies showing the effect of Bindex on the need for DXA scans, and limited data on the correlation between tibial bone thickness and femoral bone mineral density (NICE, 2017).

The US Food and Drug Administration (FDA) approved the Bindex Osteoporosis Measurement device for diagnosing osteoporosis under 510(k) (K161971) on January 9, 2017. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/K161971.pdf. (Accessed March 29, 2022).
ClinicalTrials.gov identifies Bindex for Osteoporosis Diagnostics (NCT03878732) which focuses on the clinical validation of the ultrasound device (Bindex®) and Density Index (DI), a diagnostic parameter reported by Bindex. The study completion date is listed as February of 2020 with no posted results. Refer to: https://www.clinicaltrials.gov/ct2/show/study/NCT03878732?term=NCT03878732&draw=2&rank=1. (Accessed March 29, 2022).

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Schousboe, John T.; Riekkinen, Ossi; Karjalainen, Janne. Fracture discrimination using a novel pulse-echo ultrasound device. Journal of Clinical Densitometry. October 1, 2016. Volume 19, Issue 4. Pages 532-533.© 2016.

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Code	Description
0515T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; complete system (includes electrode and generator [transmitter and battery])
0516T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only
0517T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; pulse generator component(s) (battery and/or transmitter) only
0518T	Removal of only pulse generator component(s) (battery and/or transmitter) of wireless cardiac stimulator for left ventricular pacing
0519T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter)
0520T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter), including placement of a new electrode
0521T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording, and disconnection per patient encounter, wireless cardiac stimulator for left ventricular pacing
0522T	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, wireless cardiac stimulator for left ventricular pacing

Cardiac resynchronization therapy (CRT) with wireless left ventricular (LV) endocardial pacing is unproven and not medically necessary for the treatment of cardiac arrhythmias, heart failure (HF), or for the prevention of HF as a consequence of right ventricular pacing, due to insufficient evidence of efficacy and/or safety.

Clinical Evidence

Currently, no device has been approved by the U.S. Food and Drug Administration (FDA) for provision of wireless LV pacing for CRT.

The WiSE (Wireless Stimulation Endocardially) CRT System (EBR Systems, Inc., Sunnyvale, CA) (formerly the WiCS-LV) is currently undergoing clinical trials. The WiSE CRT System is a wireless LV pacing system that works with a conventional pacemaker and/or defibrillator for patients in whom CRT is indicated. The WiSE CRT system is comprised of an ultrasonic transmitter attached to a battery unit and a tiny wireless receiver which acts as a pacing electrode. The WiSE system allows for biventricular pacing while eliminating the need for a LV pacing wire in the coronary sinus. The system allows the provider to

customize electrode placement to the optimal location for pacing, which varies among patients; this differs significantly from conventional LV pacing leads, which are limited by coronary sinus anatomy (Hayes, 2019; updated 2021).

Cang et al. (2022) conducted a systematic review and meta-analysis to determine if patients can benefit from WiSE-CRT as a way of rescue therapy for those in whom CRT failed. Five single-arm studies involving 175 HF patients with WiSE-CRT were included and evaluated for clinical outcomes including QRS duration (QRSd), ejection fraction (EF), and LV end-systolic volume. Patient follow-up period was six months. The implanted success rate ranged from 76.5 to 100%. WiSE-CRT resulted in significantly narrower QRSd [mean difference (MD): −38.21ms, 95% confidence interval (CI): −44.36 to −32.07, $p < 0.001$], improved LV ejection fraction (MD: 6.07%, 95% CI: 4.43 to 7.71, $I2 = 0\%$, $p < 0.001$), reduced LV end-systolic volume (MD: −23.47ml, 95% CI: −37.18 to −9.13, $p < 0.001$), and reduced LV end-diastolic volume (MD: −24.02ml, 95% CI: −37.01 to −11.03, $p = 0.02$). The authors concluded that leadless endocardial LV pacing resynchronization is effective for HF patients who need a device upgrade or who failed conventional CRT; however, the authors note that more clinical trials are needed. Limitations include small sample sizes, lack of comparison groups, and a short follow-up period. Reddy et al. 2017, and Auricchio et al. 2014, which were previously cited in this policy, were included in this systematic review and meta-analysis.

Sidhu et al. (2020) performed a sub analysis of the WiSE-CRT, SELECT-LV and WiCS-LV studies and reported on outcomes in 22 patients with HF who were non-responders to CRT. Six-month follow-up was available for 18 patients. Overall, 55.6% of patients had improvement in their clinical composite score and 66.7% had a reduction in LV end-systolic volume of at least 15% and/or absolute improvement in LV ejection fraction of at least 5%. The study is limited by lack of comparison group, and the small number of study participants limits the generalizability of these results. Further studies are required to determine the overall benefit in this patient population.

The WiCS-LV Post Market Surveillance Registry assessed the safety and efficacy of the WiSE-CRT system in a real-world setting. Ninety patients from 14 European centers underwent implantation. Successful implantation and delivery of biventricular endocardial pacing was achieved in 94.4% of patients. Acute (within 24 hours), 1- to 30-day, and 1- to 6-month complications rates were 4.4%, 18.8%, and 6.7%, respectively. There were three (3.3%) procedure-related deaths. At six months, 70% of patients experienced an improvement in HF symptoms. Study limitations include an observational design, lack of comparison group and lack of randomization (Sieniewicz, et al., 2020). NCT02610673

A Hayes emerging technology report found no published RCTs evaluating the WiSE system for CRT in patients with HF. Published evidence is limited to reports from nonrandomized single-arm trials and registry data. These reports suggest that endocardial CRT with the WiSE system may be a treatment option for patients with HF who do not respond to conventional CRT or who have contraindications to LV lead implantation. Further evidence is needed to better characterize the safety and efficacy of the device (Hayes, 2019; updated 2021).

The pivotal Stimulation of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients (SOLVE CRT) study is currently recruiting participants. Initially designed as a randomized blinded sham-controlled trial, the study design was modified due to the impact of the COVID-19 pandemic on patient enrollment to a two-phase trial: a randomized phase (enrollment completed in 2019) and a single-arm phase (starting in 2021) (Singh et al., 2021). NCT02922036

Reference(s)

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Reddy VY, Miller MA, Neuzil P, et al. Cardiac Resynchronization Therapy with Wireless Left Ventricular Endocardial Pacing: The SELECT-LV Study. J Am Coll Cardiol. 2017;69(17):2119-2129.

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Sieniewicz BJ, Betts TR, James S, et al. Real-world experience of leadless left ventricular endocardial cardiac resynchronization therapy: A multicenter international registry of the WiSE-CRT pacing system. Heart Rhythm. 2020 Aug;17(8):1291-1297.

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Code	Description
0525T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; complete system (electrode and implantable monitor)
0526T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; electrode only
0527T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; implantable monitor only
0528T	Programming device evaluation (in person) of intracardiac ischemia monitoring system with iterative adjustment of programmed values, with analysis, review, and report
0529T	Interrogation device evaluation (in person) of intracardiac ischemia monitoring system with analysis, review, and report
0530T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; complete system (electrode and implantable monitor)
0531T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; electrode only
0532T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; implantable monitor only

Intracardiac ischemia monitoring systems (e.g., AngelMed Guardian System) are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The AngelMed Guardian® System is a fully implanted electrocardiography (ECG) device intended for monitoring patients with acute coronary syndrome (ACS) history and high recurrence risk. AngelMed is intended to alert patients to seek emergency care to reduce time to treatment and detect asymptomatic ACS (ECRI, 2020; updated 2022).

The AngelMed Guardian System received U.S. Food and Drug Administration (FDA) premarket approval (P150009) on April 9, 2018. The AngelMed Guardian System is indicated for use in patients who have had prior ACS events and who remain at high risk for recurrent ACS events. The AngelMed Guardian System is indicated as an adjunct to patient recognized symptoms. The system detects potential ongoing ACS events, characterized by sustained ST segment changes, and alerts the patient to seek medical attention for those potential ACS events. Additional FDA information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P150009. (Accessed March 19, 2022).

In a 2022 Hayes analysis research brief, one randomized controlled trial (RCT) published in two abstracts evaluating the AngelMed Guardian System for patients with ACS was identified. The Hayes analysis reports there is currently not enough published, peer-reviewed literature to perform a full assessment to evaluate the evidence related to the AngelMed Guardian System.

An ECRI product brief (2020; updated 2022) notes that evidence is too limited in quality and quantity to evaluate whether AngelMed cardiac monitoring is beneficial to patients. The ALERTS RCT suggests AngelMed may assist patients to seek care promptly when the device alerts; however, the RCT is at high risk of bias from serious protocol breaches. Additionally, AngelMed has potential to increase adverse event risks by leading some patients not to pursue immediate care if an AngelMed alert does not accompany their ACS symptoms. The product brief states large, multicenter RCTs that adhere to predefined endpoints, intent-to-treat analysis, and standardized outcomes are needed. The report authors conclusion is that the evidence is inconclusive.

Gibson et al. (2019) reported the results of the ALERTS (AngelMed for Early Recognition and Treatment of STEMI; NCT00781118) trial. The ALERTS trial was a multicenter, randomized trial of an implantable cardiac monitor that alerts patients with rapidly progressive ST-segment deviation. Subjects at high-risk of ACS (n = 907) were randomized to a control (alarms deactivated) or treatment group for 6 months, after which alarms were activated in all subjects. The primary safety endpoint was absence of system-related complications (> 90%). The composite primary efficacy endpoint was cardiac/unexplained death, new Q-wave myocardial infarction, or detection to presentation time > 2 h. Safety was met with 96.7% freedom from system-related complications (n = 30). The efficacy endpoint for a confirmed occlusive event within 7 days was not significantly reduced in the treatment compared with control group (16 of 423 [3.8%] vs. 21 of 428 [4.9%], posterior probability = 0.786). Within a 90-day window, alarms significantly decreased detection to arrival time at a medical facility (51 min vs. 30.6 h; Pr [pt < pc] > 0.999). In an expanded analysis using data after the randomized period, positive predictive value was higher (25.8% vs. 18.2%) and false positive rate significantly lower in the ALARMS ON group (0.164 vs. 0.678 false positives per patient-year; p < 0.001). The authors noted that although the trial did not meet its pre-specified primary efficacy endpoint, results suggest that the device may be beneficial among high-risk subjects in potentially identifying asymptomatic events. Additionally, Holmes et al. (2019) published previously unreported results from the ALERTS trial that focused on pre-hospital delays during ACS events. The study appears to include events collected after the randomization period, when all participants had the alarm on. The authors reported reduced delays, with 55% (95% confidence interval [CI]: 46% to 63%) of ED visits for ACS events < 2 h compared with 10% (95% CI: 2% to 27%) in the Alarms OFF group (p < 0.0001) and shorter median pre-hospital delay for myocardial infarction: 12.7 h for Alarms OFF and 1.6 h in Alarms ON subjects (p < 0.01). The findings of this latest publication are limited by what appears to be inclusion of events outside of the randomization period, which results in breaking the randomization benefit and could introduce possible biases.

Fischell et al. (2010) combined outcomes of 2 first in-human case series: the Brazilian CARDIOSAVER study (n = 20) and the U.S. DETECT study (n = 17). Intracardiac monitoring was performed in 37 patients at high risk for acute coronary syndromes. The implanted monitor continuously evaluated the patients' ST segments sensed from a conventional pacemaker right ventricle apical lead, and alerted patients to detected ischemic events. During follow-up (median 1.52 years, range 126 to 974 days), 4 patients had ST-segment changes of ≥ 3 SDs of their normal daily range, in the absence of an elevated heart rate. This in combination with immediate hospital monitoring led to angiogram and/or intravascular ultrasonography, which confirmed thrombotic coronary occlusion/ruptured plaque. The median alarm-to-door time was 19.5 min (6, 18, 21, and 60 min, respectively). Alerting for demand-related ischemia at elevated heart rates, reflective of flow-limiting coronary obstructions, occurred in 4 patients. There were 2 false-positive ischemia alarms related to arrhythmias, and 1 alarm due to a programming error that did not prompt cardiac catheterization. The author's concluded that shifts exceeding 3 SD from a patient's daily intracardiac ST-segment range may be a sensitive/specific marker for thrombotic coronary occlusion. Patient alerting was associated with a median alert-to-door time of 19.5 min for patients at high risk of recurrent coronary syndromes who typically present with 2- to 3-h delays. These studies did not evaluate final clinical outcomes and is limited by lack of comparison group.

Reference(s)

ECRI Institute. AngelMed Guardian System (Angel Medical Systems, Inc.) for monitoring patients at high risk of acute coronary syndrome. Plymouth meeting (PA): ECRI Institute; 2020 Jan 17. (Custom product brief). Updated February 23, 2022.

Fischell TA, Fischell DR, Avezum A, et al. Initial clinical results using intracardiac electrogram monitoring to detect and alert patients during coronary plaque rupture and ischemia. J Am Coll Cardiol. 2010 Sep 28;56(14):1089-98.

Gibson CM, Holmes D, Mikdadi G, et al. Implantable cardiac alert system for early recognition of ST-segment elevation myocardial infarction. J Am Coll Cardiology. 2019 April 23; 73(15); 1928-1930.

Hayes Inc. Evidence analysis research brief. The AngelMed Guardian System for management of acute coronary syndrome. Landsdale, PA: Hayes, Inc. January 10, 2022.

Holmes DR Jr, Krucoff MW, Mullin C, et al. Implanted monitor alerting to reduce treatment delay in patients with acute coronary syndrome events. J Am Coll Cardiol. 2019 Oct 22;74(16):2047-2055.

Code	Description
0559T	Anatomic model 3D-printed from image data set(s); first individually prepared and processed component of an anatomic structure
0560T	Anatomic model 3D-printed from image data set(s); each additional individually prepared and processed component of an anatomic structure (List separately in addition to code for primary procedure)
0561T	Anatomic guide 3D-printed and designed from image data set(s); first anatomic guide

Code	Description
0562T	Anatomic guide 3D-printed and designed from image data set(s); each additional anatomic guide (List separately in addition to code for primary procedure)

Due to insufficient evidence of safety and/or efficacy, the use of three dimensional (3D) printed anatomic models is unproven and not medically necessary for all indications including but not limited to:

- Surgical planning
- Manufacturing of customized devices

Clinical Evidence

Three dimensional (3D) printed anatomic models are models that are created in a 3-dimensional technology using 3D printers. These 3D printed models are derived from patient imaging and can be used to plan and rehearse procedures (e.g., evaluating approaches for inserting a cardiac valve) or to manufacture customized devices. The use of 3D printed models as part of preoperative planning is thought to improve patient outcomes and reduce surgery time. Anatomic 3D models are also used for medical education, such as informing patients or training students about procedures.

Omari et al.(2022) conducted a systematic review on 3D printed models for patient-specific interventions in otology and auricular management with the goal of exploring present use of 3D printed patient specific otologic interventions along with state of evidence, strengths, limitations, and future possibilities. Data on the manufacturing process and interventions was identified through PubMed, EMBASE, the Cochrane Library, and Web of Science. A total of 590 studies were extracted with 63 considered eligible for inclusion. Of the studies for outer ear interventions 73% were utilized. The consensus of the reports was optimistic including increased surgical precision, quick manufacturing and operation time, reduced cost, and complications. Limitations to the report were the poor quality due to studies failing to use relevant objective outcomes, compare new interventions, and sufficiently describe manufacturing. The authors conclude that although promising, it remains unclear if 3D-Printing improves patient outcomes. Furthermore, there is insufficient reporting which makes the manufacturing and reproducibility of the 3D-printed interventions compromised.

A 2021 ECRI clinical evidence assessment was conducted on the use of 3D printed anatomic models for orthopedic surgical planning focusing on outcomes from the use of 3D printing in orthopedic surgery compared with those of conventional orthopedic surgical procedures. The evidence search dates were from January 2016 to June 2021 with a review of 2 systematic reviews, 5 clinical studies, 2 systematic review abstracts, 2 clinical studies, for a total of 2,212 patients reported on. The studies utilized reported on patients with different conditions necessitating orthopedic surgery. The studies show utilizing 3D patient-specific anatomic models for procedure planning reduces operative time, though is not a benefit over conventional surgical approaches regarding functional status, complication rates, and other patient-oriented outcomes. The limitations of the evidence consist of low-quality evidence, the need for large-sample, multicenter Randomized Controlled Trials (RCT's) which would address the evidence gap and establish 3D printing's efficacy in a clinical setting. Other limitations consist of variation in outcomes reported, surgical procedure limits comparison in studies, high risk of bias, lack of follow up, and the studies conducted were outside the United States, thus results may not be generalized to the United States healthcare system. The 3D anatomic models may benefit surgical approach in planning for complex anatomy orthopedic surgeries, but there is a lack in high-quality RCTs to define benefits in orthopedic surgery (ECRI 2021).

ECRI issued a clinical evidence assessment in 2021 on the use of 3D printed anatomic models for neurologic surgical planning. This assessment consisted of 7 studies: 2 nonrandomized comparison studies, 1 pre-post treatment study, and 4 case series. The results suggested 3D printed models may have potential advantages in neurological surgery planning, however the studies were found to have a high risk for bias, too few patients, low quality, and quantity to be conclusive in determining the effects of patient outcomes. Larger high quality comparison studies reporting on patient outcomes are needed to define the benefits of 3D printing models in planning neurologic surgery (ECRI 2021).

In 2021 ECRI issued a clinical evidence assessment on the use of 3D printed anatomic models for cardiovascular surgical planning. The assessment consisted of evidence from 3 small studies, 2 comparison studies, and 1 case series. The studies proposed 3D-printed models may have possible advantages in the planning of cardiovascular surgery, however the evidence is too inadequate in quantity, quality, and high risk for bias. Due to these limitations the studies cannot determine how utilizing 3D printed models affects patient outcomes compared to conventional planning. Greater sophisticated quality comparison studies

that report on the results of patients, with longer follow up are required to define the benefits of 3D printing models (ECRI 2021).

A 2021 Hayes report that focused on the use of 3D printed implants for complex lower extremity reconstruction indicated that there is an insufficient quantity of published clinical data to evaluate 3D printed implants for complex lower extremity reconstruction (Hayes, 2021).

Hayes issued a report in 2019 on the use of three-dimensional printed orthopedic implants for knee, hip, and spinal indications which indicated that the overall quality of the body of evidence was moderate in size, but very low in quality. The Hayes report indicated that there is a need for larger, well-designed controlled trials to better determine risks and benefits over the long term and to define patient selection criteria. Hayes updated the report in 2021 and found that the evidence published since the 2019 report would not likely change their earlier conclusions (Hayes, 2019; Updated November 2021).

ECRI issued a report for the MySpine® Patient-specific Guide in 2021. The MySpine Patient-specific Guide system is comprised of a set of custom-made anatomic models intended to provide intraoperative assistance in pedicle screw placement during spinal surgery. The system uses 3D printing to create physical models of the target vertebrae and screw placement guides with tubes at each screw's preplanned position and angle. The ECRI report indicated that the evidence suggests that MySpine allows the surgeon to customize parameters such as trajectory and screw dimensions during preoperative planning and may improve pedicle screw placement accuracy over freehand implantation; however, published studies include too few patients and are at too high a risk of bias to be conclusive (ECRI 2021).

Xicheng et al.(2021) conducted a Randomized Controlled Trial (RCT) on 3D printed models in preoperative ventricular septal defect repair and its utility for congenital heart disease repair. The study was accomplished at the time of consent where guardians of candidates for ventricular septal defect repair were provided comprehensive description of anatomy, purpose of surgery, complications and risks using 3D vs 2D prints. Data was composed from a questionnaire completed by patients and guardians and medical records which were statistically evaluated. The outcomes of the study display advancements in ratings of the understanding of ventricular septal defect anatomy, potential complications, and surgical procedure in the group that used the 3D model with no difference in overall ratings of consent process. Comparable in the two groups was the clinical outcomes as represented by the duration of intensive care stay and intubation duration. The conclusion of the study is that 3D printing is an effective tool for consent in congenital heart surgery however, the impact of 3D printing used on long term outcomes remains to be defined.

Hasan et al. (2020) compared the migration of cementless, 3D-printed total knee arthroplasty (TKA) to cemented TKA of a similar design up to two years of follow-up using radio stereometric analysis (RSA) known for its ability to predict aseptic loosening. A total of 72 patients were randomized to either cementless 3D-printed or a cemented cruciate retaining TKA. RSA and clinical scores were evaluated at baseline and postoperatively at three, 12, and 24 months. A mixed model was used to analyze the repeated measurements. The mean maximum total point motion (MTPM) at three, 12, and 24 months was 0.33 mm (95% confidence interval (CI) 0.25 to 0.42), 0.42 mm (95% CI 0.33 to 0.51), and 0.47 mm (95% CI 0.38 to 0.57) respectively in the cemented group, versus 0.52 mm (95% CI 0.43 to 0.63), 0.62 mm (95% CI 0.52 to 0.73), and 0.64 mm (95% CI 0.53 to 0.75) in the cementless group ($p = 0.003$). However, using three months as baseline, no difference in mean migration between groups was found ($p = 0.497$). Three implants in the cemented group showed a > 0.2 mm increase in MTPM between one and two years of follow-up. In the cementless group, one implant was revised due to pain and progressive migration, and one patient had a liner-exchange due to a deep infection. The authors concluded that the cementless TKA migrated more than the cemented TKA in the first two-year period. This difference was mainly due to a higher initial migration of the cementless TKA in the first three postoperative months after which stabilization was observed in all but one maligned and early revised TKA. The authors indicated that a longer follow-up is needed to determine whether the biological fixation of the cementless implants will result in an increased long-term survivorship.

Moralidou et al. (2020) conducted a systematic review of the existing literature for the use of 3D pre-operative planning in primary total hip arthroplasty (THA). The review focused on (1) the accuracy of implant sizing, restoration of hip biomechanics and component orientation; (2) the benefits and barriers of this tool; and (3) current gaps in literature and clinical practice. A total of 43 full scientific articles were reviewed. Clinical studies have highlighted the accuracy of 3D pre-operative planning in predicting the optimal component size and orientation in primary THAs. Component size planning accuracy ranged between 34-100% and 41-100% for the stem and cup, respectively. The absolute, average difference between planned and achieved values of leg length, offset, center of rotation, stem version, cup version, inclination and abduction were 1 mm, 1 mm, 2 mm, 4°,

7°, 0.5° and 4° respectively. The benefits of 3D pre-operative planning include 3D representation of the human anatomy for precise sizing and surgical execution. The Barriers of 3D pre-operative planning include increased radiation dose and learning curve. According to the authors, the long-term evidence investigating this technology is limited. Emphasis should be placed on understanding the health economics of an optimized implant inventory as well as long-term clinical outcomes.

In a systematic review, Burnard et al. (2020) assessed the clinical evidence for efficacy and safety of both patient-specific (PS) and Off-The-Shelf (OTS) three-dimensional printing (3DP) spinal implants through review of the published literature. The aim was to evaluate the clinical utility of 3DP devices for spinal surgery. A systematic literature review of peer-reviewed papers featured on online medical databases evidencing the application of 3DP (PS and OTS) surgical spine implants was conducted in accordance with PRISMA guidelines. Twenty-two peer-reviewed articles and one book-chapter were eligible for systematic review. The published literature was limited to case reports and case series, with a predominant focus on PS designs fabricated from titanium alloys for surgical reconstruction in cases where neoplasia, infection, trauma, or degenerative processes of the spine have precipitated significant anatomical complexity. The authors concluded that PS and 3DP OTS surgical implants have demonstrated considerable utility for the surgical management of complex spine pathology. The reviewed literature indicated that 3DP spinal implants have also been used safely, with positive surgeon- and patient-reported outcomes. However, these conclusions are tentative as the follow-up periods are still relatively short and the number of high-powered studies was limited.

Malahias et al. (2020) performed a systematic review on the performance of highly coated titanium acetabular cups produced via 3D printing in primary and revision total hip arthroplasty (THA) procedures. The aim of the study was to find the revision rate and the rate of aseptic loosening of highly porous titanium cups used in primary THA cases and in revision cases with acetabular bone loss. The authors reviewed 16 studies, all observational, which included 11,282 patients; ten studies were retrospective and six prospective. At the conclusion of the review, the authors determined there was moderate quality evidence which demonstrated that the use of highly porous titanium acetabular components in both primary and revision THA cases was associated with satisfactory clinical outcomes. The overall survival rate in primary surgical cases was 99.3% and 93.5% for revisions. While the results were positive, further research of higher quality is required to generate more evidence-based conclusions regarding the longevity of highly porous titanium acetabular implants compared with conventional titanium equivalents. Limitations included a lack of well-designed prospective studies, randomization, and blinding. Furthermore, 3D-printed cups were used in only three of the reviewed studies, limiting the implication of this study to the topic of interest for this policy.

Tuncay and van Ooijen (2019) performed a systematic review to evaluate the application of 3D printing to cardiac valve disease. The 29 included papers showed that the most reported application areas are preoperative planning (63%), followed by training (19%), device testing (11%), and retrospective procedure evaluation (7%). According to the authors, current technology allows for accurate printing of cardiac anatomy in materials that resemble the properties of the actual heart and vessels. The authors indicated that the actual clinical benefit of 3D printing remains to be proven.

In 2018 The Radiological Society of North America (RSNA) and 3D printing special interest group (SIG) published a document regarding medical 3D printing and suitability for clinical scenarios. The document reports on the clinical scenarios where difficulty in pathology requires a transformation of clinical imaging into a physical model. The conclusion being common clinical standards concerning proper use, information and material management, and quality control are required to safeguard the greatest possible clinical benefit from 3D printing.

Lau and Sun (2018) performed a systematic review to analyze the clinical applications and accuracy of 3D printing in congenital heart disease (CHD), as well as to provide an overview of the software tools, time and costs associated with the generation of 3D printed heart models. A total of 28 studies met selection criteria for inclusion in the review. More than half of the studies were based on isolated case reports with inclusion of 1-12 cases (61%), while 10 studies (36%) focused on the survey of opinion on the usefulness of 3D printing by healthcare professionals, patients, and others, and the remaining one involved a multicenter study about the clinical value of 3D printed models in surgical planning of CHD. According to the authors, the analysis shows that patient-specific 3D printed models accurately replicate complex cardiac anatomy, improve understanding and knowledge about congenital heart diseases and demonstrate value in preoperative planning and simulation of cardiac or interventional procedures, assist surgical decision-making and intra-operative orientation, and improve patient-doctor communication and medical education. The authors indicated that most of the studies on 3D printing of CHD are case reports so the actual clinical value of 3D technology could not be confirmed due to the potential bias in the study design. Future studies should include more cases of different types of CHD to investigate their clinical value on patients' outcomes.

Langridge et al. (2018) performed a systematic review of the uses of 3D printing within surgical training and assessment. Overall, 49 studies were identified for inclusion in the qualitative analysis. Heterogeneity in study design and outcome measures used prohibited meaningful meta-analysis. 3D printing has been used in surgical training across a broad range of specialties but most commonly in neurosurgery and otorhinolaryngology. The authors concluded that 3D printing technology has a broad range of potential applications within surgical education and training. Although the field is still in its relative infancy, several studies have already demonstrated its usage both instead of and in addition to traditional educational methods. The authors indicated that within the current literature review there is a lack of high-quality randomized control studies to assess the effectiveness of 3D printing within the preoperative planning setting. Most evidence related to the usage of 3D printing and their effect on clinical endpoints is an underexplored area with the majority of literature focusing on anecdotal case reports without assessing comparable clinical endpoints. The authors recommended that future studies should compare 3D printed models with current best surgical practice when measuring use within the preoperative planning setting. The implication of these findings on patient care is however unclear.

Diment et al. (2017) performed a systematic review to evaluate the clinical efficacy and effectiveness of using 3D printing to develop medical devices across all medical fields. Of the 3084 abstracts screened, 350 studies met the inclusion criteria. Only 21 studies were RCTs. The majority of RCTs were 3D-printed anatomical models for preoperative planning and guides for aiding surgery. The main benefits of these devices were decreased surgical operation times and increased surgical accuracy. All medical fields that assessed 3D-printed devices concluded that they were clinically effective. The fields that most rigorously assessed 3D-printed devices were oral and maxillofacial surgery and the musculoskeletal system, both of which concluded that the 3D-printed devices outperformed their conventional comparators. However, the efficacy and effectiveness of 3D-printed devices remain undetermined for the majority of medical fields. The authors concluded that 3D-printed devices can play an important role in healthcare, but more rigorous and long-term assessments are needed to determine if 3D-printed devices are clinically relevant before they become part of standard clinical practice.

Reference(s)

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Code	Description
0567T	Permanent fallopian tube occlusion with degradable biopolymer implant, transcervical approach, including transvaginal ultrasound

Fallopian tube occlusion with a degradable biopolymer implant is investigational, unproven and not medically necessary as a permanent form of contraception due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

FemBloc® is a non-surgical, permanent female contraceptive system that is performed in the office setting. FemBloc consists of a temporary biopolymer that initiates a wound healing response in the fallopian tubes to form a permanent closure with scar tissue. Over time, the biopolymer completely exits the uterine cavity and fallopian tubes naturally (Femasys® website).

No published results from clinical studies that evaluated this form of contraception were identified.

Currently, clinical trials are underway to assess the safety and efficacy of FemBloc.

Reference(s)

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Code	Description
0581T	Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral
19105	Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma

Cryoablation of breast carcinoma and fibroadenoma is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The National Comprehensive Cancer Network (NCCN) does not mention cryotherapy for the treatment of breast cancer in its clinical practice guidelines in oncology (NCCN, 2022).

Van de Voort et al. (2021) performed a systematic review and meta-analysis of 37 articles which included 1266 patients that underwent a variety of ablation to treat small breast cancers and whether the intervention was an effective method to treat early-stage breast cancer with tumors ≤ 2 cm. Analysis included comparison of the five different ablation therapies and complication rates. The number of articles reviewed by intervention were 24 radiofrequency ablation (RFA), 1 microwave ablation (MWA), 5 laser ablation, 3 high intensity focused ultrasound (HIFU) and 8 cryoablation. Complete ablation and complication rates by intervention were RFA 92% and 9.4%, MWA 87% and 13%, Laser Ablation 64% and 17.7%, HIFU 61.8% and 12.1% and Cryoablation 80.3% and 5%. The authors concluded that an overall complete ablation rate for all patients was a combined 86%. Cryotherapy could be considered a promising alternative to surgical resection and potentially reduce treatment burden, morbidity and improve cosmetic outcome. However, the studies analyzed were non-comparative and small-sized therefore the results should not lead to conclusions, but a basis for larger randomized controlled trials.

Pusceddu et al. (2019) performed a systemic review of the available evidence on cryoablation in the treatment of solid tumors, including breast cancer. The authors stated that although this ablation method had the advantage of being a minimally invasive

procedure, due to the small sample size of the available studies, reliable and definitive conclusions on the usefulness of cryoablation in patients with breast cancer could not be drawn. They further stated that other aspects of this technology, including technical issues, indications, efficacy, imaging follow-up, and possible advantages over other percutaneous ablative methods need to be clarified.

In a retrospective case series, Edwards et al. (2004) reported on the early experience of cryoablation for the percutaneous treatment of breast fibroadenomas. Fifty-three sites were involved, ablating 310 fibroadenomas. Early follow-up data showed that the procedure was well tolerated on 256 lesions, with infrequent minor complications immediately after the procedure. At 6- and 12-months post procedure, the remaining fibroadenoma volume progressively involuted. Patient satisfaction was rated high at both intervals. The authors concluded that office-based cryoablation of breast fibroadenomas is encouraging, compared to high-volume tertiary centers. They stated that more follow-up is necessary to determine long-term results and residual mammographic changes.

Reference(s)

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Pusceddu C, Paliogiannis P, Nigri G, et al. Cryoablation in the management of breast cancer: evidence to date. Breast Cancer. Version 2.2022.

van de Voort EMF, Struik GM, Birnie E, et al. Thermal ablation as an alternative for surgical resection of small (≤ 2 cm) breast cancers: a meta-analysis. Clin Breast Cancer. 2021 Mar 17: S1526-8209(21)00059-8.

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

Myringotomy and Tympanostomy Tube Placement Under Local Anesthesia (Tula) System is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The Tubes Under Local Anesthesia (Tula) System is intended to insert ear tubes (tympanostomy tubes) into the eardrum in children and adults, using local anesthesia in a physician's office, to treat repeated ear infections (recurrent acute otitis media) or fluid in the ear (otitis media with effusion). The Tula® System consists of the Tula Iontophoresis System and the Tula Tube Delivery System. The Tula Iontophoresis System, which includes individually fitted disposable ear plugs and ear sets, delivers a local anesthetic solution, TYMBION™, to the eardrum resulting in numbness of the eardrum. The Tula Tube Delivery System is then used to place the ear tube in the eardrum, The Tula system received FDA premarket approval (P190016) on November 25, 2019. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P190016 (Accessed May 4, 2022).

A 2022 Hayes Evidence Analysis Research Brief identified three single-arm clinical study abstracts and one systematic review assessing automated tympanostomy tube systems for pediatric individuals. These included two articles addressing the Tula system (Tusker Medical). The Hayes Evidence Analysis Research Brief concludes there is not enough published, peer-reviewed literature to evaluate the evidence addressing the efficacy and safety of automated tympanostomy tube placement systems.

In the 2022 Clinical Practice Guideline: Tympanostomy Tubes in Children (Update) by Rosenfeld et al. the 2013 guideline recommendations were reevaluated and updated with evidence-based recommendations for patient selection and surgical indications for the management of tympanostomy tubes in children. The update does not contain specific recommendations regarding office insertion of tubes in children without anesthesia, however states "Risks associated with general anesthesia can be eliminated by inserting tubes in the office setting without general anesthesia, when appropriate, based on shared decision making between the clinician and family."

Lustig et al. (2020, included in the 2022 Hayes Evidence Analysis Research Brief) published the results of a prospective multi-center case series evaluating the safety, technical success, and tolerability of tympanostomy tube (TT) placement under local

anesthesia in an office setting (OTTER study). A total of 337 children across 18 different sites, ages 6 months through 12 years of age, were included in the study. Lidocaine/epinephrine iontophoresis was the method used for anesthesia and tube placement was done using the Tula integrated, automated myringotomy and Tube Delivery System (TDS). Pain was rated by participants 5 to 12 years old using the Faces Pain Scale-Revised (FPS-R) tool, which is used to rate pain from 0 (no pain) to 10 (very much pain). Bilateral tubes were placed successfully in 85.8% of children less than 5 years of age and 89.2% of children 5 to12 years of age. For tube placement itself, mean FPS-R score was 3.30 (standard deviation [SD] = 3.39). 5-minute post-procedure mean FPS-R score was1.69 (sd = 2.43). Authors note that an unexpected benefit of the in-office procedure was the avoidance of using additional medications that are often given in conjunction with general anesthesia during standard TT placement. 91.8% of implant tubes were still present at the 6 month follow up. Limitations include lack of comparison group, efficacy outcomes, or information about long-term tube retention as follow-up is ongoing. Additional high-quality evidence is needed to confirm the safety and efficacy of this technology.

Yen et al. (2020) conducted a prospective, multicenter, single-arm study (ADEPT) to evaluate the safety, tolerability, and technical success of lidocaine iontophoresis and a tympanostomy tube placement system for adults in an office setting. The investigation aimed to show the system is suitable before initiating a pediatric investigation, designed with input from physician advisers to meet FDA requirements. The study evaluated 30 individuals ages 21 to 83 years receiving tympanic membrane anesthesia and tube placement recruited in 8 community-based practices. The integrated myringotomy and tube delivery system was utilized for the tube placement, and tolerability of placement was measured using a patient-reported visual analog scale from 0mm-100mm; 0mm being no pain and 100mm being the worst possible pain. The participant's average pain score was compared to the performance goal of 45mm. The baseline measures included otoscopy, tympanometry, and audiometry up to 28 days preprocedural, and the technical success and safety post-procedure was evaluated for three weeks. The study resulted in twenty-nine individuals with successful placement in all indicated ears. Inadequate tympanic membrane anesthesia with no tube placement attempted occurred in one individual. The average pain score was statistically superior to the performance goal of tolerability at 9.4 (15.7) mm. Non-serious events relative to device, procedure, or drug were demonstrated in seven individuals. Limitations to the study include the risk of bias, lack of efficacy outcomes, and the lack of a control group to compare safety and tolerability. The study evaluated adults, limiting performance generalization to a pediatric population; larger, controlled studies are needed to compare the investigational system to existing options

In 2019 The American Academy of Otolaryngology (AAC) published a Position Statement on in office TT tube placement. The statement notes that "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."

Cofer et al. (2017, included in the 2022 Hayes Evidence Analysis Research Brief). noted that a tympanostomy tube system has been developed to allow tympanostomy tube placement in a single pass on conscious patients under moderate sedation A prospective study was conducted at 4 U.S. centers involving 128 children and 253 tympanostomy tube placements. The outcome of the study showed an 88.3 % success rate in performing the procedure under moderate sedation with adverse effects (AEs) within normal rates. The authors concluded that the feasibility of doing tympanostomy tube placement in an office setting using moderate sedation offered additional choices to physicians and parents. This study was limited by lack of a control group or efficacy outcomes.

Cohen et al. (2015) indicated that two complementary technologies have recently been developed comprising an iontophoresis system (IPS) for delivering local anesthesia and an integrated TDS subsequently eliminating the need for general anesthesia in an operating room setting. These investigators evaluated behavioral support techniques used during a clinical study of the new technology for pediatric in-office tube placement without general anesthesia or physical restraints. As part of an institutional review board (IRB)-approved, prospective, 9-center case series, pediatric patients requiring tube insertion underwent in-office treatment using the new procedure. The behavior management techniques included preparation, distraction, coaching, and reinforcement for co-operation. The entire procedure was videotaped, and 2 independent coders used the validated FLACC (face, legs, activity, cry, consolability) scale to code behavioral distress across 5 procedural phases. A total of 70 pediatric patients aged 8 months to 17 years (m = 7.0 years; 51 % girls) were enrolled in the study, and 68 had video recordings available for analysis. Of the 68 recordings analyzed, 63 patients completed the procedure and had tubes placed without sedation. Mean FLACC scores ranged from 0.05 to 2.38 (m = 1.25,sd= 0.82) and median (mdn) FLACC scores ranged from 0 to 1 (mdn = 0, inter-quartile range [IQR] = 0.05), which indicated "mild" distress. During iontophoresis, eardrum tap (anesthesia assessment), and tube delivery, older children displayed lower distress and girls had higher FLACC scores during the eardrum tap procedural phase. The authors concluded that when combined with the evidence-based behavioral techniques, office-based

local anesthesia and tube delivery resulted in minimal distress, suggesting that the new procedure may be a viable method of conducting tympanostomy tube placement in children without having to use general anesthesia. A randomized trial with a comparison or control group is needed to establish the efficacy of in-office tympanostomy tube placement without general anesthesia.

Zeiders et al. (2015, included in the 2022 Hayes Evidence Analysis Research Brief). conducted a prospective, single-arm study at 9 otolaryngology sites in the US. Participants included pediatric patients aged 6 months to less than 22 years who required tube placement. The participants were prepared for the procedure using behavioral support techniques and tube placement was attempted under local anesthesia using the IPS in conjunction with the TDS. No physical restraints were allowed nor was the use of anxiolytics, analgesics, or sedatives permitted. Safety was evaluated via the occurrence of AEs and success rates for tube placement under local anesthesia were determined. Tolerability of the procedure was evaluated using the 5-point Wong-Baker FACES Pain Rating Scale and parental satisfaction was assessed using a post-operative survey. A total of 70 participants (127 ears) were enrolled in the study [mean (SD) age of 7.0 (3.9) years]. No serious AEs were observed in the 70 enrolled participants. Tube placement using the TDS was successful in 96.6 % (114/118) of attempted ears. A single TDS was required in 105 ears, while more than 1 device was required in 9 ears. Of the 70 patients enrolled in study, 63 (90.0 %) successfully received tubes in all indicated ears during their in-office visit. The mean (SD) change in pain score from pre-anesthesia to post-surgery was + 0.9 (1.8). Favorable ratings for overall satisfaction with the in-office procedure were obtained from 96.9 % (63/65) of respondents. Tube retention at 2 weeks was 99.1 %. As only 15 patients were enrolled who were 3 years old or younger, the ability to generalize these results to younger patients was limited. The authors concluded that the use of the IPS and TDS technologies enabled safe, reliable, and tolerable placement of tubes in awake, unrestrained pediatric patients. This study was limited by lack of a control group or relevant efficacy outcomes.

Reference(s)

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Code	Description
0584T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; percutaneous
0585T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; laparoscopic
0586T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; open
60659	Unlisted laparoscopy procedure, endocrine system

Code	Description
G0341	Percutaneous islet cell transplant, includes portal vein catheterization and infusion
G0342	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
G0343	Laparotomy for islet cell transplant, includes portal vein catheterization and infusion

Autologous pancreatic islet cell transplantation following total pancreatectomy for non-malignant conditions is proven and medically necessary per the UnitedHealth Group Transplant Review Guidelines: Solid Organ Transplantation.

Allogeneic islet cell transplantation is unproven and not medically necessary for the treatment of diabetes due to insufficient evidence of safety and/or efficacy.

Coverage may be reviewed when the treatment is:
- Performed under a clinical trial; and
- A clinical trial benefit exists; and
- The trial conforms to the provisions of that benefit.

Generally, since diabetes does not meet the definition of a life-threatening illness found in most commercial benefit plans, allogeneic islet cell transplants will not be covered even in patients with a life-threatening clause in their benefit plan. The benefit plan must be checked carefully for the definition of life-threatening illness and other coverage provisions for investigational, experimental and "promising but unproven" treatments.

Clinical Evidence

Lablanche et al. (2018) conducted a multicenter, open label, randomized controlled trial to assess the efficacy and safety of islet transplantation compared with insulin therapy in patients with type 1 diabetes. Eligible patients had severe hypoglycemia or hypoglycemia unawareness, or kidney grafts with poor glycemic control. Fifty patients were randomly assigned to immediate islet transplantation (n = 26) or insulin treatment (n = 24). The primary outcome was proportion of patients with a modified β-score of 6 or higher at 6 months after first islet infusion in the immediate transplantation group or 6 months after randomization in the insulin group. The primary analysis included all patients who received the allocated intervention; safety was assessed in all patients who received islet infusions. Median follow-up was 184 days in the immediate transplantation group and 185 days in the insulin therapy group. At 6 months, 64% of patients in the immediate islet transplantation group had a modified β-score of 6 or higher versus none of the 22 patients in the insulin group. At 12 months after first infusion, bleeding complications had occurred in 7% of infusions, and a decrease in median glomerular filtration rate from 90·5 mL/min to 71·8 mL/min was observed in islet recipients who had not previously received a kidney graft and from 63·0 mL/min to 57·0 mL/min in islet recipients who had previously received a kidney graft. The authors concluded that islet transplantation effectively improves metabolic outcomes. Although studies with longer-term follow-up are needed, islet transplantation seems to be a valid option for patients with severe, unstable type 1 diabetes who are not responding to intensive medical treatments. However, immunosuppression can affect kidney function, necessitating careful selection of patients.

A prospectively maintained database of patients undergoing total pancreatectomy with islet auto transplantation (TPIAT) was reviewed by Morgan et al. (2018). Islet function was inferred from daily insulin requirement. Pain relief was evaluated by healthcare use and narcotic use. Quality of life (QOL) was measured with the RAND 12-Item Short Form Survey. One hundred and ninety-five patients underwent TPIAT. Fifty-six (29%) patients had pancreatic operations before TPIAT, 37 (19%) patients were diabetic preoperatively, and 52 (27%) patients were smokers. Insulin independence was achieved in 29%, 28%, and 23% of patients at 1, 2, and 5 years postoperative. Nonsmokers with a shorter duration of chronic pancreatitis and no earlier pancreas operation were more likely to be insulin free. Median number of preoperative emergency department visits and hospitalizations were 6.6 and 4.3 annually, respectively, compared with 0 at 1, 2, and 5 years postoperative. Median oral morphine equivalents were 214 mg/kg pre-operation and 60, 64, 69, at 1, 2, 5 years postoperative. Preoperative, 1, 2, 5 years postoperative QOL scores were 29, 36, 34, and 33 (physical) and 39, 44, 42, and 42 (mental health). Genetic pancreatitis patients were more often narcotic free and had better QOL than patients with pancreatitis of other causes. At 5 years, overall survival was 92.3%. The authors concluded that total pancreatectomy with islet auto transplantation is a durable operation, with islet function, pain relief, and QOL improvements persisting to 5 years postoperative. Patients with genetic pancreatitis, short duration of disease, and nonsmokers have superior outcomes.

Health Quality Ontario (2015) sought to determine the clinical effectiveness of islet transplantation in patients with type 1 diabetes, with or without kidney disease. The authors conducted a systematic review of the literature on islet transplantation for type 1 diabetes, including relevant health technology assessments, systematic reviews, meta-analyses, and observational studies. The search yielded 1,354 citations that examined islet transplantation alone, islet-after-kidney transplantation, and simultaneous islet-kidney transplantation. Low to very low quality of evidence exists for islet transplantation in patients with type 1 diabetes with difficult-to-control blood glucose levels, with or without kidney disease. High quality of evidence exists for the specific glycemic control outcome of insulin independence compared with intensive insulin therapy. For patients without kidney disease, islet transplantation improves glycemic control and diabetic complications for patients with type 1 diabetes when compared with intensive insulin therapy. Results for health related QOL outcomes were mixed, and AEs were increased compared with intensive insulin therapy. For patients with type 1 diabetes with kidney disease, islet-after-kidney transplantation or simultaneous islet-kidney transplantation also improved glycemic control and secondary diabetic complications, although the evidence was more limited for this patient group. Compared with intensive insulin therapy, AEs for islet-after-kidney transplantation or simultaneous islet-kidney transplantation were increased, but were less severe than with whole pancreas transplantation. The authors concluded for patients with type 1 diabetes with difficult-to-control blood glucose levels, islet transplantation may be a beneficial therapy to improve glycemic control and secondary complications of diabetes. There is uncertainty in the estimates of effectiveness because of the generally low to very low quality of evidence.

Hering et al. (2016) evaluated the effectiveness and safety of a standardized human pancreatic islet product in patients in whom impaired awareness of hypoglycemia (IAH) and severe hypoglycemic events (SHEs) persisted despite medical treatment. A multicenter, single-arm, phase 3 study of the investigational product purified human pancreatic islets (PHPI) was conducted at eight centers in North America. Forty-eight adults with type 1 diabetes (T1D) for > 5 years, absent stimulated C-peptide, and documented IAH and SHEs despite expert care were enrolled. Each patient received immunosuppression and one or more transplants of PHPI. The primary end point was the achievement of HbA1c < 7.0% at day 365 and freedom from SHEs from day 28 to day 365 after the first transplant. The primary end point was successfully met by 87.5% of subjects at 1 year, and by 71% at 2 years. The median HbA1c level was 5.6% at both 1 and 2 years. Hypoglycemia awareness was restored, with highly significant improvements in Clarke and HYPO scores. No study-related deaths or disabilities occurred. Five of the patients experienced bleeds requiring transfusions, and two had infections attributed to immunosuppression. Glomerular filtration rate decreased significantly on immunosuppression, and donor-specific antibodies developed in two patients. The authors concluded that transplanted PHPI provided glycemic control, restoration of hypoglycemia awareness, and protection from SHEs in subjects with intractable IAH and SHEs. Safety events occurred related to the infusion procedure and immunosuppression, including bleeding and decreased renal function. They further state that islet transplantation should be considered for patients with T1D and IAH in whom other, less invasive current treatments have been ineffective in preventing SHEs. This is a single-arm study and further investigation is needed before clinical usefulness of this procedure is proven.

Kumar et al. (2016) performed a literature search for studies discussing any technical aspect of pancreatectomy with intraportal autologous islet transplantation (IAT). Thirty-five papers were included in the meta-analysis: all single-center case series. The indications, surgical approach to pancreatectomy with IAT, islet yield, static pancreas preservation prior to islet digestion, portal vein access, absolute islet infusion volumes, and portal venous pressure changes during transfusion were evaluated. The authors concluded that IAT is considered a "last resort" when alternative approaches have been exhausted. Pre-morbid histology and prior surgical drainage adversely influence islet yields and may influence the clinical decision to perform pancreatectomy and IAT. Following pancreas digestion, absolute numbers of islets recovered, and smaller islet size predict rates of insulin independence following IAT. Islet volumes and portal venous pressure changes are important factors for the development of complications. Surgical access for IAT includes intra-operative, immediate or delayed infusion via an "exteriorized" vein, and radiological percutaneous approaches.

The American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2022) states that islet auto transplantation should be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes. Both patient and disease factors should be carefully considered when deciding the indications and timing of this surgery. Surgeries should be performed in skilled facilities that have demonstrated expertise in islet auto transplantation.

Reference(s)

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Code	Description
0631T	Transcutaneous visible light hyperspectral imaging measurement of oxyhemoglobin, deoxyhemoglobin, and tissue oxygenation, with interpretation and report, per extremity

Hyperspectral imaging is unproven and not medically necessary for measurement of oxyhemoglobin, deoxyhemoglobin, and tissue oxygenation in patients with circulatory compromise due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Hyperspectral imaging is a noninvasive assessment that provides color coded maps of oxygenated tissue, allowing qualitative and quantitative measurements with high spectral resolution (Sen, 2018). Hyperspectral imaging (HSI) technology uses transcutaneous measurements of oxyhemoglobin (HT-Oxy) and deoxyhemoglobin (HT-Deoxy) concentrations by employing wavelengths of visual light that penetrate to 1 to 4 mm below the skin. By analyzing a wide spectrum of light rather than simply assigning primary colors, a two-dimensional, color-coded "oxygen map" is created. This device can be used as a noninvasive screening tool for determining tissue oxygenation and the severity of peripheral vascular disease (PVD) and critical limb ischemia (CLI).

HyperView™ (Hypermed Imaging, Inc.) is a handheld portable diagnostic imaging device that reports an approximate value of oxygen saturation, oxyhemoglobin level and deoxyhemoglobin level in superficial tissue. OxyVu (Hypermed Imaging, Inc.) was a cart-based mobile imaging system designed to assess oxyhemoglobin, deoxyhemoglobin and oxyhemoglobin saturation in superficial tissue but is no longer produced or sold.

Lopez-Moral et al. (2022) conducted a 1-year prospective cohort study to compare the potential healing prognosis of the different routine noninvasive techniques implemented in the International Working Group Diabetic Foot Guidelines with the use of HSO in patients with diabetic foot ulcers (DFUs). In 21 patients with a diabetic ulcer, HIS predicted ulcer healing with a sensitivity of 93% and a specificity of 71%. Transcutaneous oxygen pressure values showed the best diagnosis potential in 14 patients with wound healing with a sensitivity of 91% and a specificity of 100%. The authors concluded that HIS is a promising test to predict healing of diabetic ulcers, but in this study transcutaneous oxygen pressure predict ulcer healing the best. The authors noted that the results should be interpreted with caution due to the small study size and that further studies should be pursued to verify the healing prognosis of HAS in a larger sample size and use of a control group for comparison. Furthermore, the superiority of this tool, as compared to other clinical or imaging tools, also needs to be demonstrated.

Hayes, in a 2021 Evolving Evidence Review, reported there were no clinical studies or systematic reviews addressing the clinical validity or clinical utility of HIS for the assessment of peripheral artery disease (PAD) of the lower leg, nor were there any relevant guidelines or position statements identified. While formative research was identified, it does not provide data needed to inform the clinical application of HSI in this context, and whether it performs the same, worse, or better than clinical alternatives.

Kohler et al. (2021) performed a prospective observational study including 22 patients with soft tissue reconstruction to explore HSI as a new tool in flap monitoring to improve sensitivity compared to established monitoring tools. Flap perfusion was assessed by standard clinical parameters, Doppler ultrasound, and HSI on t0 (0 h), t1 (16–28 h postoperatively), and t2 (39–77 h postoperatively). HSI records light spectra from 500 to 1000 nm and provides information on tissue morphology, composition, and physiology. These parameters contain tissue oxygenation (StO2), near-infrared perfusion- (NIR PI), tissue hemoglobin- (THI), and tissue water index (TWI). Total flap loss was seen in n = 4 and partial loss in n = 2 cases. Every patient with StO2 or NIR PI below 40 at t1 had to be revised. No single patient with StO2 or NIR PI above 40 at t1 had to be revised. Significant differences between feasible (StO2 = 49; NIR PI = 45; THI = 16; TWI = 56) and flaps with revision surgery [StO2 = 28 (p <

0.0001). The authors concluded HSI provides valuable data in free fap monitoring. The technique seems to be superior to the gold standard of flap monitoring. StO2 and NIR PI deliver the most valuable data and 40 could be used as a future threshold in surgical decision making. The limitations of this study include its small sample size and the heterogeneity of the study's endpoint. Also, to improve selectivity in future studies with higher case numbers, the authors suggested that it may be of interest to split individual flap composition (fasciocutaneous, myocutaneous) and by the entity (e.g., ALT, latissimus dorsi, subscapular). Findings from this proof-of-concept study are however insufficient to demonstrate the validity and clinical utility of this technology.

Saiko et al. (2020) conducted a systematic review of HSI systems that have been assessed in patients, published over the past 32 years. The systematic review included 140 studies, including 10 different HSI systems. Current in vivo HSI systems generate a tissue oxygenation map. Tissue oxygenation measurements may help to predict those patients at risk of wound formation or delayed healing. No safety concerns were reported in any studies. A small number of studies have demonstrated the capabilities of in vivo label-free HSI, but further work is needed to fully integrate it into the current clinical workflow for different wound etiologies. The authors note that as an emerging imaging modality for medical applications, HSI offers great potential for non-invasive disease diagnosis and guidance when treating patients with both acute and chronic wounds. They however conclude that they were unable to draw any firm conclusions concerning the effectiveness of the described HSI techniques. Future hyperspectral imaging studies are required to more fully quantify the tissue-oxygenation-based assessment that can provide subclinical physiological status to combine with visual clinical assessment.

Ma et al. (2019) also conducted a systematic review which provided an overview of these current diagnostic techniques to determine tissue perfusion in patients with PAD and healthy controls. Twenty studies describing 10 different techniques were found. The authors identified two publications related to HSI, both of which described in detail below. The authors found while using contact-free methods, such as HSI, laser speckle contrast imaging (LSCI), or MRI, may be preferable, especially when patients have foot ulcers, newer diagnostic techniques, such as HIS and LSCI require additional larger prospective cohort trials to fully assess the effectiveness.

Chiang et al. (2017, included in Saiko 2020 and Ma 2019 systematic reviews above) compared the use of OxyVu to that of established modalities such as transcutaneous oxygen measurement (TCOM) and ankle-brachial index (ABI) in patients with peripheral vascular disease (PVD). 294 participants were recruited and divided into three distinct groups. Participants underwent measurements of lower limbs at a standardized point using the hyperspectral device generating outputs including HT-Oxy, HT-Deoxy, HT-Sat, TCOM and skin temperature. The authors state that HT-Sat was the most sensitive output as it took into account both the concentration of oxyhemoglobin and deoxyhemoglobin and concluded the study demonstrated reliability of the hyperspectral device in PVD patients when compared to other established methods and it could be a useful screening tool in PVD. Limitations included lack of a standardized tool for measurement thus reliance on clinical judgement, only two target points for area assessment, and that 25% of participants were active smokers which identified slightly higher ABI recordings. These findings do not however demonstrate the incremental clinical utility of this approach over other established non-invasive approaches.

Chin et al. (2011, included in Saiko 2020 and Ma 2019 systematic reviews above) conducted a diagnostic study on 126 patients to determine if HIS could accurately assess the presence or absence of PAD and accurately predict PAD severity. All patients underwent standard noninvasive lower extremity arterial flow studies, including measurement of the ankle-brachial index (ABI); segmental pressures for the upper thigh, lower thigh, calf, dorsalis pedis, posterior tibial, metatarsal, first digit areas, and second to fifth digits if first digit pressures were < 50 mm Hg and arterial Doppler waveforms of the dorsalis pedis and posterior tibial arteries. HSI data for participants was collected using the OxyVu system and the vascular technicians were blinded to the results. The primary comparative analysis showed no significant differences in hyperspectral oxyhemoglobin values for patients with versus without PAD. In contrast, the analysis of the deoxyhemoglobin values showed statistically significant differences for non-PAD vs PAD limbs. Data also suggested a significant correlation between deoxyhemoglobin values and ABI ($p = 0.001$). The authors concluded that HSI presents an interesting new development for the diagnostic imaging and evaluation of PAD but does not provide a breakthrough to replace existing bedside technology. Future study and understanding of how this technology works may identify it as a valuable tool for the prediction of wound healing in severely ischemic patients. The findings of this study do not demonstrate the incremental clinical utility of this approach over other established non-invasive approaches, such as ABI.

The U.S. Food and Drug Administration (FDA) cleared the HyperView™ Hyperspectral Tissue Oxygenation Measurement system under its 510(k) premarket notification process as substantially equivalent to predicate devices. For additional information, refer to:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K161237
https://www.accessdata.fda.gov/cdrh_docs/pdf16/K161237.pdf
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Code	Description
0647T	Insertion of gastrostomy tube, percutaneous, with magnetic gastropexy, under ultrasound guidance, image documentation and report

Percutaneous gastrostomy tube insertion by ultrasound guidance is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The percutaneous ultrasound gastrostomy is a novel procedure that has emerged as an alternative to a percutaneous endoscopic gastrostomy (PEG) or percutaneous radiological gastrostomy (PRG). It can be performed by a non-surgical provider at a patient's bedside.

Reis et al. (2022) conducted a prospective, observational, non-randomized cohort study to compare the safety and efficacy of percutaneous ultrasound guided (PUG) gastrostomy tube placement versus percutaneous radiologic gastrostomy (PRG) placement. The authors comparted 25 patients who sustained PUG placement between April 2020 and August 2020 with 25 patients who sustained PRG placement between February 2020 and March 2020. The PUG procedure was performed at bedside or in an interventional radiology (IR) suite without fluoroscopy. The PRG procedures were all performed in an IR suite with fluoroscopy. The analysis detected no statistical difference in the patient populations with the exception the PUG group ($p < .001$) had more COVID-19 patients. Intra-procedure pain medication usage was not statistically significantly different between groups ($p = 1.0$). Intra-procedure sedation was somewhat higher in the PUG group with midazolam 1.12 mg versus 0.8mg ($p = .355$). The PRG group had shorter procedure length of time ($p = .076$) than the PUG procedure (30.5 $\pm$14.1 minutes vs 39.7 $\pm$17.9 minutes). Each group had a techn8ilical success rate of 96% and complication rate of 8%. The researchers concluded that PUG is comparable to PRG gastrostomy tube placement with regards to complications but is a safe option for gastrostomy tube placement in patients who are critically ill. Limitations of the study included lack of randomization, non-contemporary controls, and a sample size too small to demonstrate non-inferiority with the established procedure.

In a prospective, single-arm clinical trial with historical matched controls, Accorsi et al. (2021) conducted a study of PUG insertion in 25 adult patients and compared its safety and efficacy to 25 patients who received PRG. Out of 150 adult patients referred to have PUG insertion, 25 adult patients were enrolled in this study. For comparison, a retrospective cohort of 25 patients who underwent PRG were selected based on score matched criteria. The setting for PUG insertion was either beside or in the IR department. Primary outcomes included procedural success and any post -procedural adverse event (AE) at 30 days. In secondary outcomes, sedation requirements, hospital length of stay, and procedural duration were included. According to the researchers results, procedural success rate was 100% for both PUG and PRG groups. Number of AEs statistically significantly different between the 2 groups: mild AEs ($p = 0.16$), moderate AE's ($p = 0.31$) and there were no severe AEs or 30-day procedure-related mortality. Except for 8 PRG insertions as they had no sedation, the sedation requirements showed no substantial difference in the PUG versus PRG group with Midazolam ($p = 0.35$) or Fentanyl ($p = 0.14$). The hospital length of stay was not significant different between the 2 groups ($p = 0.70$), but procedural duration was longer for PUG than PRG ($p < 0.001$). The researchers concluded that PUG is effective and safe in comparison to PRG. However, further prospective, randomized control trials studies are necessary to address limitations of small sample size, which may have been too small to demonstrate non-inferiority, outcomes of adverse events and operators with ultrasound experience versus non-experienced operators.

In a Clinical Evidence Assessment, ECRI (2021) concluded that evidence for PUMA-G for gastrostomy tube placement is inconclusive due to limited data. In comparison to PRG, the studies in the assessment suggested that PUMA-G is safe and effective. However, due to small sample size, limited retrospective design, lack of randomization, and single-center focus, further randomized, controlled studies which compare PUMA-G to other devices for gastrostomy tube placement are needed to address these gaps. (Authors Reis 2022 and Accorsi 2021 which are discussed in this policy, are included in this Clinical Evidence Assessment.)

In a report by Cool et al. (2020), the authors describe the initial first-in-human experience on five participants with the Percutaneous ultrasound gastrostomy (PUG). Experienced interventional radiologists used the Point-of-care Ultrasound Magnetically Aligned Gastrostomy kit (PUMA-G System) on all patients. This kit contained a reusable external handheld magnet, a single use orogastric balloon catheter which contained a bar magnet within the balloon and a coil tipped guidewire. The patients received prophylactic antibiotics and moderate sedation for the procedure. All five gastrostomy insertions proved success using the PUG technique without requiring conversion to a conventional fluoroscopic insertion technique. The participants were observed over a 30-day timeframe and found no short-term adverse outcomes. The authors concluded that the PUG technique provides a feasible method for removing the need for endoscopes and fluoroscopy; however, this is a novel technique with no RCTs or long-term data.

The US Food and Drug Administration (FDA) approved the PUMA-G system for gastrostomy insertions under 510(k) (K183057) on April 10, 2019. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm. (Accessed May 22, 2022).

For information on current clinical trials studying percutaneous ultrasound gastrostomy techniques, refer to www.clinicaltrials.gov. (Accessed May 22, 2022).

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Code	Description
0651T	Magnetically controlled capsule endoscopy, esophagus through stomach, including intraprocedural positioning of capsule, with interpretation and report

Magnetically controlled capsule endoscopy is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Geropoulos et al. (2021) performed a systematic review and meta-analysis looking at magnetically controlled capsule endoscopy (MCCE) versus conventional gastroscopy. The aim of this study is to systematically review the performance of magnetically controlled capsule endoscopy and evaluate its potential as a less invasive diagnostic method in the detection of gastric lesions. There were 7 studies were included, with a total of 916 patients and 745 gastric lesions. The mean capsule endoscopy examination time was 21.92 ±8.87 minutes. The pooled overall sensitivity of magnetically controlled capsule endoscopy was 87%. Subgroup analysis showed that the sensitivity of identifying gastric ulcers was 82% gastric polyps was 82% and gastric erosions was 95%. Magnetically controlled capsule endoscopy had minimal adverse events and was tolerated by most. MCCE its use in upper abdominal complaints due to the rapid passage of the capsule. The time of MCCE is also much longer than conventional gastroscopy. Authors note that the magnetically controlled capsule endoscopy demonstrated an acceptable sensitivity of identifying gastric lesions. But well-designed randomized studies are needed to identify the risks and benefits of this new technique, as well as to determine its role as a replacement for conventional gastroscopy. The study by Liao et al. (2016) described below is included in this systematic review.

Jiang et al. (2020) conducted a prospective single centered, blinded, randomized controlled trial comparing the clinical application of the second-generation MCCG with higher image resolution and frame rate for upper gastrointestinal tract compared with the first-generation. The first generation presented challenges including rapid transit time thru the esophagus and duodenum and longer gastric examination time. The second-generation MCCG (MCCG-2) was developed with higher image resolution and adaptive frame rate, and the authors aimed to evaluate its clinical availability for UGI examination in this study. Patients undergoing MCCG examination between May to June 2019 were prospectively enrolled and randomized to swallow the first-generation MCCG (MCCG-1) or MCCG-2 in a 1:1 ratio. The main outcomes included visualization of the esophagus and duodenum, operation-related parameters, image quality, maneuverability, detection of lesions, and safety evaluation. Eighty patients were enrolled. In the MCCG-2 group, frames captured for esophageal mucosa and Z-line were 171.00 and 2.00, significantly increased from those in the MCCG-1 group (97. and .00 .028, respectively). The gastric examination time was shortened from 7.78 ±.97 minutes to 5.27 ±.74 minutes, with the total running time of the capsule extended from 702.83 minutes to 1001.99. MCCG-2 also greatly improved the image quality and maneuverability No statistical difference existed in the detection of lesions between the 2 groups, and no adverse events occurred. MCCG-2 showed better performance in mucosal visualization, examination duration, and maneuverability, making better diagnosis of UGI diseases a possibility. There are limitations to this study including the lesion detection rate was not significantly different between the 2 groups mostly because of the small sample size, necessitating further large-scale studies to test the diagnostic ability compared with conventional endoscopy. Second, the assessment of maneuverability and image quality was in some way subjective, which may skew interpretation. Larger more robust studies are needed to validate MCCG as a promising examination modality for the entire GI tract.

In a comparative study, Liao et al.(2016) compared the performance of MCE with conventional gastroscopy in detecting gastric lesions. A magnetically controlled capsule endoscopy (MCE) system was designed to explore the stomach. A multicenter blinded study comparing MCE with conventional gastroscopy in 350 patients (mean age, 46.6 y), with upper abdominal complaints scheduled to undergo gastroscopy at a tertiary center in China from August 2014 through December 2014. All patients underwent MCE, followed by conventional gastroscopy 2 hours later, without sedation by an interventionist blinded to the findings of the MCE. The sensitivity, specificity, positive predictive value, and negative predictive value of detection of gastric focal lesions by MCE was calculated, using gastroscopy as the standard. MCE detected gastric focal lesions in the whole stomach with 90.4% sensitivity (95% confidence interval [CI], 84.7%-96.1%), 94.7% specificity (95% CI, 91.9%-97.5%), a positive predictive value of 87.9% (95% CI, 81.7%-94.0%), a negative predictive value of 95.9% (95% CI, 93.4%-98.4%), and 93.4% accuracy (95% CI, 90.83%-96.02%). MCE detected focal lesions in the upper stomach (cardia, fundus, and body) with 90.2% sensitivity (95% CI, 82.0%-98.4%) and 96.7% specificity (95% CI, 94.4%-98.9%). MCE detected focal lesions in the lower stomach (angulus, antrum, and pylorus) with 90.6% sensitivity (95% CI, 82.7%-98.4%) and 97.9% specificity (95% CI, 96.1%-99.7%). MCE detected 1 advanced gastric carcinoma, 2 malignant lymphomas, and 1 early-stage gastric tumor. MCE did not miss any lesions of significance (including tumors or large ulcers). Among the 350 patients, 5 reported 9 adverse events (1.4%) and 335 preferred MCE over gastroscopy (95.7%). There are study limitations including, the MCE preparation is slightly longer than conventional gastroscopy and it takes longer to perform an MCE (approx. 30 minutes). Lastly, the preference of MCE over gastroscopy observed in this study might be biased because the gastroscopy was performed without sedation. The author

notes that this novel MCE has a high diagnostic accuracy and is a promising alternative for patient-friendly screening for gastric diseases. Larger studies are needed to confirm the efficacy of this novel technique.

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Code	Description
0658T	Electrical impedance spectroscopy of 1 or more skin lesions for automated melanoma risk score

Electrical impedance spectroscopy for automated melanoma risk score is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Electrical impedance spectroscopy (EIS) is a device for the diagnosis of cutaneous lesions using a handheld probe with electrodes that are applied to tissue which emit alternating electric currents to measure electrical impedance differences between benign and malignant tissue. The device generates a numeric score, as well as a positive or negative result. The score is between 0 and 10 and with 0 being considered benign, and 10 malignant. This minimally invasive process does not impact future histopathological interpretation (Fried et al. 2020).

In the 2022 practice guideline for cutaneous melanoma, the National Comprehensive Cancer Network (NCCN) states that patients presenting with a suspicious pigmented lesion should undergo an excisional biopsy (elliptical, punch or saucerization). If excisional biopsy is inappropriate due to the location or the lesion is very large, a full thickness incisional or punch biopsy of the thickest portion is an acceptable option. In the common follow up recommendations for all patients, this guideline states that pre-diagnostic clinical modalities (i.e., total-body photography and sequential digital dermocopy), and other imaging technologies (et, reflectance confocal microscopy, electrical impedance spectroscopy) may enhance early detection of new primary melanoma in patients with a high mole count and/or the presence of clinically atypical nevi.

Kolla et al. (2022) conducted a pilot study to evaluate whether clinician diagnostic confidence, sensitivity, specificity and accuracy can be increased by adding EIS measurement scores to clinical and dermoscopic images of lesions clinically suspicious for melanoma. Three pigmented lesions specialists and three 4th-year medical students completed an online survey to evaluate 34 melanocytic lesions suspicious for melanoma. For each lesion, participants provided their diagnosis, biopsy recommendation, and confidence in diagnosing a lesion as benign or malignant based on history and clinical and dermoscopic images, and again after receiving an EIS score. The authors found that the addition of EIS scores increased mean biopsy sensitivity for melanoma/severely dysplastic nevi from 70% to 84% ($p = .014$) and mean diagnostic accuracy from 74% to 86% ($p = .005$). Mean diagnostic confidence increased for all histopathologic categories for both students and dermatologists (all $p < .05$). In this pilot study, the authors concluded that EIS increased novice and expert diagnosticians' confidence regarding dermoscopically equivocal melanocytic lesions. Further studies are needed to explore how EIS can help clinicians reassure patients regarding the management of clinically dysplastic melanocytic nevi. Limitations of the study include the small sample size of participants and the number of lesions included as well as the potential for selection bias in the choice of lesions reviewed in a clinical setting.

A Hayes Evidence Analysis Research brief, published in August 2021, found a review only of abstracts suggests that there is a sufficient quantity of published, peer-reviewed, human, clinical data to evaluate electrical impedance spectroscopy as an aid in the diagnosis of melanoma in a health technology assessment (HTA). A search of the peer-reviewed, published literature identified 5 clinical study abstracts evaluating EIS as a diagnostic aid for melanoma, including 3 cross-sectional studies and 2 cohort studies, all of which evaluated the clinical validity of EIS. Reference standards include dermoscopy (2 abstracts) and histopathology (3 abstracts). Full-text review is required to confirm abstract content and, therefore, conclusions about the safety and effectiveness of this technology cannot be made until a full assessment has been completed. (Whether an Evidence

Analysis Research Brief with a sufficient quantity of published literature will be considered for a full HTA is up to the discretion of the Scientific Directors and is based on whether the topic is an emerging, evolving, controversial, and/or disruptive technology, as well as overall client interest.) The analysis also showed 3 Clinical Trials in progress. For further details, refer to http://www.clinicaltrials.gov/.

Pathiraja and colleagues (2020) conducted a systematic review including a search of Embase Classic, Embase and Medline databases for studies conducted from 1980 to February 2018 that reported on the use of electrical impedance technology in the detection of pre-malignant and malignant conditions. The ability to distinguish between tissue types was defined as the primary endpoint, and other points of interest were also reported. After a search of 731 articles identified on this technology, 51 studies reported with sufficient data for analysis; 4 of the 51 studies focused on skin melanoma and NMSC (including the Malvehy trial mentioned below) . All four studies involved large-scale multicenter trials involving 2933 patients. All the trials were conducted in vivo, using a similar methodology. All the studies showed the electrical impedance technology was able to distinguish both melanomatous and non-melanomatous skin tumors with very high sensitivities > 95%. They also noted that the sensitivity of the technique increased further as the Breslow thickness of the malignant tissue increased. All the studies were also able to identify statistically significant differences between normal tissue, nonmalignant atypical lesions and non-melanomatous skin cancers. The authors concluded that electrical impedance technology provides a novel method for the detection of malignant tissue, with these large studies of skin cancer showing encouraging results. While these studies provided promising insights into the potential of this technology as an adjunct in screening, diagnosis and intra-operative margin assessment, the authors concluded that customized development as well as multi-center clinical trials need to be conducted before it can be reliably employed in the clinical detection of malignant tissue.

In a 2020 prospective study of 101 patients with 200 skin lesions, Sarac et al. evaluated the diagnostic accuracy of EIS for non-melanoma skin cancer, mainly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), however lesions with a clinical pre-diagnosis of sarcoma, melanocytic naevi, benign epithelial or dermal tumors were included. Patients had lesions excised, and EIS performed while in the operating room. Results showed a significant difference in the EIS mean scores between benign and malignant lesions. The standard deviation (SD) was significantly lower in benign lesions (6.18 ±2.1) than malignant tumors (8.02 ±1.3). There was no statistically significant difference in EIS scores between BCC and SCC. For malignant tumors, the median EIS scores ranged between 5 and 10. Nearly all epithelial malignant tumors had median EIS of 8; only invasive SCC had a median EIS of 9. In addition, the median score of cutaneous sarcomas was 10. The benign lesions (melanocytic naevi, neurofibroma, epidermal cyst and other benign lesions, including fibrous papules of the nose, syringoma and solar elastosis) had median EIS scores of 5 and lower. Although secondary excisions, seborrheic keratosis, and inflammatory reactions are categorized as benign lesions, they had median EIS scores of 6, 7.5 and 6.5, respectively. The authors concluded that while EIS showed good ability to differentiate between benign and malignant lesions, it does not replace the diagnostic gold standard which is histopathology. Instead, it can be used to support early clinical diagnosis. Additional prospective trials with larger numbers of tumors are required to test the sensitivity and specificity of this method.

In a 2019 clinical practice guideline of care for the management of primary cutaneous melanoma (CM), the American Academy of Dermatology acknowledged emerging diagnostic technologies, and stated that bedside diagnosis will continue to improve with further Investigation of existing, noninvasive imaging/electrical data acquisition and evaluation tools including electrical impedance spectroscopy combined with digital dermoscopy. Despite these emerging technologies, biopsy with histopathological examination remains the first step in establishing a definitive diagnosis of CM. (Swetter et al. 2019)

Svoboda et al. (2019) conducted a comparative study reviewing clinician accuracy for diagnosing melanoma on the basis of electrical impedance spectroscopy score plus morphology versus lesion morphology alone. In total, 164 dermatology trainees completed an online survey presenting clinical images of 45 pigmented lesions (28 benign, 17 melanoma). For each image, respondents were asked if they would recommend biopsy on the basis of morphologic assessment alone, and then asked again once presented with the corresponding EIS score (along with positive and negative predictive values4). The proportion of clinical decisions for which the addition of EIS score altered the decision to biopsy was calculated. In addition, the sensitivity, specificity, and proportion of missed melanomas and benign biopsies were determined for morphologic assessment alone and for morphologic assessment plus EIS score. Significance testing was performed using McNemar test for categorical variables and paired t tests for continuous variables. Overall, 7380 clinical decisions (164 respondents 3 45 lesions) were made on the basis of morphology alone and 7380 were made on the basis of morphology plus EIS score. The decision to biopsy was made in 4527 of 7380 cases on the basis of morphology alone and 4553 of 7380 cases on the basis of morphology plus EIS. The EIS results altered the individual biopsy decision in 24.3% of cases (Table I). The addition of the EIS score resulted in 402 fewer missed melanomas and a net decrease of 376 benign biopsies (p \ .001, Table II). When including the EIS score, the mean

sensitivity of respondents for ruling out melanoma increased from 80.7% to 95.2% (p \ .001) and mean specificity from 50.4% to 58.6% (p \ .001). A diagnostic device is only useful if it affects clinical management and improves accuracy. In this study, EIS score led to a change in the decision to biopsy in 25% of cases and improved diagnostic accuracy, resulting in fewer biopsies of benign lesions and more biopsies of melanomas, without significantly changing the total number of biopsies. A higher specificity was seen in this study compared with the EIS pivotal trial (58.6 vs 34.4%),4,5 which measured the specificity of the device alone. This suggests that respondents utilized the EIS information synergistically with the clinical image, rather than basing decisions solely on the EIS results. The authors concluded that EIS had a meaningful impact on the decision to biopsy pigmented lesions with atypical features. When combined with morphologic assessment, EIS score led to improved accuracy without significantly changing the overall biopsy rate.

A limitation of this study was that additional clinical data, such as patient history, risk factors, and dermoscopic images, were not available to participants. In addition, as this study only included trainees, the results might not extrapolate to more experienced clinicians.

In a 2018 Cochrane Systematic Review, Ferrante di Ruffano et al. reviewed the literature on the diagnostic accuracy of dermoscopy and spectroscopy-based computer- assisted (CAD) techniques for diagnosing skin cancer in adults. The objective was to determine the accuracy of CAD systems for diagnosing cutaneous invasive melanoma and atypical intraepidermal melanocytic variants, basal cell carcinoma (BCC) or cutaneous squamous cell carcinoma (cSCC) in adults, and to compare its accuracy with dermoscopy. Inclusion criteria consisted of studies of any design that evaluated CAD alone, or in comparison with dermoscopy, in adults with lesions suspicious for melanoma or BCC or cSCC and compared with a reference standard of either histological confirmation or clinical follow-up. Out of 42 studies that met the inclusion criteria, only two used EIS. The results showed across all CAD systems (including EIS) there was considerable variation in the hardware and software technologies used, the types of classification algorithms employed, methods used to train the algorithms, and which lesion morphological features were extracted and analyzed. This was true even between studies evaluating CAD systems. Meta-analysis found CAD systems had high sensitivity for correct identification of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in highly selected populations, but with low and very variable specificity. Regarding EIS specifically, Nevisense was the only system used in the two large prospective studies. These studies had overlapping recruitment periods and study centers, so there may have been overlap of participants. The results showed in a total of 2389 lesions with a finding of 368 melanomas, summary sensitivity of 97.0% (95% CI 94.7% to 98.3%) and specificity of 33.6% (95% CI 31.6% to 35.7%). Accuracy data for 226 invasive melanomas, showed a summary sensitivity of 98.2% (95% CI 95.4% to 99.3%) and specificity of 38.0% (95% CI 36.0% to 40.1%). 644 malignancies or highly dysplastic lesions, had a summary sensitivity of 93.5% (95% CI 91.3% to 95.1%) and specificity of 32.6% (95% CI 30.4% to 34.8%), including one Merkel cell carcinoma. Some benign lesions are more difficult to distinguish from malignancy using both Derm-CAD and Spectro-CAD systems, particularly seborrheic keratoses which proved problematic for the Nevisense system, however the reporting of benign diagnoses by CAD result was very poor. The authors concluded that in highly selected patient populations, all CAD types demonstrate high sensitivity and could prove useful as a back-up for specialist diagnosis to assist in minimizing the risk of missing melanomas. However, the evidence base is currently too poor to understand whether CAD system outputs translate to different clinical decision-making in practice. Insufficient data are available on the use of CAD in community settings, or for the detection of keratinocyte cancers. The evidence base for individual systems is too limited to draw conclusions on which might be preferred for practice.

On June 28, 2017, the Nevisense™ (SciBase III, Stockholm, Sweden) device received FDA clearance through the premarket approval process. This device is indicated for use on cutaneous lesions with one or more clinical or historical characteristics of melanoma, when a dermatologist chooses to obtain additional information when considering biopsy. Nevisense should not be used on clinically obvious melanoma. Nevisense is indicated only for use on:

- Primary skin lesions with a diameter between 2 mm and 20 mm;
- Lesions that are accessible by the Nevisense probe;
- Lesions where the skin is intact (i.e., non-ulcerated or non-bleeding lesions);
- Lesions that do not contain a scar or fibrosis consistent with previous trauma;
- Lesions not located in areas of psoriasis, eczema, acute sunburn, or similar skin conditions;
- Lesions not in hair-covered areas;
- Lesions which do not contain foreign matter;
- Lesions not on special anatomic sites (i.e., not for use on acral skin, genitalia, eyes, mucosal areas)

Refer to the following for complete information:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150046. (Accessed March 31, 2022).

For information on current clinical trials on the use of the Nevisense device, refer to https://www.clinicaltrials.gov/. (Accessed March 30, 2022).

Malvehy et al. (2014, included in the Pathiraja systematic review above) conducted an international, multicenter, prospective, and blinded clinical trial on the efficacy and safety of the Nevisense system in distinguishing benign lesions of the skin from melanoma compared to the histopathological gold standard (HSG). This took place at five sites in America, and 17 in Europe. Patients with an even distribution of low, medium, and high-risk skin lesions selected for total excision (to rule out melanoma) were asked to participate in the study. A total of 1,951 patients with 2,416 lesions were enrolled. 1,943 lesions were eligible for evaluation with the primary efficacy endpoint. All eligible skin lesions in the study were examined with the EIS-based Nevisense system, photographed, removed by excisional biopsy, and subjected to histopathological evaluation. The results showed of the 1,942 eligible lesions, 265 were cutaneous melanoma, 55 were non melanoma skin cancer (NMSC) including basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs). Nevisense correctly identified 256 melanomas, and all of the NMCs resulting in observed sensitivity of 96.6% and 100% respectively. Of 157 naevi with severe dysplasia, Nevisense gave a positive reading for 132 of them, seven out of eight actinic keratoses had a positive reading, and one Merkel cell carcinoma was correctly identified. Of the remaining 1457 lesions, 501 were diagnosed as negative, yielding an observed specificity of 34 4%. The positive predictive value (PPV) of Nevisense was 21 1% and the negative predictive value (NPV) was 98 2%. Only 3 adverse events were defined as definitely related to the device and were mild. The authors concluded that Nevisense has been shown to be an accurate and safe device that should be used in conjunction with the clinical risk assessment for patients with suspicion of melanoma in the intended use population.

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Code	Description
0664T	Donor hysterectomy (including cold preservation); open, from cadaver donor
0665T	Donor hysterectomy (including cold preservation); open, from living donor
0666T	Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor
0667T	Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor

Code	Description
0668T	Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary
0669T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each
0670T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each

Uterus transplantation is investigational, unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Absolute uterine factor infertility (AUFI) is a condition where a woman cannot get pregnant because she lacks a uterus which can be linked to either a congenital or acquired abnormality. AUFI affects approximately 3-5% of the female population. Uterus transplantation (UTx) has been introduced as a treatment option for these women but is currently considered experimental. Success of this procedure is not only defined by organ function but delivery of a healthy offspring (Brännström et al. 2018). Future studies are needed to further evaluate the safety and efficacy of UTx as well as to better define suitable donors and recipients.

A clinical evidence assessment from ECRI (2022) reveals the evidence for treating AUFI with UTx is inconclusive. Only one systematic review was found, and current available evidence lacked the volume of patients to conclusively characterized the risks and successes for the procedure. Additional robust studies are needed to further evaluate the safety and efficacy of this technology.

Fronek and colleagues (2021) reported results on ten patients receiving UTx which is a rapidly evolving solution for women with uterine infertility and a growing field of study. The study compared the efficacy of UTx from five deceased donors and five live donors. Recipients included for the trial had to meet the following criteria: 18-40 years of age with AUFI, desire for a child, current relationship with a male partner and in good health. All surgeries were open laparotomies with no intraoperative complications. Results demonstrated early uterine graft removal on two recipients due to thrombosis and one due to chronic rejection. Of the remaining seven recipients with viable uterine grafts, all seven underwent embryo transfers with five becoming pregnant; two of those five suffered miscarriages and three achieved a live birth (two from a live donor and one from a deceased donor). It was concluded that the study demonstrated mid-term viability of 70% of the uterine grafts and if UTx was performed, it should be considered for those women who have never given birth. Limitations included small number of participants, small number of viable births and graft loss.

Seven patients with uterine infertility were evaluated by Johannesson et al. (2015) after viable uteri following UTx. Six of the seven patients had AUFI due to congenital uterine agenesis and the other participant had undergone a hysterectomy due to cervical cancer. The transplanted uteri were from a patient's mother, sister or a family friend. Immunosuppression followed a standardized protocol and all recipients were initially seen in follow up twice a week for the first month and then every two weeks thereafter for 6 months. The follow up visits included routine blood tests, clinical examination of transplanted uterus, cervical culture and biopsies, transvaginal and abdominal ultrasounds along with doppler ultrasounds. A total of nine rejection episodes during the first postoperative year was found and successfully treated with temporary therapy and steroids. The authors concluded the levels of immunosuppression in addition to the low number of rejection episodes indicated a sufficient protocol was used to effectively suppress the immune system and avoid damage to the grafted uterus. In summary the authors felt the outcomes after one year demonstrated successful uterus transplant with continued menstruation and unaltered uterine artery blood flow. However, UTx is presently at its experimental stage and future research is warranted.

In a scientific paper from the Royal College of Obstetricians and Gynaecologists (Jones 2021), it suggests while UTx offers an alternative possibility for women with AUFI, it is still under investigation.
In a 2018 committee opinion, the American Society for Reproductive Medicine (ASRM) states uterus transplantation is an experimental procedure for the treatment of AUFI.

In a 2018 American College of Obstetricians and Gynecologists (ACOG) committee opinion on Müllerian agenesis, a congenital malformation, ACOG states that while uterine transplantation has resulted in live births, it is currently considered experimental and not widely available.

Clinical trials for uterus transplantation are currently ongoing. Refer to the following website for more information: https://clinicaltrials.gov/ct2/home. (Accessed March 17, 2022).

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Code	Description
0672T	Endovaginal cryogen-cooled, monopolar radiofrequency remodeling of the tissues surrounding the female bladder neck and proximal urethra for urinary incontinence
53860	Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence

Radiofrequency (RF) therapy, including but not limited to cryogen-cooled monopolar radiofrequency (CMRF), monopolar RF, multipolar RF, RF-lifting and temperature-controlled RF therapies for the treatment of stress urinary incontinence (SUI) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Transurethral and transvaginal radiofrequency therapy (RF) therapy involves the use of non-ablative thermal levels of radiofrequency energy for tissue remodeling by shrinking and stabilizing the endopelvic fascia, thus improving the support for the urethra and bladder neck. It is proposed that the RF causes an immediate retraction of existing collagen and subsequent activation of fibroblasts that results in the creation of new collagen (Viveve Solutions). RF therapies are proposed to treat SUI, however, there is insufficient published evidence from well-conducted, randomized, controlled trials that these treatments improve the net health outcome compared to other available treatments for stress urinary incontinence.

THERMIva™ is a non-surgical treatment that uses radiofrequency (RF) energy to gently heat tissue, without discomfort or downtime. THERMIva RF is FDA cleared for dermatological and general surgical procedures for electrocoagulation and hemostasis. THERMIva has FDA approval for dermatologic conditions, surgery, and surgical nerve alation. THERMIva has a CE Mark and EU Approved for Vulvovaginal Laxity or for treatment of loose tissues of the vulva and vagina. ThermiVa does not have FDA or EU approval for incontinence or the leaky bladder or rectum, atrophy or vaginal dryness, prolapse or fallen bladder/rectum, or orgasmic dysfunction.

The SURx Transvaginal System is a radiofrequency device that has been specifically designed as a transvaginal treatment of urinary stress incontinence. This device is no longer being marketed in the United States.
The Renessa System is a non-surgical radiofrequency device that uses a balloon catheter system to deliver low temperature radiofrequency energy to the submucosa of the bladder neck and urethra. The controlled heat applied by a radiofrequency

device, causes the tissue in the lower urinary tract to become firmer after healing and therefore, increases resistance to involuntary leakage. In 2013, Verathon acquired Renessa® by Novasys Medical®, and rebranded it as the Lyrette™ Transurethral SUI system.

In an Emerging Technology Report (ETR) from Hayes (2021) regarding the Viveve System for stress urinary incontinence (SUI), Hayes noted that other radiofrequency devices have been used in the past to treat SUI but that they were more invasive probes and that the systems are no longer being used to treat SUI due to safety concerns. The ETR indicated that the Viveve System is currently being used off label for vaginal rejuvenation procedures and that Viveve Medical is expected to seek specific marketing clearance in the US for treatment of SUI pending results from the Prospective US Radiofrequency SUI Trial (PURSUIT, NCT04720352) clinical trial that is currently recruiting. The report concluded that additional published evidence from the larger randomized PURSUIT trial is needed to characterize the magnitude and duration of benefit of the Viveve System in reducing SUI symptoms.

The National Institute for Health and Care Excellence (NICE) Transvaginal laser therapy for stress urinary incontinence Interventional procedures guidance indicates that the evidence on long-term safety and efficacy is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page. Further research should report long-term safety and efficacy outcomes, the type of laser and energy used, treatment protocols, and patient selection including age, menopausal status and severity of stress urinary incontinence (2021).

Stachowicz et al. (2021) performed a comprehensive literature review for articles pertaining to RF energy use in women for genitourinary complaints with regard to stress urinary incontinence (SUI), genitourinary syndrome of menopause (GSM), female sexual dysfunction (FSD), and overactive bladder (OAB). By altering the approach and location of energy application, many new devices have been marketed for treatment of conditions such as SUI, GSM, FSD, and OAB. Available studies demonstrate promising efficacy and favorable safety; however, interpretation of studies is greatly limited by poor study quality and reporting. Currently, it appears that RF energy can potentially treat a variety of genitourinary conditions, but more robust data are needed to substantiate evidence-based use.

The American College of Obstetricians and Gynecologists (ACOG) issued a Committee Opinion (2020) noting that the FDA has not cleared or approved any energy-based medical device for the treatment of vaginal symptoms related to menopause, urinary incontinence or sexual function. They recommend prospective studies that use validated measures of quality of life, body image and sexual function to understand the true benefits and harms of these procedures be done by those without a financial interest in the outcomes.

Allan et al. (2020) conducted a twelve-month single site, randomized, unblinded feasibility study investigating the effectiveness of CMRF as a treatment for female SUI. The study included 35 women with 21 of them receiving one treatment and 14 receiving two treatments. Twenty-five women completed the 12-month follow-up, with 9 women dropping out of the first group and 3 women dropping out of the second group. The authors concluded that this feasibility study indicates there is promising efficacy and safety of CMRF therapy for treating SUI although there was a decrease in efficacy noted between 6 months and 12 months post-procedure; however, this study did not show benefit from a second CMRF treatment at 6 weeks. The percentage of women showing a > 50% reduction from baseline in leakage volume at 12 months was similar between groups. Limitations that the authors noted include the age and weight disparity between the groups in that the first group had a mean age of 41.0 years and a lower BMI (24.5) while the second group was older with a mean age of 46.1 years and an average BMI of 26.0. They also noted that there were 3 women in group 2 who were post-menopausal while group 1 had none. The authors recommend additional studies with a larger number of women, inclusion of a sham treatment group, longer time between treatments and a longer follow-up period.

In the VIveve Treatment of the Vaginal Introitus to Evaluate Effectiveness (VIVEVE I) randomized controlled trial (RCT), Krychman et al. (2017) evaluated the safety and efficacy of surface-cooled, monopolar radiofrequency therapy for the treatment of vaginal laxity. The prospective, single-blinded, sham-controlled study involved 186 women treated in nine study centers in Canada, Italy, Spain and Japan. The active treatment group included 108 women who completed the study while the sham group included 56 women who completed the study. No vaginal laxity was achieved by 43.5% of the treated group and 19.6% of the control group and the treated group also showed greater improvement in sexual function. The authors concluded that a single treatment of CMRF was found to be safe and was associated with improved vaginal laxity and improved sexual function. Limitations of the study noted by the authors include the small sample size, the short (6 month) follow up period, the lack of a

control for multiplicity of secondary end points and that the number of participants was not consistent with two of the sites contributing the majority of the subjects.

Lalji and Lozanova (2017) conducted a prospective, multi-center, non-randomized study evaluating the safety and efficacy of monopolar radiofrequency treatment for addressing mild to moderate SUI as well as vulvo-vaginal laxity. The study included 27 women who were treated with 3 once-weekly sessions that included intra-vaginal treatment then treatment of labia majora and the perineum. The authors noted that the treatments were well tolerated with no adverse events observed. Improvement in the SUI condition was evaluated weekly and at a 1-month follow-up visit. Sixteen women (59.3%) reporting decrease in the amount of leakage with 15 women (55.6%) becoming leak free at the 1-month visit. Data assessing vulvo-vaginal laxity were collected before the first treatment and at the 1-month follow-up visit with 100% of the women reporting improvement on the non-standardized subjective vulvo-vaginal laxity questionnaire (VVQL). The authors reported that 1 month after the last treatment, all participants (100%) evaluated their vulvo-vaginal sensation to be slightly, moderately, or very tight. They stated that future studies with longer follow-up are needed to understand how the results develop over time as the collagen remodeling process takes up to 90 days to fully complete and that further controlled study is needed to confirm the data. Limitations of the study include the small sample size, the short follow-up period and the lack of a control group.

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

Kang et al. (2015) conducted a systematic review of randomized and quasi-randomized trials of transurethral radiofrequency collagen denaturation versus no treatment/sham treatment, conservative physical treatment, mechanical devices, drug treatment, injectable treatment for urinary incontinence (UI) or other surgery for UI in women. The authors sought to compare the transurethral radiofrequency collagen denaturation (TRCD) versus no treatment/sham treatment, conservative physical treatment, mechanical devices, drug treatment, injectable treatment for UI or other surgery for UI in women. The review included one small sham-controlled randomized trial of 173 women performed in the United States. Participants enrolled in this study had been diagnosed with stress UI and were randomly assigned to transurethral radiofrequency collagen denaturation (treatment) or a sham surgery using a non-functioning catheter (no treatment). Mean age of participants in the 12-month multi-center trial was 50 years (range 22 to 76 years). Of three patient-important primary outcomes selected for this systematic review, the number of women reporting UI symptoms after intervention was not reported. No serious adverse events were reported for the transurethral radiofrequency collagen denaturation arm or the sham treatment arm during the 12-month trial. Owing to high risk of bias and imprecision, the authors downgraded the quality of evidence for this outcome to low. The effect of transurethral radiofrequency collagen denaturation on the number of women with an incontinence quality of life (I-QOL) score improvement ≥ 10 points at 12 months was as follows: RR 1.11, 95% CI 0.77 to 1.62; participants = 142, but the confidence interval was wide. For this outcome, the quality of evidence was also low as the result of high risk of bias and imprecision. The authors found no evidence on the number of women undergoing repeat continence surgery. The risk of other adverse events (pain/dysuria (RR 5.73, 95% CI 0.75 to 43.70; participants = 173); new detrusor overactivity (RR 1.36, 95% CI 0.63 to 2.93; participants = 173); and urinary tract infection (RR 0.95, 95% CI 0.24 to 3.86; participants = 173) could not be established reliably as the trial was small. Evidence was insufficient for assessment of whether use of transurethral radiofrequency collagen denaturation was associated with an increased rate of urinary retention, hematuria and hesitancy compared with sham treatment in 173 participants. The GRADE quality of evidence for all other adverse events with available evidence was low as the result of high risk of bias and imprecision. The authors found no evidence to inform comparisons of transurethral radiofrequency collagen denaturation with conservative physical treatment, mechanical devices, drug treatment, injectable treatment for UI or other surgery for UI. The authors concluded it is unknown whether transurethral radiofrequency collagen denaturation, as compared with sham treatment, improves patient-reported symptoms of UI. Evidence is insufficient to show whether the procedure improves disease-specific quality of life. Evidence is also insufficient to show whether the procedure causes serious adverse events or other adverse events in comparison with sham treatment, and no evidence was found for comparison with any other method of treatment for UI.

To assess treatment efficacy and quality of life in women with stress urinary incontinence 3 years after treatment with nonsurgical transurethral radiofrequency collagen denaturation (Renessa), Elser et al. performed a prospective study including 139 women with stress urinary incontinence due to bladder outlet hypermobility. Radiofrequency collagen denaturation was performed using local anesthesia in an office setting. Assessments included incontinence quality of life (I-QOL) and urogenital distress inventory (UDI6) instruments. In total, 139 women were enrolled and 136 women were treated (mean age 47 years). At 12 months, significant reductions existed from baseline in the median number of daily (-0.61) and weekly (-4.0) leaks caused by

activity, and 50% of the subjects experienced at least 50% fewer leaks compared with baseline (52% of evaluable participants). (Elser 2009) At the 18-month follow-up, data were available on 60 women (44%). The study found incontinent episodes decreased whereas quality of life and participant satisfaction with the procedure increased (Elser 2010). At 36 months, 63 patients were lost to follow-up and 76 patients remained. With the intent-to-treat analysis (n = 139) revealed significant improvements in quality of life at 36 months. Mean I-QOL score improved 17 points from baseline (p = .0004), while mean UDI-6 score improved (decreased) 19 points (p = .0005). The authors concluded that transurethral collagen denaturation is a low-risk, office-based procedure that results in durable quality-of-life improvements in a significant proportion of women for as long as 3 years. The long-term durability of this minimally invasive procedure in women with SUI may be a beneficial intervention for women with this condition who wish to avoid or postpone surgery. The results also confirm that the treatment has a good safety profile, with no serious adverse events reported at any time during this or previous trials. Limitations of this study include the dropout rate with regard to patients completing all of the in-office assessments and a lack of a control group. (Elser 2011)

Appel et al., (2006) performed a prospective, randomized, controlled clinical trial to demonstrate the 12 months safety and efficacy of transurethral radiofrequency energy (RF) collagen micro-remodeling in women with stress urinary incontinence (SUI). Women with SUI, bladder outlet hypermobility, and leak point pressure (LPP) > or = 60 cmH (2)O were randomized to RF micro-remodeling or "sham treatment." Adverse events (AEs) were recorded. 110 women underwent RF micro-remodeling and 63 underwent virtually identical "sham treatment" (with the exception of RF delivery). The 12 months RF micro-remodeling safety profile was statistically no different than that of sham treatment (a brief bladder catheterization). Seventy-four percent of women with moderate to severe baseline SUI experienced > or = 10 point I-QOL score improvement at 12 months (p = 0.04). Women who underwent RF micro-remodeling demonstrated LPP elevation at 12 months, while sham treated women demonstrated LPP reduction (p = 0.02). The authors concluded non-surgical, transurethral RF micro-remodeling is a safe treatment for women with SUI. In women with moderate to severe SUI, this novel therapy resulted in statistically significant improvement in quality of life of a magnitude associated with patient satisfaction with the treatment. Women who underwent RF micro-remodeling demonstrated a statistically significant elevation in mean LPP at 12 months.

In 2006, the U.S. Food and Drug Administration (FDA) approved the Viveve® System under its 510(k) premarket notification process as substantially equivalent to predicate devices for use in general surgical procedures for electrocoagulation and hemostasis. (501K 1254). In 2002, the SURx® Transvaginal System received marketing clearance through the U.S. Food and Drug Administration (FDA) 510 (k) process for shrinkage and stabilization of female pelvic tissue for treatment of Type II stress urinary incontinence due to hypermobility in women not eligible for major corrective surgery. (K020126) This device is no longer being marketed in the United States. Refer to the following website for more information (use product code GEI): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm (Accessed March 23, 2022).

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Code	Description
0692T	Therapeutic ultrafiltration

The use of aquapheresis (ultrafiltration) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Aquapheresis (ultrafiltration) is a method of removing excess salt and water from the body and assists in restoring proper fluid balance for patients with fluid overload unresponsive to medical management.

The 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure does not provide specific recommendations for ultrafiltration (UF) for the treatment of heart failure (HF), but notes that “many aspects of ultrafiltration including patient selection, fluid removal rates, venous access, prevention of therapy-related complications, and cost require further investigation”.

Wobbe et al. (2021) conducted a systematic review and meta-analysis on the impact of UF therapy in hospitalized patients with acute decompensated heart failure (ADHF). Eight RCTs were included which consisted of 801 participants. Several different types of UF devices were used which included the Aquadex System 100, NxStage System One and the PRISMA System. Primary outcomes included amount of fluid removal, number of patients re-hospitalized for heart failure during follow-up and the incidences of adverse effects; secondary outcomes included weight loss and all-cause mortality. The authors found UF effectively removed a larger volume of fluid without significantly changing the patient’s serum creatinine; in addition, it showed a reduction in the risk of worsening heart failure and a reduction in readmissions to the hospital. They concluded that UF was a valid alternative treatment to diuretics with improvement of quality of life, however the lack of physician experience and associated costs are obstacles to the widespread use of this technique; and additional studies are needed to investigate the adverse occurrences for UF. Limitations included protocol differences amongst the interventions, potential bias with funding, heterogeneity for certain outcomes due to small number of studies and search term adaptability to locate study selection.

Wang et al. (2021) conducted a meta-analysis to assess the safety and efficacy of UF. A total of 12 studies were included which contained 1197 patients that were over the age of 18 and had a diagnosis of acute heart failure; in each of the 12 studies there was an ultrafiltration group of patients and a group on diuretics. Outcomes assessed were all-cause rehospitalizations, fluid and weight loss, adverse events and mortality. The authors found that UF was more effective at removing fluid than diuretics; this was contributed to the speed and duration of fluid and that it could be more easily controlled for specific patient conditions. In addition, the patients in the study had already been exposed to diuretics thus possibly decreasing their efficiency. There was inconsistent agreement about which group had more adverse effects, but the authors agreed rehospitalization for heart failure patients was less for the UF group. The conclusion was UF appears to be suitable for certain kinds of patients but, future studies should identify what types of patients are best suited to receive UF and the safety and efficacy of its use. Limitations included a high heterogeneity about weight loss and lack of information to assess the bias of the RCTs. [This review is included in Wobbe (2021)].

A recent ECRI report states that Aquadex SmartFlow™ (previously FlexFlow) is a blood ultrafiltration system to provide life support by replacing renal function in children with critical kidney failure or fluid overload (ECRI 2021). The findings are however inconclusive due to too few data on outcomes and comparisons in addition to high risk of bias due to lack of controls. In 2016, Costanzo et al. conducted the Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial. The authors tested the theory that heart failure patients treated with UF would have a longer period of time to their first heart failure event within 90 days of discharge than those who had received adjustable intravenous loop diuretics (ALD).

Secondary outcomes were classified as efficacy, clinical, and safety variables. Out of 224 patients, 110 were randomized into a group receiving UF and 114 into a group receiving ALD; three patients withdrew before the study started. The Aquadex FlexFlow System was utilized for the UF group and received UF at an average rate of 138 ±47 ml/h for an average of 80 ±53 hours. The ADL group of participants received an average dose of furosemide-equivalent intravenous loop diuretic of 271.26 ±263.06 mg for an average of 100 ±78 hours. After 90 days, out of 221 patients, 165 completed the study, 31 died, 9 were lost to follow-up, 3 withdrew consent, 7 were removed due to medical reasons identified by their physician and 6 did not finish due to other causes. Analysis of the data showed the UF group tended to have a longer first time to a heart failure event but experienced a larger number of adverse events. The results should be interpreted with caution as the study was prematurely terminated by the sponsor before its completion against the opinion of the study's Steering Committee. Furthermore, serious adverse events deemed to be related to study therapy occurred in a higher number of patients in the aquapheresis than in the diuretic group (16 [14.6%] vs. 6 [5.4%]; p = 0.026), raising concerns about the safety of this therapeutic approach. [This trial is included in Wobbe (2021) and Wange (2021)].

For the multicenter Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, Bart et al. (2012) evaluated the efficacy and safety of ultrafiltration (UF) compared to stepped pharmacologic care for the treatment of patients with persistent congestion and worsening renal function. 188 patients with a diagnosis of acute decompensated heart failure (ADHF) and worsening renal function defined by an increase serum creatinine of ≥ 0.3 mg/dL from baseline were randomized into two groups. For the UF group, fluid status was managed by the Aquadex System 100 at a rate of 200 mL/h and continued until the patients' signs and symptoms of congestion were improved. For the pharmacologic group, care to increase, decrease or continue current diuretic doses was dependent on urine output and clinical response. Daily assessments were done until signs and symptoms of congestion were optimized. The authors found that the stepped pharmacologic approach was superior to UF on the primary outcome (bivariate change from baseline in the serum creatinine level and body weight). While there were similar amounts of weight loss between the two approaches, UF was associated with a higher rate of serious adverse events (72% vs. 57%, p = 0.03). [This trial is included in Wobbe (2021) and Wange (2021)].

In the UNLOAD trial, Costanzo et al. (2010) analyzes UF against standard intravenous (IV) diuretics in hospitalized patients with volume overloaded HF. Two hundred participants with heart failure were randomized into two groups; one group received IV diuretics and the other UF (Aquadex System 100). Furthermore, the diuretic group was split into two: one group received continuous IV diuretics and the other IV bolus diuretics. Primary outcomes were weight loss and dyspnea assessment forty-eight hours after randomization. Secondary endpoints included fluid loss at 48 hours, functional capacity, rehospitalizations, and unscheduled visits in 90 days. The authors found that more patients treated with UF had successful results, as indicated by fewer rehospitalizations and unscheduled office or ED visits. Another key finding was that hypokalemia occurred less frequently in the UF group versus those treated with continuous IV diuretic infusion. Limitations included number of participants, lack of blinding thus introducing bias along with inadequacy of dosing of the diuretics for patients. The authors concluded that even though UF was associated with less rehospitalizations, additional randomized studies are needed.

Clinical trials of aquapheresis and ultrafiltration are currently ongoing. Refer to the following website for more information: https://clinicaltrials.gov/ct2/home (accessed March 17, 2022).

In a 2010 guideline, the Heart Failure Society of America (HFSA) indicates ultrafiltration is another option to consider when congestion fails to improve in response to diuretic therapy. However, this recommendation is based on expert opinion due to lack of clinical evidence available.

In an International Network of Agencies for Health Technology Assessment (INAHTA) brief, the U.S. Department of Veterans Affairs (VA) determined if ultrafiltration should be used for VA patients with decompensated heart failure (2010). Their conclusion indicated additional research is needed with greater population, blinded studies and long-term follow up.

On February 24, 2020, the FDA granted premarket approval for the Aquadex FlexFlow® System (K192756) for continuous ultrafiltration therapy for temporary or extended use in adult and pediatric patients weighing 20 kilograms or more whose fluid overload is unresponsive to medical management, including diuretics. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192756.pdf. (Accessed March 17, 2022)

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Code	Description
0694T	3-dimensional volumetric imaging and reconstruction of breast or axillary lymph node tissue, each excised specimen, 3-dimensional automatic specimen reorientation, interpretation and report, real-time intraoperative

Clinical Evidence

Three-dimensional volumetric imaging and reconstruction of breast or axillary lymph node tissue is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

There are no widely accepted techniques for breast volume measurement due to a lack of information regarding the accuracy and comparability of each method. Many have not met the requirements of reproducibility, patient compliance, and cost efficiency, which has limited the use of breast volume measurement methods in routine clinical practice.

Killaars et al. (2020) conducted a clinical assessment comparison study. In this study the investigators evaluated whether the Vectra XT 3D imaging system is a reliable tool for determination of breast volume in clinical practice. It was compared with the current gold standard in literature, magnetic resonance imaging (MRI) and current clinical practice. Breast volumes of 29 patients (53 breasts) were evaluated. 3D images were acquired by Vectra XT 3D imaging system. Pre-existing breast MRI images were collected. Both imaging techniques were used for volume analyses, calculated by two independent investigators. Breast volume estimations were done by plastic surgeons during outpatient consultations. All volume measurements were compared using paired samples t-test, intra-class correlation coefficient, Pearson's correlation, and Bland–Altman analysis. The authors concluded that the 3D imaging system measures lower volumes for breasts than MRI. However, 3D measurements show a linear association with MRI and had excellent reliability, making them an objective and reproducible measuring methods suitable for clinical practice. The study did not aim to investigate the reproducibility of plastic surgeon's estimation. The answers obtained were limited to this study design. Future research should focus on reproducibility of plastic surgeon's estimation of breast parameters to see if 3D breast volumes are superior in the clinical assessment of breasts. This could increase the clinical utility of 3D imaging for breast assessment and could represent an important step toward a more standardized approach to breast surgery.

Lee et al. (2016) conducted a retrospective review on 25 patients to determine the validity of 3D scanning technology and software for evaluating breast volume. Bilateral breast volumes were obtained preoperatively by three methods: the water-displacement technique, MRI-based volumetry, and 3D scanning using the Axis Three scanner. Due to a lack of MRI performance on some patients, 7 specimens were not recorded, leaving only 18 specimens of the removed breast tissue for comparison to the 3D scan. The authors analyzed the various methods used noting the cost effectiveness of each, the length of each procedure, the impact for the patient and sensitivity of the equipment. The authors found the 3D scan to have excellent reliability when compared to the water-displaced and MRI methods. Limitations of the study included a small number of

patients, retrospective review, lack of standardization in the points for the 3D scan, and potential errors in calculation of breast weight. Future studies of the 3D scan are warranted and should include verification and validation of the use of the 3D scan, more robust RCTs and long-term outcomes.

Reference(s)

Killaars et. al. Clinical Assessment of Breast Volume: Can 3D Imaging Be the Gold Standard? Plast Reconstr Surg Glob Open. 2020 Nov 25;8(11). Lee WY, et al. Three-dimensional surface imaging is an effective tool for measuring breast volume: a validation study. Arch Plast Surg. 2016 Sep;43(5):430-7.

Code	Description
0766T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, initial treatment, with identification and marking of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; each additional nerve (List separately in addition to code for primary procedure)
0767T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, initial treatment, with identification and marking of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; first nerve
0768T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, subsequent treatment, including noninvasive electroneurographic localization (nerve conduction localization), when performed; first nerve
0769T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, subsequent treatment, including noninvasive electroneurographic localization (nerve conduction localization), when performed; each additional nerve (List separately in addition to code for primary procedure)

Transcutaneous magnetic stimulation (tMS) by focused low-frequency electromagnetic pulse for the treatment of chronic pain is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Hayes (2022) published an Evolving Evidence Review for Axon Therapy (Neuralace Medical Inc.) for Chronic Nerve Pain. The report indicated that a review of the evidence suggests that the quantity of published, peer-reviewed clinical data is insufficient to evaluate this technology for the treatment of chronic nerve pain in adults. No relevant systematic reviews addressing the use of Axon Therapy (NeuraLace Medical Inc.) for the treatment of chronic neuropathic pain were identified.

Leung and colleagues (2014) stated peripheral nerve injury can result in the formation of neuroma/nerve entrapment, a persistent peripheral neuropathic pain state that is often refractory to invasive interventions or medications; thus; there is a need to develop innovative non-invasive therapy in treating post-traumatic peripheral neuropathic pain states. A new intervention, transcutaneous magnetic stimulation (tMS), is derived from the use of transcranial magnetic stimulation in which a rapid discharge of electric current is converted into dynamic magnetic flux for modulating neuronal functions. In a case-series study, low-frequency (0.5 Hz) tMS was developed over the site of neuroma/nerve entrapment in 5 patients who have failed both steroid injection and conventional pain medications; 400 pulses of stimulation were delivered per treatment session. Each patient received 3 to 4 sessions of treatment over a period of 2 months. Pre- and post-intervention spontaneous pain levels were evaluated with NRS; 5 patients with post-traumatic neuroma/nerve entrapment pain received the treatment. Average pre- and post-scores (±SD) on the NRS were 5.00 (±1.41) and 0.80 (±1.10), respectively, with an average pain reduction of 84 (±21.91) % in the NRS after 3 to 4 treatments within 2 months. This analgesic effect appeared to be sustainable with repeated treatment delivered at a 6- to 8-week duration. Pre-treatment tactile allodynia found in 3 patients resolved after the initial 2-month treatment sessions. The authors concluded that tMS offered a non-invasive therapeutic option for neuroma-related neuropathic pain conditions. Moreover, these researchers stated that RCTs are needed to validate the efficacy of this treatment modality; additional studies are also needed to examine the underlying electrophysiological mechanisms of the observed analgesic benefit.

Reference(s)

Hayes, Inc. Evolving Evidence Review. Axon Therapy (Neuralace Medical Inc.) for Chronic Nerve Pain. Lansdale, PA: Hayes, Inc., August, 2022.

Leung A, Fallah A, Shukla S. Transcutaneous magnetic stimulation (TMS) in alleviating post-traumatic peripheral neuropathic pain states: a case series. Pain Med. 2014 Jul;15(7):1196-9.

Code	Description
31634	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, with assessment of air leak, with administration of occlusive substance (e.g., fibrin glue), if performed

Bronchoscopic treatment of bronchopleural or bronchoalveolar fistulas with an occlusive substance, such as fibrin glue, is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

A retrospective study of patients with prolonged air leaks (PAL) who underwent customized endobronchial silicone blocker (CESB) placement was conducted by Mehta et al. (2018). The air leak was localized using a balloon occlusion test. The CESB was uniquely designed by molding silicone stent pieces into a conical shape, deployed with rigid bronchoscopy into the appropriate segment, and reinforced with cyanoacrylate glue to prevent migration. In patients with alveolopleural fistulae (APF), pleurodesis was performed after leak resolution to prevent recurrence. Following this, the CESB was removed after 6 weeks. Forty-nine CESBs were placed in 31 patients. The PALs included APF (n = 16), bronchopleural fistula (n = 14), and airway-mediastinal fistula (n = 1). The average diameter of the CESB used was 7.9±2.9 mm. There was resolution of the PAL in 26 of 31 patients (84%). The CESB migrated in 5 patients with no adverse events. Pleurodesis was performed in 13 of 16 patients with APF, to prevent recurrence. No other significant complications were observed. The authors concluded that CESBs represent a safe, effective approach in the management of PAL. This is an uncontrolled study with a small sample size.

Tsilimigras and colleagues (2017) conducted a systematic review to investigate the role and the efficacy of BioGlue® in these scenarios. Twelve studies with a total number of 194 patients were included. One hundred seventy-eight patients were treated for alveolar air leaks (AAL), 14 for BPF and 2 for lymphatic leaks. BioGlue® was utilized at the time of initial operation in 172 (96.7%) patients for AAL, while at secondary intervention in 13 (92.9%) for BPF and 1 (50%) for lymphatic leak. In the AAL cases, only 2 out of 4 studies showed statistically significant reduction in duration of air leak, duration of intercostal drainage and length of stay when BioGlue® was applied. The authors concluded that although BioGlue® has been shown to be efficient in treating AAL; it should be used with caution against BPF. It has low bio absorbability and its non-autologous nature can trigger an inflammatory response. There is a risk of toxicity and lung fibrosis as well. Due to the small sample of patients, no definite conclusions concerning its efficacy can be drawn. Future randomized controlled trials are warranted to establish its benefit in current clinical practice.

Cardillo et al. (2015) retrospectively reviewed the records of 3,832 patients who underwent pulmonary anatomic resections. The overall incidence of BPFs was 1.4%. Primary bronchoscopic treatment was performed in 35 of 52 patients with a fistula of less than 1 cm and with a viable stump. The remaining 17 patients underwent primary operation. The fistula was cured with endoscopic treatment in 80% and with operative repair in 88.2%. Cure rates were 62.5% after pneumonectomy and 86.4% after lobectomy. The cure rate with endoscopic treatment was 92.3% in very small fistulas, 71.4% in small fistulas, and 80% in intermediate fistulas. The cure rate after surgical treatment was 100% in small fistulas, 75% in intermediate fistulas, and 100% in very large fistulas. The authors concluded that bronchoscopic approach shows promising results in all but the largest BPFs and that very small and intermediate fistulas with a viable bronchial stump can be managed endoscopically, using mechanical abrasion, polidocanol sclerosing agent, and cyanoacrylate glue. Bronchoscopic treatment can be repeated, and if it fails, does not preclude subsequent successful surgical treatment. The study is limited by its retrospective design.

West et al. (2007) conducted a meta-analysis of six case series to address whether bronchoscopic or other minimal access approaches to the closure of BPFs were effective compared to a conventional re-thoracotomy. There was a 30% cure rate using a range of bronchoscopic techniques including cyanoacrylate or fibrin glue application, YAG laser therapy, injection of the vein sclerosant polidocanol and racheo-bronchial stenting. The mortality was 40% in these patients reflecting the very high mortality with BPFs. Many patients required multiple bronchoscopic procedures and further drainage procedures. The authors noted

that, at the time, bronchoscopic treatment for BPF's had so far only been reported in small case series but may offer further treatment options in patients too unwell to undergo re-thoracotomy.

American Association for Thoracic Surgery (AATS) consensus guidelines for the management of empyema associated with BPF recommend that in context of empyema:

- Closure of BPFs should be attempted with a combination of primary closure and buttressing with a well vascularized transposed soft-tissue pedicle.
- Transposition of the omentum is preferred over skeletal muscle flaps or mediastinal soft tissue, and this should be attempted after the purulent fluid has been drained completely and the pleural cavity has a surface of granulation tissue. (Shen et al., 2017).

The guidelines note that bronchoscopic interventions (including cyanoacrylate-based glue, fibrin compounds, gelatin sponges, chemical cautery, endobronchial silicon spigots and submucosal injection of tissue expanders) have been used in some centers with mixed results based on several case reports and small series.

Reference(s)

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West D, Togo A, Kirk AJ. Are bronchoscopic approaches to post-pneumonectomy bronchopleural fistula an effective alternative to repeat thoracotomy? Interact Cardiovasc Thorac Surg. 2007 Aug;6(4):547-50.

Code	Description
33274	Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (e.g., fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (e.g., interrogation or programming), when performed
33275	Transcatheter removal of permanent leadless pacemaker, right ventricular, including imaging guidance (e.g., fluoroscopy, venous ultrasound, ventriculography, femoral venography), when performed

Right ventricular leadless pacemakers are unproven and not medically necessary for treating cardiac arrhythmias due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Leadless pacemakers (LPs) are much smaller than traditional pacemakers and do not require surgery to implant. They are delivered directly into the ventricle of the heart through the femoral vein using a steerable catheter that eliminates the need to surgically create a pocket for the pacemaker and leads. The devices are designed to be retrievable so they can be repositioned during implantation and later retrieved if necessary. Although short- and intermediate-term nonrandomized studies and registries have demonstrated good safety, efficacy, and procedural feasibility, no randomized controlled trials have yet been performed comparing a leadless system to a transvenous pacing system.

The Micra™ Transcatheter Pacemaker System (TPS) (Medtronic) received FDA premarket approval (PMA) (P150033) on April 6, 2016. On January 15, 2020 the FDA approved a supplement (S061) to the original PMA approving the Micra™ AV Transcatheter Pacing System. Additional information is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P150033. (Accessed May 13, 2022).

The Aveir™ VR Leadless Pacemaker System (Abbott) received FDA premarket approval (PMA) (P150035) on March 31, 2022. Aveir is a modification of the Nanostim device removed from the market due to premature battery depletion. Additional

information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150035. (Accessed May 13, 2022).

An ECRI report concluded that evidence from a systematic review of low-quality studies, a case series, and a prospective case series of primarily observational studies of the Nanostim device, suggests the Aveir LP may be an effective pacemaker, but the evidence is not sufficient to determine how well this device works compared with other leadless devices or transvenous pacemakers (ECRI, 2022).

A Hayes report evaluated the safety and efficacy of the Micra TPS as an alternative to traditional transvenous pacemakers for the management of patients with bradycardia or atrioventricular block. The report concluded that the evidence is of low quality due to study limitations and relatively limited follow-up periods. Additionally, the lack of evidence directly evaluating patient-centered outcomes limits conclusions that can be made as to the clinical significance of any benefits introduced by use of the device. Due to these limitations, there remains substantial uncertainty regarding the safety and efficacy of the device for the treatment of adult patients indicated for single-chamber pacing, and the overall conclusion of the report was that there is potential but unproven benefit for this device. Well-designed and well-conducted controlled trials with longer follow-up are needed to compare this device with transvenous pacemakers (Hayes, 2022).

Ngo et al., 2021 performed a systematic review and meta-analysis to evaluate the safety and efficacy of right ventricular LPs. The primary safety outcome was major complications, and the primary efficacy end point was acceptable pacing capture threshold (≤2 V). The authors identified 36 observational studies of Nanostim and Micra LPs, with most (69.4%) reporting outcomes for the Micra device. Eight studies used the same cohort as other included studies but reported outcomes at different follow-up times, leaving 28 studies with unique patient cohorts. For Micra, the pooled incidence of complications at 90 days (n = 1608) was 0.46% (95% CI, 0.08%–1.05%) and at 1 year (n = 3194) was 1.77% (95% CI, 0.76%–3.07%). In 5 studies with up to 1-year follow-up, Micra was associated with 51% lower odds of complications compared with transvenous pacemakers (3.30% versus 7.43%; odds ratio [OR], 0.49; 95% CI, 0.34–0.70). At 1 year, 98.96% (95% CI, 97.26%–99.94%) of 1376 patients implanted with Micra had good pacing capture thresholds. For Nanostim, the reported complication incidence ranged from 6.06% to 23.54% at 90 days and 5.33% to 6.67% at 1 year, with 90% to 100% having good pacing capture thresholds at 1 year (pooled result not estimated because of the low number of studies). Although these findings are promising, the data were entirely observational, and most studies had a small sample size and short follow-up time of less than one year. Further results from well-designed randomized controlled trials with longer follow-up time are needed to determine longer-term safety and efficacy of LPs to support the widespread adoption of these novel devices in clinical practice. (Tjong 2018b, Duray 2017, Roberts 2017, Reynolds 2016, Ritter, 2015, Reddy 2015, Knops 2015 and Reddy 2014, previously cited in this policy, are included in the Ngo systematic review.)

European Society of Cardiology guidelines on cardiac pacing and cardiac resynchronization therapy make the following recommendations:

- LPs should be considered as an alternative to transvenous pacemakers when no upper extremity venous access exists or when risk of device pocket infection is particularly high, such as previous infection and patients on hemodialysis (IIa, B).
- LPs may be considered as an alternative to standard single lead ventricular pacing, taking into consideration life expectancy and using shared decision-making (IIb, C).

Although a promising technology, potential retrieval issues at the end of service are a limitation. Data from randomized controlled trials is needed to compare clinical outcomes between leadless pacing and traditional single-chamber transvenous pacing (Glikson et al., 2021).

An ECRI report concluded that evidence from nonrandomized studies comparing Micra VR with transvenous pacemakers shows that Micra works well for delivering ventricular pacing in patients with bradycardia from atrioventricular (AV) block or sinus node dysfunction. Nevertheless, studies are needed to validate Micra for AV-synchronous pacing and longer-term pacing (> 2 years) and to compare it with other leadless systems (ECRI, 2020).

Dar et al. (2020) reported a comparison of the retrieval process for Nanostim versus Micra transcatheter LPs. The list of retrievals for the Micra TPS was obtained from Medtronic, whereas Nanostim data was obtained from centers that participated in the Leadless II study. Details of retrieval such as indication, days post implantation, complications, and post procedure device management were obtained from the manufacturer database for each site, and any missing details were obtained from individual operators. Extractions performed on the same day were labeled as “Early” and thereafter were labeled as “Late.” A

total of 113 retrievals were attempted (73 in Nanostim and 40 in Micra TPS). The most common reasons for retrieval were battery advisory and inadequate pacing threshold (n = 16) for Nanostim and Micra, respectively. Success rate in Nanostim group was around 90% (66/73) compared with 100% in Micra group (p = 0.049). Late retrieval occurred in 50% of Micra TPS cases (20/40) compared with 100% of Nanostim LP cases. Median time to extraction was 46 days for Micra TPS and 256 days for Nanostim LP (p < 0.001). Rate of serious adverse events with Nanostim extraction was 3% (n = 2/73). The authors concluded that overall, LPs extraction is feasible and safe to perform irrespective of the duration and type of the device.

The prospective MARVEL 2 (Micra Atrial tRacking using a Ventricular accELerometer 2) study assessed the performance of an automated, enhanced accelerometer-based algorithm downloaded to the Micra LP for up to 5 hours in patients with AV block. The primary efficacy objective was to demonstrate the superiority of the algorithm to provide AV synchronous (VDD) pacing versus VVI-50 pacing in patients with sinus rhythm and complete AV block. The primary safety objective was to demonstrate that the algorithm did not result in pauses or heart rates of > 100 beats/min. Seventy-five patients from 12 centers were enrolled; an accelerometer-based algorithm was downloaded to their LPs. Among the 40 patients with sinus rhythm and complete AV block included in the primary efficacy objective analysis, the proportion of patients with ≥ 70% AV synchrony at rest was significantly greater with VDD pacing than with VVI pacing (95% vs. 0%; p < 0.001). The mean percentage of AV synchrony increased from 26.8% (median: 26.9%) during VVI pacing to 89.2% (median: 94.3%) during VDD pacing. There were no pauses or episodes of oversensing-induced tachycardia reported during VDD pacing in all 75 patients. The authors noted the observational period and sample size of this study were limited and might not reflect the total variability of use conditions in the long term. Thus, results must be confirmed in larger patient populations with longer follow-up (Steinwender et al., 2020).

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society guidelines on the evaluation and management of patients with bradycardia state that pacing with entirely leadless devices is an emerging area of interest that requires further investigation before incorporation into clinical practice (Kusumoto et al., 2019).

A NICE report concluded that the evidence on the safety of leadless cardiac pacemaker implantation for bradyarrhythmias shows that there are serious but well-recognized complications. The evidence on efficacy is inadequate in quantity and quality (NICE, 2018).

Tjong et al. (2018a) conducted a propensity score-matched analysis to provide a balanced comparison of leadless and transvenous single-chamber pacemaker (PM) therapies. Leadless patients from 3 experienced leadless implant centers were propensity score matched to VVI-R patients from a contemporary prospective multicenter transvenous PM registry. A total of 635 patients were match-eligible (leadless: n = 254; transvenous: n = 381), of whom 440 patients (median age 78 years; interquartile range 70-84 years; 61% men) were successfully matched (leadless: n = 220 vs transvenous: n = 220). The complication rate at 800 days of follow-up was 0.9% (95% confidence interval [CI] 0%-2.2%) in the leadless group vs 4.7% (95% CI 1.8%-7.6%) in the transvenous group when excluding PM advisory-related complications (p = .02). When including these PM advisory-related complications, the complication rate at 800 days increased to 10.9% (95% CI 4.8%-16.5%) in the leadless group vs 4.7% (95% CI 1.8%-7.6%) in the transvenous group (p = .063). As participants in the two cohorts were included from different medical centers, quality of care and experience, as well as unmeasured patients' factors, may explain some of the differences in complication rates between groups.

The LEADLESS II IDE trial is an ongoing prospective, multicenter, international observational study to confirm the safety and effectiveness of the Aveir Leadless Pacemaker System in individuals indicated for ventricular demand pacing.

Reference(s)

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Code	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
93264	Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional
C2624	Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components

Implantable wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring (e.g., CardioMEMS) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Notes:
- Monitoring – for members with an existing implanted device, monitoring is a covered service
- Removal – removal of an implantable wireless pulmonary artery pressure sensor is a covered service in the rare instance when it might be required

The CardioMEMS HF System (Abbott) is a wireless monitoring sensor implanted into the pulmonary artery during a minimally invasive right heart catheterization. The system is designed to remotely measure and communicate pulmonary artery pressure (PAP) to guide heart failure (HF) management with the goal of reducing hospitalizations.

The CardioMEMS HF System received U.S. Food & Drug Administration (FDA) premarket approval (P100045) on May 28, 2014. The device was originally indicated for wirelessly measuring and monitoring PAP and heart rate in New York Heart Association (NYHA) class III HF patients who have been hospitalized for HF in the previous year. On February 21, 2022, the FDA approved

an expanded indication to include patients with NYHA class II HF who have been hospitalized for HF in the previous year and/or have elevated natriuretic peptides.

Clinical Evidence

Thakker et al. (2022) performed a systematic review and meta-analysis evaluating the role of remote PAP monitoring devices in patients with New York Heart Association (NYHA) class III or greater HF. Both randomized and non-randomized studies were included. Five trials identifying baseline characteristics were included in the systematic review and 2 trials evaluating hospitalization rates were included in the meta-analysis. Baseline characteristics included an average age of 64.6 years, male predominance, mean BMI of 29.6, predominance of HFrEF, hypertension the most prevalent comorbidity and a mean PA pressure of 27.2 mm Hg. In the meta-analysis, there were 401 hospital admissions, with 168 in the treatment group and 233 in the control group. The follow-up periods ranged from 90 days to 12 months. There was a total of 64 adverse events, mostly non-serious. Patients who underwent remote pulmonary artery monitoring were less likely to be hospitalized compared with patients who did not (Odds Ratio: 0.52; 95% Confidence Interval 0.39, 0.69). Study limitations include varied study periods across trials and lack of randomization in some trials as well as lack of analysis of possible biases in the reviewed studies. (The CHAMPION study noted below is included in the review.)

A Hayes technology assessment concluded that low-quality evidence suggests the use of CardioMEMS implantable hemodynamic monitor as an adjunct to standard care for managing adult patients with symptomatic NYHA class III HF failure benefits health outcomes by leading to a consistent reduction of hospitalization risk and mean PAP values with some improvements in cardiac function. However, data on the effects of the device on mortality and health-related quality of life (QOL) were inconclusive due to inconsistent findings, short duration of follow-up and variability in reported outcome measures. The device appears to be safe and poses no major risks. Additional large well-designed comparative studies that conduct long-term assessments extending beyond 1-year post implantation are needed (Hayes, 2022).

An ECRI report concluded that evidence shows that CardioMEMS monitoring is safe and reduces hospitalizations in patients with moderate HF. However, reports of electric and fire hazard related to CardioMEMS interrogation devices raise safety concerns. Until these are addressed, physicians and patients should exercise caution. The current evidence is too limited in quality and quantity to determine how CardioMEMS affects mortality, physical function and QOL. The data is also insufficient to determine whether CardioMEMS benefits patients with mild HF and how CardioMEMS compares with other HF monitoring systems (ECRI, 2022).

CHAMPION

The multicenter, pivotal CHAMPION trial evaluated patients with NYHA class III HF and a previous hospital admission for HF. Patients were randomly assigned to management with a CardioMEMS system (treatment group) or to a control group. In the treatment group, clinicians used daily measurement of PAP in addition to standard of care versus standard of care alone in the control group. The primary efficacy endpoint was the rate of HF-related hospitalizations at 6 months. The safety endpoints assessed at 6 months were freedom from device-related or system-related complications and freedom from pressure-sensor failures. All analyses were by intention to treat. At 6 months, 83 HF-related hospitalizations were reported in the treatment group (n = 270) compared with 120 in the control group (n=280; rate 0.31 versus 0.44, hazard ratio [HR] 0.70, 95% CI 0.60-0.84, p < 0·0001). At the end of 6 months, clinicians continued to receive PAP information for an additional 13 months. During the entire follow-up (mean 15 months [SD 7]), the treatment group had a 39% reduction in HF-related hospitalization compared with the control group (153 versus 253, HR 0.64, 95% CI 0.55-0.75; p < 0·0001). Eight patients had device-related complications and overall freedom from device-related complications was 98.6% (97.3-99.4) compared with a prespecified performance criterion of 80% (p < 0·0001); and overall freedom from pressure-sensor failures was 100% (99.3-100.0). The study design was not powered beyond the primary 6-month outcomes. Additional limitations include lack of analysis on cardiac-specific mortality and single blinding which has the potential to introduce investigator bias during communication with patients. Participants in the control group were allowed to crossover to the treatment group and receive CardioMEMS at 18 months. In this group, the authors reported sustained efficacy of hemodynamic-guided management of HF to reduce hospital admissions, both during a randomized clinical trial setting, as well as in a follow-up setting more typical of clinical practice (Abraham et al., 2011; Abraham et al., 2016). Clinicaltrials.gov NCT00531661.

GUIDE-HF

The GUIDE-HF trial (Lindenfeld et al., 2021) evaluated whether hemodynamic-guided management using remote PAP monitoring could reduce HF events and mortality in patients with HF across the spectrum of symptom severity, including

patients with elevated natriuretic peptides but without a recent HF hospitalization. The randomized arm of 1000 patients was a multicenter, single-blind study at 118 centers in the U.S. and Canada. Following successful implantation of a PAP monitor, patients with all ejection fractions, NYHA class II–IV HF, and either a recent HF-related hospitalization or elevated natriuretic peptides were randomly assigned (1:1) to either hemodynamic-guided HF management based on PAP (n = 497) or standard of care (n = 503). The primary endpoint was a composite of all-cause mortality and total HF events (HF-related hospitalizations and urgent HF-related hospital visits) at 12 months assessed in all randomly assigned patients. Safety was assessed in all patients. There were 253 primary endpoint events (0·563 per patient-year) in the treatment group and 289 (0·640 per patient-year) in the control group (hazard ratio [HR] 0·88, 95% CI 0·74–1·05; p = 0·16). The overall study analysis did not show a benefit of hemodynamic-guided management of HF on the primary outcome of mortality and HF events compared with the control group. However, a pre-COVID-19 impact analysis showed a possible benefit for the primary endpoint, driven by a reduction in HF hospitalizations. The authors reported no apparent benefit on all-cause mortality at 12 months. Study limitations include single blinding which has the potential to introduce investigator bias during communication with patients, the 12-month duration of follow-up and the effects of the COVID-19 pandemic in limiting data collection. The trial also includes an ongoing, single-arm, observational study (n = 2600). Clinicaltrials.gov NCT03387813.

PASSPORT-HF

PASSPORT-HF is an ongoing prospective, randomized, multicenter trial evaluating the effects of a hemodynamic-guided, HF nurse-led care approach using the CardioMEMS HF-System. Clinicaltrials.gov NCT04398654

Joint clinical practice guidelines from the American Heart Association, American College of Cardiology and the Heart Failure Society of America on the management of HF make the following recommendations regarding remote monitoring (Heidenreich et al., 2022):

- 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 guideline-directed medical therapy (GDMT) with optimal device therapy, the usefulness of wireless monitoring of PAP by an implanted hemodynamic monitor to reduce the risk of subsequent HF hospitalizations is uncertain.
- In patients with NYHA class III HF with a HF hospitalization within the previous year, wireless monitoring of the PAP by an implanted hemodynamic monitor provides uncertain value.

Further study of these devices is needed before they can be recommended for routine clinical care.

Class of Recommendation: 2b (weak). Level of Evidence: B-R (moderate-quality evidence from one or more randomized controlled trials or meta-analysis of such studies)

A National Institute for Health and Care Excellence (NICE) report concluded that evidence on the safety and efficacy of percutaneous implantation of pulmonary artery pressure sensors for monitoring treatment of chronic heart failure is adequate to support using this procedure provided that standard arrangements are in place for clinical governance, consent and audit (NICE, 2021).

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Code	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
53453	Periurethral transperineal adjustable balloon continence device; removal, each balloon
53454	Periurethral transperineal adjustable balloon continence device; percutaneous adjustment of balloon(s) fluid volume

Transperineal periurethral balloon continence devices (e.g., ProAct™) are unproven and not medically necessary for the treatment of urinary incontinence due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

According to the manufacturer (Uromedica Plymouth, Minnesota), the ProACT system is used 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. The device consists of two adjustable balloon implants placed bilaterally at the bladder neck or at the apex of the prostatic remnant. The ACT® device is used for women, and the balloons are surgically placed on either side of the bladder neck, providing compression. The ACT device is currently in clinical trials and not available in the United States. A normal amount of effort is still required to urinate, and the pressure from the balloons will help guard against unintentional urine loss, such as during a sneeze or cough.

On November 24, 2015, the ProACT device received FDA Premarket Approval as a Class III device. Further information may be found at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P130018. (Accessed April 5, 2022)

An ECRI 2021 Clinical Evidence Assessment focused on ProACT's safety and effectiveness and how ProACT compares with artificial urinary sphincters (AUSs) or other adjustable continence balloons (ACBs). This review encompassed a search of literature published January 1, 2016, through September 22, 2021. One systematic review by Larson (2019) was reviewed with meta-analysis reporting on 1,264 patients. Although evidence from many case series synthesized in a meta-analysis supports limited conclusions on ProACT's safety and effectiveness—that ProACT relieves SUI in most treated men through 3.5-years mean follow-up—failure and complication rates may outweigh benefits for more than one-fifth of treated patients. No evidence is available to compare ProACT with full-cuff AUSs, ACBs, or other devices marketed in the United States for treating SUI in men after prostate surgery. ECRI's search of ClinicalTrials.gov for relevant ongoing trials identified a single-arm U.S. post approval study that may not address the evidence gaps. NCT03767595. Multicenter controlled trials that directly compare ProACT with other ACBs, AUSs, and other treatment options for SUI are needed. An ongoing single-arm study will assess long-term (five-year) adverse events (AE) and QOL scores. The report overall conclusion is that evidence for this device is inconclusive.

Munier et al. (2020) conducted a two center retrospective case series of 26 patients implanted with the ProACT device to treat persistent stress urinary incontinence (SUI) after radical prostatectomy who had insufficient improvement from sub urethral slings. The primary endpoint was continence, defined as 0 pads per day (PPD). The secondary endpoints were 50% decrease in PPD and increases in the Incontinence Quality of Life score (IQOL). Refilling and complications were also reported. The mean follow-up was 36 months (±20; min 14-max 128). Five patients have had adjuvant radiotherapy (18%). All patients presented with persistent stress urinary incontinence, using 2.3 PPD (±1; min 1-max 6), and only one sling was removed due to infection. 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 PPD decreased from 2.6 to 1. The average IQOL score of those 8 patients increased by 20 points, from 53.4 up to 74.2 (p = .005). Overall, 26 patients (96.3%) were improved. The remaining patient was not implanted because of an intraoperative urethral injury and is considered a failed case (3.7%). He had instead an AUS implantation. Three patients (14.8%) needed peri-urethral balloon replacement. The authors concluded that ProACT

implantations are effective and without significant complications. This study is limited by a small number of participants, and a lack of a comparison group.

A 2020 Hayes Health Technology Assessment report on the ProACT device implantation for the treatment of post-prostate surgery induced urinary incontinence (UI) in adult men unresponsive to 6 to 12 months of more conservative treatment found an overall low-quality body of evidence that demonstrated improvement from baseline in key clinical outcomes among men receiving ProACT implantation. The body of evidence lacks controlled studies to determine if the ProACT device is similar, better, or worse than other available treatments with respect to patient outcomes. Single-arm studies consistently reported improvements from baseline in some key clinical outcomes. Other patient outcomes were assessed by too few studies or assessed inconsistently across studies, precluding firm conclusions. Available evidence regarding potential harms suggests that the ProACT device may be associated with a moderate risk of complications, including revision and explanation; however, there is insufficient evidence to determine the relative safety of the ProACT device compared with other available treatments (Hayes, 2020).

Angulo and colleagues (2019) completed a systematic review and meta-analysis on adjustable devices ATOMS and ProACT. The objective of this study was to assess efficacy and safety of Adjustable Transobturator Male System (ATOMS) compared to Adjustable Continence Therapy (proACT) for male SUI according to literature findings. 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). Significant heterogeneity was evidenced, due to variable incontinence severity baseline, difficulties for a common reporting of complications, different number of adjustments and time of follow-up and absence of randomized studies. Despite the limitations that studies available are exclusively descriptive and the follow-up is limited, the authors concluded that literature findings confirm ATOMS is more efficacious, with higher patient satisfaction and better durability than ProACT to treat male stress incontinence.

Nash et al. (2019, included in Angulo systematic review above) presented a paper with the 4-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 SUI. The clinical study involved 11 clinical sites. A total of 124 subjects met study criteria and 123 were implanted with ProACT. Baseline and outcomes for 68 patients who completed 4-year follow-up visits are 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. The results showed statistically significant improvements during follow-up 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. One procedure-related SAE (retention) was reported among the 68 subjects; the SAE was resolved without clinical meaningful sequalae. The authors concluded that these results confirm the long-term safety and efficacy of this newly FDA-approved therapy, showing significant improvements in both objective and subjective measures of SUI in mild, moderate, and severely incontinent male patients. They also note that the implant procedure is minimally invasive, and complications are generally mild and easily resolvable. These findings are limited by the lack of a comparison group and a large loss to follow up.

Noordhoff et al. (2019, included in Angulo systematic review above) conducted a retrospective multicenter case series to evaluate the outcome of adjustable continence balloons in the treatment of SUI after transurethral resection of the prostate (TURP). In two tertiary centers, adjustable continence balloons were implanted in 29 patients with post-TURP SUI between 2007 and 2018. Endpoints of this were patient-reported changes in pad count and complications. Dry was defined as no pad or one security pad. Preoperative UI was mild in 7 (24%), moderate in 12 (41%), and severe in 10 (35%) patients. The median follow-up duration was 21 months. The results showed within 30 days postoperatively, a Clavien-Dindo grade less than or equal to II complication occurred in 24% of the patients. Reintervention rate was 24%. Six and 12 months after implantation, the International Prostate Symptom Score (IPSS) quality-of-life item improved significantly from 5 preoperatively to 3 and 1, respectively. At last visit (median 21 months after implantation), the outcome on continence had improved in 76% of the patients, including, 45% dry patients. After a median follow-up of 28 months, all but one patient reported improvement on the Patient Global Impression of Improvement (PGI-I) scale. In detail, 10 patients reported "very much better" condition compared

with before the implantation, 10 patients "much better," two patients "a little better," and one patient "no change." Daily pad use decreased from three (IQR, 2-5) to one (IQR, 0-2) pads/day ($p < 0.001$). According to the authors, this is the first study reporting results of adjustable continence balloons in the treatment of post-TURP SUI. They concluded that the therapy was found to be safe and efficient. These findings are limited by lack of comparison group and small sample size.

A report from the 6th International Consultation on Incontinence, regarding the surgical treatment of post- prostatectomy stress urinary incontinence (PPUI) in men, states that AUS is the preferred treatment for men with moderate to severe SUI after radical prostatectomy (RP). Male slings are an acceptable approach for men with mild to moderate SUI. Injectable agents have a poor success rate in men with SUI. Although there are several series reporting the outcomes of different surgical interventions for PPUI, there is still a need for prospective randomized clinical trials. Recommendations for future research include standardized workup and outcome measures, and complete reporting of adverse events at long-term (Averbeck 2019).

Larson (2019, included in Angulo systematic review above) performed a systematic review and meta-analysis of adjustable continence therapy for the treatment of male stress urinary incontinence. Nineteen studies (n = 1264) met inclusion criteria. No randomized controlled trials were identified and no data on controls were presented. Patients used 4.0 (95% confidence interval [CI] 2.6 to 5.4) pads per day prior to implantation and 1.1 (95% CI 0.5 to 1.7) pads per day post-implantation. Incontinence quality of life improved by 30.8 points from baseline to post-implantation. Post-implantation, 60.2% of patients were considered "dry" and 81.9% of patients were considered "dry" or improved greater than 50%. The rate of intraoperative perforation of the bladder or urethra was 5.3%, the rate of infection was 2.2%, and the rate of urinary retention was 1.5%. The estimated overall all-cause revision rate was 22.2% during a mean follow-up of 3.6 years. The findings are limited by lack of data from any comparison interventions.

In 2019 American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) published guidelines for incontinence after prostate treatment. The guidance indicates:

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

The guidelines note, “While the adjustable balloon devices have been shown to improve incontinence, providers should be aware of an increased incidence of intraoperative complications and need for explanation within the first two years compared to the male sling and artificial urinary sphincter (AUS). Given the limited clinical experience of implanters across the United States, providers should obtain specialty training prior to device implantation.” In addition, the 2017 guideline published by the AUA/SUFU on the surgical treatment of female SUI did not include adjustable continence therapy (ACT).

A 2018 European Association of Urology (EAU) guideline concluded that very limited short-term evidence suggests that the non-circumferential compression device (ProACT®) is effective for treatment of post-prostatectomy SUI (evidence level 3). The device is associated with a high failure and complication rate leading to frequent explanation (Nambiar et al., 2018).

Crivellaro et al. (2016, included in Angulo systematic review above) conducted a systematic review to report the results in terms of efficacy (pad count, 24-hour pad test, QOL questionnaires) and safety (complication rate and type of complications) of all surgical devices approved for the treatment of SUI after radical prostatectomy (RP). Inclusion criteria were number of patients higher than 30, mean follow up longer than 12 months and definition of a successful outcome as the use of 0 to 1 safety pads a day. 51 papers met the inclusion criteria with a total sample size of 4022 patients. Efficacy (0-1 safety pads) was on average 65.7% for AUS, 48.2% for Invance Sling, 48.8% for Advance Sling, 64.2% for ProACT. The overall complication rate was 19.43% for AUS, 7.4% for Invance Sling, 12.3% for Advance Sling, 12.3% for ProACT. The authors concluded that due to the poor overall quality of available studies, it was not possible to identify or refute clinically important differences between the alternative surgical procedures. The data seems to suggest that while AUS has the highest efficacy in the treatment of SUI following RP it is also associated with the highest complication rate, but this may be due to the longest follow up. Larger rigorous trials are needed in order to support this evidence.

Venturino et al. (2015, included in Angulo systematic review above) conducted a case series to evaluate the functional results, morbidity, and quality of life of the adjustable continence balloons ProACT for the treatment of male SUI after prostate surgery considering both short- and long-term results. Between 2002 and 2012, twenty-two consecutive male patients were implanted with the ProACT device. Continence was defined by the use of 0 pads daily, and the quality of life was assessed by validated

questionnaires. Only 1 patient (4.5%) was immediately continent after ProACT implantation, and the other 21 men (95.5%) needed ≥ 1 balloon refillments postoperatively. The baseline daily pad number decreased from a mean of 5.9 pads (range, 3-12 pads) to a mean of 1.7 pads (range, 0-5 pads) per day after refilling but increased to a mean of 3.9 (range, 0-10) at the last follow-up visit. After balloon adjustments, 4 patients (18%) were continent and 18 patients (82%) showed an improvement with a 95% rate of subjective satisfaction. Revision and explanation rates were 73% and 55%, respectively. At a median follow-up of 57 months, only 1 patient (4.5%) remained dry, and only 10 patients (45%) remained satisfied with the procedure, whereas 12 patients (55%) were unchanged and dissatisfied. The authors concluded that the ProACT device appears to be safe and efficacious in the short term, and that the postoperative readjustment allows the achievement of a short-term continence status. They also note that in the long term, the ProACT does not appear to be an ideal device for durable continence and patients' satisfaction. This study is limited by the lack of comparison group and small sample size.

The National Institute For Health and Care Excellence (NICE) has published two guidelines on the use of implantable adjustable compression devices for the treatment of SUI:

- Current evidence on the safety and efficacy of extraurethral (non-circumferential) retropubic adjustable compression devices for SUI in women is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. (IPG 576, 2017)
- For the management of SUI in men, the panel determined that implanted adjustable compression devices should only be chosen as an intervention for patients enrolled in a randomized controlled trial. (CG97, 2010)

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Code	Description
69705	Nasopharyngoscopy, surgical, with dilation of eustachian tube (i.e., balloon dilation); unilateral
69706	Nasopharyngoscopy, surgical, with dilation of eustachian tube (i.e., balloon dilation); bilateral

Balloon dilation is unproven and not medically necessary for treating eustachian tube dysfunction (ETD) due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Eustachian tube dysfunction (ETD) is a condition where the tubes do not open up properly causing pressure, pain or a muffled sensation that occur in the ear.

In a 2022 systematic review, Raymond et al. examined eleven studies (all case series or case reports) of eighty-one patients on the effectiveness of balloon Eustachian tube dilation for the treatment of baro-challenge eustachian tube dysfunction. Seventy-two patients from 10 studies underwent balloon eustachian tube dilation; nine patients in one study underwent laser eustachian tuboplasty (LET). All patients were symptomatic with barometric pressure preoperatively. Outcome measures included symptom resolution, ability to return to work, equalization problems (EP) scores, Eustachian Tube Dysfunction Questionnaire (ETDQ-7) scores, and pressure chamber testing parameters. On meta-analysis, after balloon dilation eustachian tuboplasty (BDET), 82.5% had improvement in ability to Valsalva, 79.1% were able to return to work, and 84.3% showed improvement in any symptoms. Of 25 patients with individual ETDQ-7 scores, 79.1% had improvements. In four case series with 36 patients, ETDQ-7 scores decreased by 1.2, and of 20 patients with preoperative ETDQ-7 scores > 2.0, there was a mean decrease of 2.1. The authors concluded that eustachian tube procedures appear to be effective at improving symptoms of baro-challenge ETD, but that higher quality evidence is needed to support making definite recommendations for the use of balloon Eustachian tube dilation or LET for these patients. The review is limited by lack of comparison group undergoing a different treatment in any of the included study.

Choi et al. (2021) conducted a prospective, multicenter, randomized, 1:1 parallel group pilot study to evaluate the efficacy and safety of navigation-guided balloon eustachian tuboplasty (BET) compared to medical management (MM) in patients with chronic ETD. There was a total of 38 ears of 31 patients, 19 ears of 16 patients assigned to the BET group and 19 ears of 15 patients as controls completed the planned treatment and 6 weeks of follow-up. The primary outcome measure was improvement in the ETDQ-7 score at follow-up. Secondary outcome measures included changes in symptoms during follow-up, changes in the score for each subcategory of ETDQ-7, type of tympanometry, pure tone audiometry, and the ability to perform the Valsalva maneuver. At 6 weeks post procedure, the results showed less symptomatic dysfunction and significant reduction in EDTQ-7 scores. Tympanogram improvement in the BET group at 6 weeks compared to the control group was 36.5% vs. 15.8% respectively, with a positive modified Valsalva maneuver. Additionally, air–bone gap change was significantly decreased in the BET group compared to the control group. The authors concluded that this study suggests that navigation-guided BET is a safe and superior treatment option compared to MM alone in patients with chronic ETD. This study is limited by a lack of participants' masking to the intervention, a small number of participants and short term follow up. Future studies should include larger sample sizes, and clarification of inclusion criteria regarding type of ETD.

A 2021 Hayes health technology assessment, updated in 2022, states that the overall body of evidence for the use of eustachian tube balloon dilation (ETBD) for treatment of chronic ETD refractory to medical management (MM) while large in size, is considered to be low quality. Based on the results of four RCTs, one case control, one retrospective and five pre/post studies, it was concluded that patients treated with ETBD experience symptom relief and improved function, and it appears to be comparable or better than the standard of care with no major safety concerns identified, however additional high-quality studies are warranted. Furthermore, it is acknowledged that evaluating the treatment response is difficult and a combination of patient reported, and objective treatment outcomes are necessary for future research. Well-designed studies are underway that will provide additional evidence regarding the efficacy and safety of this technology. The authors concluded that this approach has potential but unproven benefit.

Alper et al. (2020-, included in ECRI report) performed a prospective case series assessment in eleven adults for changes in eustachian tube (ET) function (ETF) with balloon dilation of eustachian tube (BDET). The participants had at least one

ventilation tube inserted for chronic EDT and a history of otitis media with effusion. The changes in ETF after balloon dilation were measured by Forced Response Test (FRT), Inflation Deflation Test (IDT) and Pressure Chamber test. The test results showed positive results with pressure which suggested the BDET made it easier to open the ET and stay open longer. The authors concluded these adults with severe ETD may benefit from BDET however it may not completely resolve the patients' condition and ventilation tubes might still be required. The study is however limited by lack of comparison group.

Using data from a prospective, multicenter, randomized, controlled trial, Anand et al. (2019-included in Hayes and ECRI reports) analyzed and investigated the durability of BDET for obstructive eustachian tube dysfunction (OETD) plus medical management (MM) treatment outcomes through 52 weeks. Among subjects randomized to BDET + MM, the overall number with normalized tympanograms and ETDQ-7 scores remained comparable to those reported at 6- versus 52-week follow-up: tympanograms, 73 of 143 (51.0%) versus 71 of 128 (55.5%); ETDQ-7, 79 of 142 (55.6%) versus 71 of 124 (57.3%). The overall number of ears with normalized tympanograms also remained comparable, with 117 of 204 (57%) versus 119 of 187 (63.6%). The author's conclusions suggested that the beneficial effects of BDET + MM on tympanogram normalization and symptoms of subjects with refractory OETD demonstrated significant durability that is clinically relevant through 52 weeks. This particular publication, however, is limited to the analysis of one of the randomized arms and doesn't allow comparison to a different treatment approach.

Meyer et al. (2018, included in Hayes report above) compared eustachian tube balloon dilation versus continued medical therapy for treating persistent ETD in a prospective, multicenter, randomized controlled trial. Sixty participants were randomized to either a balloon dilation group or a control group; after 6 weeks, the control participants had the option to undergo balloon dilation if symptoms persisted. No complications were reported in either study group. Among participants with abnormal baseline assessments, improvements in tympanogram type and tympanic membrane position were significantly better for balloon dilation than control. Technical success was 100% and most procedures (72%) were completed in the office under local anesthesia. Improvements in the ETDQ-7scores were maintained through 12 months after balloon dilation. A limitation of the study was the inability to blind the participants to their treatment which can lead to a placebo effect, but since significant improvements were seen in the objective findings such as tympanometry, otoscopy, and Valsalva maneuver in the balloon dilation arm and not in the control arm, the author's believed that any placebo effect was minimal and that the improvements observed in the ETDQ-7 scores were reliable and indicated true symptom improvement. Another limitation is the short-term duration (six weeks) of the randomized portion of the study. The author's concluded balloon dilation is a safe and effective treatment for persistent ETD. Based on improved ETDQ-7 scores, balloon dilation is superior to continued medical management for persistent ETD. Symptom improvement is durable through a minimum of 12 months and procedures are well tolerated in the office setting under local anesthesia.

In a prospective, multicenter, randomized, controlled trial, Poe et al. (2017- included in Hayes and ECRI reports) assessed balloon dilation of the eustachian tube with eustachian tube balloon catheter in conjunction with medical management as treatment for eustachian tube dilatory dysfunction. Patients aged 22 years and older were assigned in a ratio of 2:1 and underwent balloon dilation of the Eustachian tube with balloon catheter in conjunction with medical management or medical management alone. The data suggest superiority of balloon dilation of the Eustachian tube with balloon catheter plus medical management compared to medical management alone: Tympanogram normalization at 6-week follow-up was observed in 51.8% (72/139) of investigational patients versus 13.9% (10/72) of controls ($p < .0001$). However, the short duration of the study limits the conclusion that can be drawn for the duration of the effect.

Wang et al. (2018- included in ECRI report) performed a meta-analysis examining balloon dilatation and laser tuboplasty for the treatment of ETD. Pub Med, Cochrane and Embase databases were searched in April of 2018 with the following results: 2 retrospective and 11 prospective studies which resulted in 1063 patients; 942 treated with balloon dilation and 121 with laser tuboplasty. Balloon tuboplasty resulted in a significant improvement of eustachian tube scores and, compared with laser tuboplasty, a greater tympanometry improvement rate. It was concluded that both procedures can improve symptoms of ETD; however, because of the limited numbers of studies reporting data it remains unclear if one procedure provides greater benefits over the other.

Huisman et al. (2018) conducted a systematic review to evaluate the success of balloon dilation in adult patients with ETD. The systematic literature search was conducted independently by two authors which resulted in 36 articles with 15 of them for inclusion in the study. All 15 included studies were case series. A total of 1,155 patients were treated with balloon dilation with follow up ranging from just after therapy to 50 months later. Conclusions suggested that balloon dilation of the Eustachian tube

can be a helpful treatment in patients with EDT, however placebo-controlled trials are still warranted. The findings are however limited by lack of comparison groups in these case series.

The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) developed a clinical consensus statement that addressed the use of balloon dilation of the eustachian tube (BDET). It was agreed by the panel members that BDET is an option for treatment of patients with obstructive eustachian tube dysfunction (OETD), however further studies are needed to refine patient selection and assess outcomes. (Tucci et al., 2019).

In a 2017 ECRI clinical evidence assessment, updated in 2021 on the Acclarent Aera Eustachian Tube Dilation System (Acclarent, Inc) for treating persistent ETD states that based on the results of one randomized controlled trial (RCT) and 4 additional small, low-quality studies, eustachian tube (ET) dilation with the Aera balloon system is safe and, when added to medical therapy, may relieve symptoms from 6 weeks up to 1 year in select patients whose ETD has not responded to medical therapy alone. Limitations include the RCT comparative outcomes only included up to 6-week follow up due to the cross-over design, and device and control group participants dropping out before receiving treatment, and at follow up. Additionally, studies are limited by one or more of the following: small study size, single-center focus, retrospective design, and lack of randomization, blinding, and control groups. While the authors consider the evidence somewhat favorable, additional RCTs would be useful to validate results.

A National Institute for Health and Care Excellence (NICE) guideline concluded that current evidence on the safety and efficacy of balloon dilation of the eustachian tube is adequate to support the use of this procedure (NICE, 2019). It notes that the procedure is not effective in all patients and evidence is limited on the benefit for repeat use. In addition, NICE also indicates the procedure is only useful for chronic eustachian tube dysfunction.

The U.S. Food and Drug Administration (FDA) approved the XprESS ENT Dilation System under 510(K) (K163509) on April 5, 2017. The device is intended for use in dilating the cartilaginous portion of the Eustachian tube for treating persistent Eustachian tube dysfunction. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K163509. (Accessed April 25, 2022).

The U.S. Food and Drug Administration (FDA) approved the Acclarent Aera Eustachian Tube Balloon Dilation System (Acclarent Inc.) under 510(k) (K171761) on January 16, 2018. The device use is intended to dilate the Eustachian tube for treatment of persistent Eustachian tube dysfunction in patients ages 18 and older. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171761.pdf. (Accessed April 25, 2022).

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Code	Description
80145	Adalimumab
80230	Infliximab
80280	Vedolizumab

Note: The above codes are used to describe therapeutic drug assays for these medications and does not apply to the use of the drugs which are reported with a different CPT code.

Laboratory measurement of antibodies and serum levels related to biologic agents (e.g., infliximab, adalimumab, vedolizumab, ustekinumab, certolizumab pegol, golumunab) for treating inflammatory bowel disease (including ulceratie colitis and Crohn's disease) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Therapeutic drug monitoring (TDM) involves measurement of drug or active metabolite levels and anti-drug antibodies (ADA), and is based on the premise that there is a relationship between drug exposure and outcomes, and that considerable inter-individual variability exists in how patients metabolize the drug (pharmacokinetics) and the magnitude and duration of response to therapy (pharmacodynamics) (Vande Casteele et al., 2017). TDM is also used to assess compliance and to guide dose adjustments or switch off therapy (e.g., where patients are relapsing despite therapeutic levels, or have developed high titer anti-drug antibodies with low levels). (British Society of Gastroenterology, 2019)

Inflammatory bowel disease (IBD), comprising mainly the 2 entities Crohn disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disease of the digestive tract. (Spencer, 2017) Inflammatory bowel disease (IBD) is often treated with immunomodulators and/or biologics. The trough concentrations of these drugs can vary due to disease severity, phenotype, degree of inflammation, use of immunomodulator, patient sex, and body mass index, as well as variability in drug clearance through immune- and non-immune-mediated mechanisms. In order to better optimize the drug concentration and clinical improvement for IBD, TDM has been used to check the drug trough concentration and assess for the presence of anti-drug antibodies (ADA) (Feuerstein et al., 2017).

Vermeire et al. (2018) conducted a systematic review of articles published January 2009 to August 2015 reporting immunogenicity to adalimumab (ADM), certolizumab pegol (CZP), golimumab, infliximab (IFX), ustekinumab, and vedolizumab in inflammatory bowel disease (IBD). Eligible articles were reviewed and quality assessed by independent reviewers. Overall, 122 publications reporting 114 studies were assessed. ADAbs were reported for all agents, but the percentage of patients developing ADAbs was extremely variable, with the highest (65.3%) being for IFX administration to patients with IBD. ADAb presence was frequently associated with a reduction in primary efficacy and a loss of response, and, for IFX, an increase in adverse events (AEs). Lower serum levels of ADM, CZP and IFX were seen in ADAbs-positive rather than ADAbs-negative patients; pharmacokinetic data were unavailable for other therapies. The authors found little information regarding the timing of ADAb development; studies reported their detection from as early as 10-14 days up to months after treatment initiation. The authors concluded that biologic therapies carry an intrinsic risk of immunogenicity, although reported rates of ADAbs vary considerably. The clinical implications of immunogenicity are a concern for effective treatment; further research, particularly into the more recently approved biologics, is required. The publication did not address whether antibody measurements improve patients' outcomes.

Adalimumab (ADA)

Assa et al. (2019) performed a nonblinded, randomized controlled trial of 78 children to investigate whether proactive drug monitoring is associated with higher rates of clinical remission in pediatric patients with Crohn's disease (CD). The patients were randomly assigned to groups that received proactive monitoring (trough concentrations measured at weeks 4 and 8 and then every 8 weeks until week 72, n = 38) or reactive monitoring (physicians were informed of trough concentrations after loss

of response, n = 40). In both groups, doses and intervals of adalimumab were adjusted to achieve trough concentrations of 5 μg/mL. The primary endpoint was sustained corticosteroid-free clinical remission at all visits (week 8 through week 72). The primary endpoint was achieved by 31 children (82%) in the proactive group and 19 children (48%) in the reactive group (p = .002). Sixteen patients in the proactive monitoring group (42%) achieved a composite outcome of sustained corticosteroid-free remission, C-reactive protein ≤0.5 mg/dL, and level of fecal calprotectin ≤150 μg/g compared with 5 patients in the reactive monitoring group (12%) (p = .003). By week 72 of treatment, 33 patients in the proactive monitoring group had received adalimumab intensification (87%) compared with 24 patients in the reactive monitoring group (60%) (p = .001). The authors concluded that proactive monitoring of adalimumab trough concentrations and adjustment of doses and intervals resulted in significantly higher rates corticosteroid-free clinical remission than reactive monitoring (measuring trough concentration after loss of response). Independent confirmation with larger sample sizes, longer follow-up, and a broader age range are necessary before these findings can be translated into routine clinical practice.

In a multicenter retrospective cohort study, Papamichael et al. (2019b) compared the long-term outcome of patients with IBD who received at least one proactive TDM of adalimumab (ADA) with standard of care, defined as empiric dose escalation and/or reactive TDM. Patients (n = 382) received either at least one proactive TDM (n = 53) or standard of care (empiric dose escalation, n = 279; reactive TDM, n = 50). Treatment failure was defined as drug discontinuation for secondary loss of response or serious adverse event or need for IBD-related surgery. Serum adalimumab concentrations and antibodies to adalimumab were measured using the Prometheus homogeneous mobility shift assay. Patients were followed for a median of 3.1 years (interquartile range, 1.4-4.8 years). Multiple Cox regression analyses showed that at least one proactive TDM was independently associated with a reduced risk for treatment failure (hazard ratio [HR]: 0.4; 95%CI: 0.2-0.9; p = 0.022). In the authors' opinion, this study provides the first evidence that proactive TDM of adalimumab may be associated with a lower risk of treatment failure compared to standard of care in patients with IBD. Long-term randomized controlled trials are needed to further validate these findings.

Baert et al. (2016) evaluated 536 prospectively collected serum samples for analysis of ADA concentration and antibodies-to-adalimumab (ATA) using homogeneous mobility shift assay. Mixed model repeated measure analysis was performed to assess the independent effects of serum ADA concentration and ATA on C-reactive protein (CRP) and response. ATA were detected in 20% of patients after a median of 34 (12.4-60.5) weeks. ATA-positive samples correlated with lower serum ADA concentration (p < 0.001). The model revealed that both lower serum ADA concentration and ATA were independently associated with future CRP (p = 0.0213 and p = 0.0013 respectively). ATA positivity was associated with discontinuation of ADA because of loss of response (OR = 3.04; 95% CI 1.039 to 9.093; p = 0.034). Further studies are needed to evaluate the impact of ATA on drug management.

In a cross-sectional study of 66 patients receiving maintenance therapy with ADA for CD or UC, Yarur et al. (2016) assessed the relationship between random serum ADA levels and histologic and endoscopic healing in patients with IBD. The results showed that mean random ADA levels were significantly lower in patients with histologic and endoscopic inflammation (9.2 [SD: 8.4] versus 14.1 [6.4] μg/mL, p = 0.03 and 8.5 [SD: 7.8] versus 13.3 [SD: 7.7], p = 0.02, respectively). The ADA level that was best associated with histologic healing was 7.8 μg/mL (receiver operating characteristic: 0.76 [p = 0.04]), whereas the ADA level that was best associated with endoscopic healing was 7.5 μg/mL (receiver operating characteristic: 0.73 [p = 0.02]). The presence of AAA was associated with lower random ADA levels (5.7 versus 12.5 μg/mL, p = 0.002) and higher C-reactive protein levels (30.3 versus 12.0, p = 0.01). The authors concluded that the measurement of random ADA levels and anti-drug antibodies may guide therapy and edify the course of incomplete responses. Further studies with larger patient populations are needed to evaluate optimal levels of ADA.

In a cross-sectional study using 118 trough sera from 71 ADA-treated CD patients, Mazor et al. (2014) assessed ADA and anti-ADA antibodies (AAA) serum levels, and examined their association and discriminatory ability with clinical response and serum CRP. High ADA trough serum concentration s were associated with disease remission (Area Under Curve 0.748, p < 0.001). A cut-off drug level of 5.85 μg/mL yielded optimal sensitivity, specificity and positive likelihood ratio for remission prediction (68%, 70.6% and 2.3, respectively). AAA were inversely related with ADA drug levels (Spearman's r = -0.411, p < 0.001) and when subdivided into categorical values, positively related with disease activity (p < 0.001). High drug levels and structuring vs. penetrating or inflammatory phenotype, but not AAA levels, independently predicted disease remission in a multivariate logistic regression model.

Karmiris et al. (2009) conducted an observational study of 168 patients with CD to assess the long-term clinical benefit of ADA in patients who failed to respond to infliximab (IFX), specifically focusing on the influence of trough serum concentration and

antibodies against ADA on clinical outcome. Trough serum concentration and antibodies against ADA were measured at predefined time points using enzyme-linked immunosorbent assays. A total of 71% and 67% of patients responded by weeks 4 and 12, respectively; among them, 61.5% demonstrated sustained clinical benefit until the end of follow-up (median [interquartile range], 20.4 [11.7-30.0] months). Of the 156 patients receiving maintenance therapy, 102 (65.4%) had to step up to 40 mg weekly and 60 (38.5%) eventually stopped ADA therapy mainly due to loss of response. Significantly lower ADA trough serum concentrations were measured throughout the follow-up period in patients who discontinued therapy as compared with patients who stayed on ADA. Antibodies against ADA were present in 9.2% of the patients and affected trough serum concentration. Serious Aes occurred in 12% of the patients. The authors concluded that in this patient population, introduction of ADA after failure of IFX therapy resulted in a sustained clinical benefit in two thirds of patients during a median follow-up period of almost 2 years. Randomized controlled studies are needed to further evaluate these findings.

Golimumab (Simponi)

A Hayes Evidence Analysis Research Brief on TDM of Golimumab (Simponi) found that there currently is not enough published peer-reviewed literature to evaluate the evidence related to TDM of golimumab for IBD in a full assessment. (April 2022)

Infliximab (IFX)

Strik et al. (2021) conducted a randomized control, multicenter study to investigate the efficacy of dashboard driven Infliximab (IFX) dosing compared to standard dosing in a prospective trial for individuals. 80 individuals were randomly assigned to receive either dashboard driven IFX dosing (precision dosing group, PG) or continued IFX maintenance treatment without adjustments of the dose and/or treatment interval (conventional dosing group, CG). IFX is administered through intravenous infusions using weight-base (5 mg/kg) with an induction schedule at week 0, 2, 6 and followed by 8-weekly maintenance treatments with a goal to achieve and maintain remission in individuals with IBD. During maintenance treatment, an association was reported between IFX trough levels (TL) of 3 mcg/ml to correlate with improved clinical outcomes. After one year, 28/32 (88%) of individuals in the PG were in sustained clinical remission versus 25/39 (64%) of the CG individuals. The authors concluded that a higher percentage of individuals receiving dashboard guided IFX dosing maintained clinical remission during one year of follow-up compared to patients who did not receive proactive dose adjustments. In the majority of patients with TLs > 3 mcg/ml dose reduction did not lead to clinical Loss of Response (LOR). However, a small proportion of patients may need higher target TLs depending on the specific treatment goal. Future trials should be performed to investigate dashboard guided dosing of IFX in individuals with IBD during induction treatment. Limitations of the study included lack of endoscopies performed due to the use of FCP as a reliable measurement of disease activity, use of drug-sensitive assay to detect glow ADA levels, but presence was clinically insignificant and a lower IFX target concentration which might not have been an optimal target.

In a systematic review and meta-analysis, Ricciuto et al. (2018) examined the effectiveness of TDM used to improve clinical outcomes in IBD patients treated with anti- anti-TNF drugs. The search identified nine studies (three RCTs, six observational), which focused on IFX maintenance therapy in adults. The results of the review showed that neither proactive nor reactive TDM was associated with superior clinical remission rates compared to empiric dose optimization. However, evidence of a cost benefit, particularly for reactive TDM vs empiric care, was identified. In several studies, TDM, particularly proactive TDM, was associated with favorable outcomes related to durability of anti-TNF response, such as lower drug discontinuation rates compared to empiric care and reactive TDM, and lower relapse rates compared to empiric care. No consistent benefit was found for endoscopic or surgical outcomes. The authors recommend additional, longer-term studies, particularly to further investigate proactive TDM, and to generate data on other anti-TNF agents, the induction period and pediatric populations.

In a systematic review and meta-analysis, Moore et al. (2016) evaluated studies that reported serum IFX levels according to outcomes in IBD. The primary outcome was clinical remission, and secondary outcomes included endoscopic remission, and CRP levels. A total of 22 studies met the inclusion criteria, including 3483 patients; 12 studies reported IFX levels in a manner suitable for determining effect estimates. During maintenance therapy, patients in clinical remission had significantly higher mean trough IFX levels than patients not in remission: 3.1 µg/ml versus 0.9 µg/ml. The standardized mean difference in serum IFX levels between groups was 0.6 µg/ml (95% confidence interval [CI] 0.4-0.9, p = 0.0002]. Patients with an IFX level > 2 µg/ml were more likely to be in clinical remission (risk ratio [RR] 2.9, 95% CI 1.8-4.7, p < 0.001], or achieve endoscopic remission [RR 3, 95% CI 1.4-6.5, p = 0.004] than patients with levels < 2 µg/ml. The authors concluded that there is a significant difference between serum IFX levels in patients with IBD in remission, compared with those who relapse, and a trough threshold during maintenance > 2 µg/ml is associated with a greater probability of clinical remission and mucosal healing.

In an observational study, Vande Casteele et al. (2015) analyzed 487 trough serum samples from 483 patients with CD who participated in 4 clinical studies of maintenance IFX therapy using a fluid phase mobility shift assay. Infliximab and ATI concentrations most discriminant for remission, defined as a CRP concentration of ≤ 5 mg/L, were determined by receiver operating characteristic curves. Based upon analysis of 1487 samples, 77.1% of patients had detectable and 22.9% had undetectable infliximab concentrations, of which 9.5% and 71.8%, respectively, were positive for ATI. An IFX concentration of > 2.79 μg/mL (area under the curve (AUC) = 0.681; 95% CI 0.632 to 0.731) and ATI concentration of < 3.15 U/mL (auc = 0.632; 95% CI 0.589 to 0.676) were associated with remission. Multivariable analysis showed that concentrations of both IFX trough (OR 1.8; 95% CI 1.3 to 2.5; p < 0.001) and ATI (OR 0.57; 95% CI 0.39 to 0.81; p = 0.002) were independent predictors of remission. The development of ATI increases the probability of active disease even at low concentrations and in the presence of a therapeutic concentration of drug during IFX maintenance therapy. Evaluation of strategies to prevent ATI formation, including therapeutic drug monitoring with selective infliximab dose intensification, is needed.

Baert et al. (2014) studied 128 consecutive patients (105 patients with CD, 23 patients with UC) who restarted IFX after a median 15-month discontinuation (range, 6-125 mo) to investigate correlations among response to treatment, infusion reactions, treatment modalities, trough levels, and antibodies to IFX. The absence of antibodies to infliximab at T + 1 (hazard ratio [HR], 0.14; 95% confidence interval [CI], 0.026-0.74; p = .021) and re – initiation with concomitant immunomodulator therapy were associated with short-term responses (HR, 6.0; 95% CI, 1.3-27; p = .019). Based on the results, the authors concluded that reinitiating IFX therapy can be safe and effective for patients with CD or UC after a median 15-month discontinuation period. Additional studies are needed to validate these findings.

In a pilot retrospective observational study, Vaughn (2014) examined the use of proactive therapeutic concentration monitoring (TCM) and titration of IFX to a target concentration for patients with IBD (n = 48) in clinical remission at a tertiary care center. The primary aim was to describe the clinical course of patients who had proactive TCM. A secondary analysis was done to assess if this strategy was superior to the standard of care. Fifteen percent of patients had an initial undetectable trough concentration. Twenty-five percent (12 of 48) of patients escalated IFX after the first proactive TCM while 15% (7 of 48) of patients de-escalated IFX therapy over the study period. A control group of 78 patients was identified. Patients who had proactive TCM had a greater probability of remaining on IFX than controls (hazard ratio, 0.3; 95% confidence interval, 0.1-0.6; log rank test; p = 0.0006). The probability of remaining on IFX was greatest for patients who achieved a trough concentration > 5 μg/mL (hazard ratio, 0.03; 95% confidence interval, 0.01-0.1; p < 0.0001 versus trough < 5 μg/mL). Fewer patients in the proactive TCM group stopped IFX (10% versus 31%, p = 0.009). Although the authors concluded that proactive TCM of IFX frequently identified patients with low or undetectable trough concentrations and resulted in a greater probability of remaining on IFX, additional studies are needed to determine clinically meaningful thresholds.

Nanda et al. (2013) conducted a systematic review and meta-analysis of studies that reported clinical outcomes and IFX levels according to patients' antibodies to infliximab (ATI) status. Thirteen studies met the inclusion criteria, with reported results in 1,378 patients with IBD. The authors concluded that the presence of ATIs is associated with a significantly higher risk of loss of clinical response to IFX and lower serum IFX levels in patients with IBD. Limitations identified include lack of published studies on this topic, lack of uniform reporting of outcomes, and a high risk of bias in all the included studies. Furthermore, the authors identified evidence of publication bias in this body of literature.

Vande Casteele et al. (2013) identified that ATI may be transient and do not always lead to a worse clinical outcome. Sustained high levels of ATI, however, may lead to permanent loss of response. IFX trough and ATI levels were measured retrospectively in 1,232 consecutive serum samples of 90 (64 CD and 26 UC) patients, 57 with previously detected and 33 without antibodies with a new homogenous mobility shift assay. The results showed that patients with low IFX trough levels at week 14 are at risk for ATI formation and IFX discontinuation. The authors recommend that IFX trough levels be measured at week 14 and at the time of lack of response. When undetectable or low, ATI should be determined and if positive followed up on consecutive time points to rule out sustained ATI. Further studies are needed to validate these findings.

In a prospective study (n = 52), Paul et al. (2013) evaluated the efficacy of TDM in IFX treatment to predict mucosal healing (MH) in IBD. IFX trough levels, antibodies to IFX concentrations, C-reactive protein levels, and fecal calprotectin were measured before IFX optimization and at week 8. A proctosigmoidoscopy was performed on the day of first IFX optimization and at week 8 in all patients with ulcerative colitis (UC). MH was defined by fecal calprotectin < 250 μg/g stools in CD and by an endoscopic Mayo score of 0 or 1 in UC. After IFX dose intensification, half of CD and UC patients achieved MH. Increase in IFX trough levels (called "delta IFX" in micrograms per milliliter) was associated with MH in both CD and UC (p = 0.001). A delta IFX > 0.5 μg/mL was associated with MH (sensitivity [se], 0.88; specificity [sp], 0.77; p = 0.0001, area under the receiver operating characteristic

curve, 0.89). On multivariate analysis, the only factor associated with MH after IFX optimization was a delta IFX > 0.5 µg/mL (likelihood ratio = 2.02; 95% confidence interval, 1.01-4.08; p = 0.048) in patients with IBD. The authors concluded that TDM of IFX strongly predicts the likelihood of achieving MH following IFX dose intensification in both CD and UC. Further studies with larger patient populations are needed to establish the efficacy of TDM.

Afif et al. (2010) conducted a retrospective review of patients (n = 155) with IBD who had human anti-chimeric antibodies (HACA) and IFX concentrations measured to determine whether the result affected clinical management. The main indications for testing were loss of response to IFX (49%), partial response after initiation of infliximab (22%), and possible autoimmune/ delayed hypersensitivity reaction (10%). HACAs were identified in 35 patients (23%) and therapeutic IFX concentrations in 51 patients (33%). In HACA-positive patients, change to another anti-tumor necrosis factor (TNF) agent was associated with a complete or partial response in 92% of patients, whereas dose escalation had a response of 17%. In patients with subtherapeutic IFX concentrations, dose escalation was associated with complete or partial clinical response in 86% of patients whereas changing to another anti-TNF agent had a response of 33%. Patients with clinical symptoms and therapeutic IFX concentrations were continued at the same dose 76% of the time and had no evidence of active inflammation by endoscopic/ radiographic assessment 62% of the time. The authors' concluded that measurement of HACA and IFX concentration impacts management and is clinically useful. Further studies are needed to validate these findings.

Vedolizumab (VDZ)

Yarur et al. (2019) conducted a prospective cohort study to assess the relationship of serum vedolizumab concentrations (SVC) during induction and endoscopic remission in 55 patients with IBD after 52 weeks of therapy with vedolizumab (VDZ). The authors also sought to assess the incidence of antibody to vedolizumab (ATV) formation, the effect of ATV on drug pharmacokinetics and efficacy, and identify variables associated with SVC through the first 30 weeks of treatment. Collected variables included demographics, clinical disease activity, biomarkers, pre-infusion SVC, and ATV measured at weeks 2, 6, 14, 22, and 30. Primary outcome was steroid-free endoscopic remission at week 52. Patients that achieved steroid-free endoscopic remission by week 52 had higher SVC at weeks 2, 6, 14, 22, and 30, but only achieved statistical significance at weeks 2 and 6. Only 3 out of the 55 study subjects (5.5%) had detectable ATV through the follow-up. Overall, there were a positive correlation between SVC and serum albumin and a negative correlation with C-reactive protein, fecal calprotectin, and body mass. Vedolizumab concentrations ≥ 23.2 mcg/ml at week 2 were associated with endoscopic remission at week 52 (OR 8.8 [95% CI 2.6-29.7], p < 0.001). VDZ concentrations during induction were associated with endoscopic remission at week 52. The authors concluded that interventional studies looking into improved efficacy with higher drug exposure are warranted.

Pouillon et al. (2019) evaluated the association between VDZ trough levels through TDM, and histological healing in UC in a single-center retrospective cohort study. Thirty-five histological samples from UC patients on VDZ maintenance therapy were included. Per-event analysis was performed. Histological healing was defined as a Nancy histological index ≤ 1. The results showed that histological healing was associated with higher VDZ trough levels during maintenance therapy in UC. Based on this analysis, the authors found that a VDZ trough level threshold of 25 µg/mL proved most optimal to predict histological healing according to the Nancy histological index. Confirmation of these data in larger, independent cohorts is needed.

In a retrospective cohort study, Dreesen et al. (2018) investigated the correlation between VDZ exposure and response to identify patient factors that affect exposure and response. Serum concentrations of VDZ were drawn on 179 consecutive patients (66 with UC and 113 with CD) before all infusions and up to week 30. Effectiveness endpoints included endoscopic healing (UC, Mayo endoscopic sub-score ≤1; CD, absence of ulcers), clinical response (physicians' global assessment), and biologic response or remission (based on level of CRP) and were assessed at week 14 (for patients with UC) and week 22 (for patients with CD). VDZ trough concentrations > 30.0 µg/mL at week 2, > 24.0 µg/mL at week 6, and > 14.0 µg/mL during maintenance therapy associated with a higher probability of attaining the effectiveness endpoints for patients with UC or CD (p < .05). Higher body mass and more severe disease (based on high level of CRP and low level of albumin and/or hemoglobin) at the start of VDZ therapy associated with lower trough concentrations of VDZ over the 30-week period and a lower probability of achieving mucosal healing (p < .05). Mucosal healing was achieved in significantly more patients with UC than patients with CD, even though a diagnosis of UC was not an independent predictor of higher VDZ trough concentrations. Prospective studies are needed to evaluate the impact of TDM on clinical management.

Ustekinumab (UST)

There is limited clinical evidence on the definitive threshold concentrations for ustekinumab (UST).

In a non-systematic review of the literature, Restellini et al. (2018) conclude that the utility of a TDM-based personalized approach for novel biologic agents, which target different inflammatory pathways, is unclear. Commercial assays for UST and VDZ are available, but there is little available guidance for clinicians regarding the use of TDM with these drugs.

The American Gastroenterological Association (AGA) Institute's technical review of the role of TDM in the management of IBD states that it "is a promising strategy" that can be used to optimize inflammatory bowel disease therapeutics. It is based on the premise that there is a relationship between drug exposure and outcomes, and that considerable interindividual variability exists in how patients metabolize the drug (pharmacokinetics) and the magnitude and duration of response to therapy (pharmacodynamics) (Vande Casteele et al., 2017).

The Institute identified knowledge gaps and future directions for TDM:
- Observational and comparative evidence is needed to define minimal effective exposure thresholds that are associated with clinically meaningful outcomes after induction and maintenance therapy.
- The maximum threshold concentration beyond which a ceiling effect is observed (i.e., above which further attempts at increased trough concentrations is highly unlikely to be effective) needs to be identified,
- Acknowledgment that such thresholds may be different for different outcomes of interest (e.g., clinical remission, endoscopic remission, fistula healing, management of CD after surgically induced remission, and left-sided UC vs pan-UC).
- Once thresholds are identified, randomized trials comparing the efficacy and safety of early optimized therapy based on TDM to target trough concentration(s) vs standard induction dosing should be evaluated.

The AGA clinical guideline for TDM in IBD (Feuerstein et al., 2017) includes the following:
- In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive TDM to guide treatment changes. (Conditional recommendation, very low quality of evidence)
- In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring due to a knowledge gap.
- There are several knowledge gaps in TDM that have been identified for which prospective observational and RCTs are warranted, which have been highlighted in the Technical Review that accompanies this guideline (Vande, Casteele et al., 2017).
- It is unclear whether TDM should be performed during induction therapy in patients with suboptimal response (as opposed to empiric dose escalation) and, if it is performed, what the target trough concentrations should be.
- Similarly, target trough concentrations when performed in the reactive setting in patients on maintenance therapy with different agents is unclear, and whether it should be different based on disease phenotype, disease state, and treatment target (clinical remission vs mucosal healing).
- Further studies are also needed to better define clinically meaningful vs insignificant anti-drug antibodies, based on titers and/or persistence on repeated testing, and at which titers can anti-drug antibodies be suppressed before needing to change drug therapies.
- Additionally, well-designed RCTs are needed that compare routine proactive TDM vs reactive TDM, and empiric dosing changes on patient relevant outcomes, and also the frequency and timing of proactive TDM.
- Finally, as newer biologic agents are approved, the use of TDM to optimize these drugs will need to be evaluated.

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*Code	Description
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score

The use of a multi-biomarker disease activity (MBDA) test is unproven and not medically necessary for managing individuals with rheumatoid arthritis (RA) due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The Vectra DA test (Crescendo Bioscience Inc., a wholly owned subsidiary of Myriad Genetics Inc.) is a multi-biomarker blood test that measures levels of 12 key proteins. A weighted algorithm based on the levels of these markers is used to calculate the multi-biomarker disease activity (MBDA) score, resulting in a single number ranging from 0 to 100 to rank disease activity. The Vectra DA test, also referred to as the MBDA test, is intended to measure disease activity in individuals who have rheumatoid arthritis (RA), with the goal of informing treatment decisions in conjunction with standard clinical assessment. The Vectra DA

test is regulated under the Food and Drug Administration's (FDA) Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the FDA is not required for this test (Hayes, 2018. Updated February 2021).

Abdelhafiz et al. (2022) directed a systematic review on the biomarkers for the diagnosis and treatment of RA. The study systematically explored through 4 different databases identifying the role of biomarkers for the diagnosis and treatment of RA. The biomarkers studied were C-reactive protein (CRP), rheumatoid factor (RF) anti-cyclic citrullinated protein (anti-CCP), 14-3-3n protein and the MBDA score. Initial MBDA scores correlated with the future responses in disease activity after 6 and 12 weeks of treatment. The MBDA was a robust predictor of radiographic development of RA, foretold remission over 1 year period, and was able to distinguish among small variances in disease activity. The authors determined the biomarkers examined are supportive tools in diagnosis, monitoring of treatment and foreseeing prognosis in patients with RA. Though, additional investigation is required to explore novel biomarkers for the pretreatment selection of potentially responsive patients before initiating therapy for a precision medicine regarding RA.

A Hayes report concluded that the accuracy of the Vectra DA test compared to established tests for assessment of RA disease activity was not established by the evidence. The report also noted that in addition to insufficient evidence of test accuracy, the published studies do not provide enough evidence to evaluate the clinical utility of the Vectra test. The February 2021 Hayes update indicates that the evaluation of the abstracts indicates that evidence regarding clinical utility is unchanged since the 2018 publication of the report (Hayes, 2018. Updated February 2021).

Fleischmann et al. (2021) compared the utility of the multi-biomarker disease activity (MBDA) score in assessing rheumatoid arthritis (RA) disease activity with that of the Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) and the Clinical Disease Activity Index (CDAI) in a multicenter, randomized, placebo-controlled trial of repository corticotropin injection (RCI) in patients with persistently active RA. Patients received 80 U of RCI twice weekly during a 12-week open-label period; those who achieved low disease activity at week 12 were randomly assigned to receive either 80 U of RCI or placebo twice weekly during a 12-week double-blind period. Changes in disease activity (measured by DAS28-ESR, CDAI, and MBDA) and correlations between MBDA scores and both DAS28-ESR and CDAI scores were assessed. Changes from baseline in DAS28-ESR and CDAI scores suggested that RCI therapy led to clinically meaningful improvements in disease activity, but improvements from baseline in MBDA scores were below the minimally important difference threshold. For the DAS28-ESR and CDAI, correlations with total MBDA and individual component scores were generally low ($r \leq 0.3$), occasionally moderate ($r > 0.3$ but < 0.5). The investigators concluded that their results suggest overall MBDA scores are not sufficiently responsive for assessing RA disease activity after RCI therapy. These findings are consistent with those seen with other RA drugs and, although they are from a clinical trial, suggest the MBDA should not be a preferred disease activity measure in clinical practice.

Curtis et al. (2021) accessed the adjusted MBDA score and performed a combined analysis of it as a prognostic test for radiographic progression in RA. A newer version of the MBDA score, adjusted for age, sex, and adiposity, has been validated in two cohorts (OPERA and BRASS) for predicting risk for radiographic progression. The investigators extend these findings with additional cohorts to further validate the adjusted MBDA score as a predictor of radiographic progression risk and compare its performance with that of other risk factors. Four cohorts were analyzed: the BRASS and Leiden registries and the OPERA and SWEFOT studies (total n = 953). Treatments included conventional DMARDs and anti-TNFs. Associations of radiographic progression (△TSS) per year with the adjusted MBDA score, seropositivity, and clinical measures were evaluated using linear and logistic regression. The adjusted MBDA score was (1) validated in Leiden and SWEFOT, (2) compared with other measures in all four cohorts, and (3) used to generate curves for predicting risk of radiographic progression. Univariable and bivariable analyses validated the adjusted MBDA score and found it to be the strongest, independent predicator of radiographic progression (△TSS > 5) compared with seropositivity (rheumatoid factor and/or anti-CCP), baseline TSS, DAS28-CRP, CRP SJC, or CDAI. Neither DAS28-CRP, CDAI, SJC, nor CRP added significant information to the adjusted MBDA score as a predictor, and the frequency of radiographic progression agreed with the adjusted MBDA score when it was discordant with these measures. The rate of progression (△TSS > 5) increased from < 2% in the low (1-29) adjusted MBDA category to 16% in the high (45-100) category. A modeled risk curve indicated that risk increased continuously, exceeding 40% for the highest adjusted MBDA scores. According to the investigators, the adjusted MBDA score was validated as an RA disease activity measure that is prognostic for radiographic progression. The adjusted MBDA score was a stronger predictor of radiographic progression than conventional risk factors, including seropositivity, and its prognostic ability was not significantly improved by the addition of DAS28-CRP, CRP, SJC, or CDAI. The investigators indicated that the limitations of the present study are that radiographs were assessed by different readers in each cohort, patient global assessments were unavailable for the Leiden cohort, and, except for one patient, TNF inhibitors were the only biologic drugs included in the four cohorts. Data on smoking were not evaluated here [46], but a prior analysis of the SWEFOT cohort found that the original MBDA score was a strong

independent predictor of progression (.TSS > 5) after adjusting for current smoking status. This study was supported by Myriad Genetics, Inc.

Baker et al. (2020) assessed the impact of adjustment of the multi-biomarker disease activity score (MBDA) for age, sex, and leptin, over the range of age and adiposity, and assessed relationships with clinical disease activity. Patients with RA, ages 18-75 years, were recruited from clinical practices and completed whole-body DXA to quantify fat mass indices (FMI, kg/m2). FMI Z-scores were calculated based on distributions in a reference population. Descriptive statistics described relationships between age, FMI Z-score, and the original MBDA and adjusted MBDA (aMBDA). Swollen joint counts (SJC) and the clinical disease activity index (CDAI) were assessed over MBDA categories. There were 104 participants (50% female) with mean (SD) age of 56.1 (12.5) and body mass index (BMI) of 28.8 (6.9). Older age was associated with higher MBDA scores in men. The aMBDA was not associated with age. The original MBDA score was associated with FMI Z-score among women (rho = 0.42, p = 0.002) but not men. The aMBDA was not associated with FMI Z-score in either women or men. The aMBDA score was lower than the original MBDA in the highest quartile of FMI in women and was higher in the lowest FMI quartiles in women and men. CDAI, SJC, and radiographic scores were similar across activity categories for the original MBDA score and aMBDA. The investigators concluded that the aMBDA demonstrated reduced associations with adiposity, particularly among women. The investigators also indicated that the aMBDA may be less likely to overestimate disease activity in women with greater adiposity and to underestimate disease activity in men and women with lesser adiposity.

Ma et al. (2020) used the multi-biomarker disease activity (MBDA) test to explore the role of biomarkers in predicting point remission and sustained remission. RA patients on > 6 months stable therapy in stable low disease activity (DAS28-ESR ≤ 3.2) were assessed every 3 months for 1 year. Baseline, intermittent (IR) and sustained (SR) remission were defined by DAS28-ESR, DAS28-CRP, simple disease activity index (SDAI), clinical disease activity index (CDAI) and ACR/EULAR Boolean criteria. Patients not fulfilling any remission criteria at baseline were classified as 'low disease activity state' (LDAS). Patients not fulfilling any remission criteria over 1 year were classified as 'persistent disease activity' (PDA). MBDA score was measured at baseline/3/6 months. The baseline MBDA score, the 6-month time-integrated MBDA score and MBDA biomarkers were used for analyses. The area under the receiver operating characteristic curve (AUROC) assessed the ability of the MBDA score to discriminate between remission and non-remission. Biomarkers were analyzed at baseline using the Mann-Whitney test and over time using the Jonckheere-Terpstra trend test. Of 148 patients, 27% were in the LDAS, 65% DAS28-ESR remission, 51% DAS28-CRP remission, 40% SDAI remission, 43% CDAI remission and 25% ACR/EULAR Boolean remission at baseline. Over 1 year, 9% of patients were classified as PDA. IR and SR were achieved in 42%/47% by DAS28-ESR, 46%/29% by DAS28-CRP, 45%/20% by SDAI, 44%/21% by CDAI and 35%/9% by ACR/EULAR Boolean criteria, respectively. By all remission criteria, baseline MBDA score discriminated baseline remission (AUROCs 0.68-0.75) and IR/SR (AUROCs 0.65-0.74). The 6-month time-integrated MBDA score discriminated IR/SR (AUROCs 0.65-0.79). Baseline MBDA score and concentrations of IL-6, leptin, SAA and CRP were significantly lower in all baseline remission criteria groups vs LDAS. They and the 6-month time-integrated values were lower among patients who achieved IR/SR vs PDA over 1 year. According to the investigators, this study demonstrated that the MBDA score and its biomarkers IL-6, leptin, SAA and CRP, differentiated between small differences in disease activity (i.e., between low disease activity and remission states). They were also predictors of remission over 1 year. The investigators indicated that the limitations of the study included the relatively small number of patients in sustained remission, particularly in the group meeting the ACR/EULAR Boolean definition and in the group with no remission at any time point, i.e., the PDA group. Secondly, because the different remission groups contained overlapping populations, it was not possible to formally compare them to each other. Thirdly, Anti-citrullinated protein antibodies (ACPA) status was not analyzed as a predictor of remission in REMIRA because the focus of this study was the MBDA score and its biomarkers and because ACPA data were incomplete. Lastly, BMI data was not collected in this study and the MBDA scores were not adjusted for adiposity.

The 2016 update of The European League Against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs indicated that although MBDA testing has been reported to improve patient monitoring during RA treatment with biological agents, this test may give falsely elevated results in patients who have an infection (Smolen et al., 2017). The 2019 EULAR updated recommendations (Smolen et al., 2020) no longer mention the Vectra DA (MBDA) test.

The American College of Rheumatology (ACR) updated their Recommended Rheumatoid Arthritis Disease Activity Measures and included the original Vectra DA test as meeting a minimum standard for regular use in most clinical settings. The content validity and structural validity of the Vectra DA test were identified as strong (consistent findings in multiple studies of good methodological quality –OR- in one study of excellent methodological quality). The reliability of the Vectra DA test was indicated as unknown (studies only of poor methodological quality) (England et al., 2019).

Curtis et al. (2019c) developed and evaluated an adjusted score for the MBDA test to account for the effects of age, sex and adiposity in patients with RA. Two models were developed to adjust MBDA score for age, sex and adiposity, using either serum leptin concentration or BMI as proxies for adiposity. Two cohorts were studied. A cohort of 325 781 RA patients who had undergone commercial MBDA testing and had data for age, sex and serum leptin concentration was used for both models. A cohort of 1411 patients from five studies/registries with BMI data was used only for the BMI-adjusted MBDA score. Univariate and multivariate linear regression analyses evaluated the adjusted MBDA scores and conventional clinical measures as predictors of radiographic progression, assessed in terms of modified total Sharp score (∆mTSS). Two models were developed, based on findings that MBDA score was higher in females than males and increased with age, leptin concentration and BMI. In pairwise regression analyses, the leptin-adjusted (p = 0.00066) and BMI-adjusted (p = 0.0027) MBDA scores were significant independent predictors of ∆mTSS after adjusting for DAS28-CRP, whereas DAS28-CRP was not, after adjusting for leptin-adjusted (p = 0.74) or BMI-adjusted (p = 0.87) MBDA score. Moreover, the leptin-adjusted MBDA score was a significant predictor of ∆mTSS after adjusting for the BMI-adjusted MBDA score (p = 0.025) or the original MBDA score (0.027), whereas the opposite was not true. According to the investigators, Leptin-adjusted MBDA score significantly adds information to DAS28-CRP and the original MBDA score in predicting radiographic progression. The investigators indicated that it may offer improved clinical utility for personalized management of RA. This study was supported by Crescendo Bioscience Inc.

Curtis et al. (2019a) compared the multi-biomarker disease activity (MBDA) score with the DAS28-CRP and CRP for predicting risk of radiographic progression in patients with rheumatoid arthritis. Published studies of the MBDA score and radiographic progression with ≥ 100 patients per cohort were evaluated. Patient-level data from studies having all three measures was pooled to: (1) determine a combined RR for radiographic progression in the high vs. not-high categories for each measure; and (2) compare the predictive ability of MBDA score vs. DAS28-CRP by comparing the rates of radiographic progression observed in subgroups created by cross-classifying the high and not-high categories of each measure. Five cohorts were identified for inclusion (total n = 929). In each, radiographic progression was more frequent with increasing MBDA scores. Among the three cohorts with requisite data, PPVs were generally similar using categories of MBDA score, DAS28-CRP or CRP but NPVs were greater for MBDA score (93-97%) than DAS28-CRP or CRP (77-87%). RRs for radiographic progression were greater when based on categories of MBDA score than DAS28-CRP or CRP and the combined RR was greater for MBDA score than DAS28-CRP or CRP. For patients cross-classified by MBDA score and DAS28-CRP, high vs. not-high MBDA score significantly predicted radiographic progression independently of DAS28-CRP. The authors concluded that high and not-high MBDA scores were associated with increased and low risk, respectively, for radiographic progression over one year. MBDA score was a better predictor of radiographic progression than DAS28-CRP or CRP. This study did not validate MBDA findings with improved treatment outcomes.

Curtis et al. (2019b) evaluated the clinical utility of the multi - biomarker disease activity (MBDA) test for rheumatoid arthritis (RA) management in routine care. Using 2011-2015 Medicare data, each patient with RA was linked to their MBDA test result. Initiation of a biologic or Janus kinase (JAK) inhibitor in the 6 months following MBDA testing was described. Multivariable adjustment evaluated the likelihood of adding or switching biologic/JAK inhibitor, controlling for potential confounders. For patients with high MBDA scores who added a new RA therapy and were subsequently retested, lack of improvement in the MBDA score was evaluated as a predictor of future RA medication failure, defined by the necessity to change RA medications again. Among 60,596 RA patients with MBDA testing, the proportion adding or switching biologics/JAK inhibitor among those not already taking a biologic/JAK inhibitor was 9.0% (low MBDA), 11.8% (moderate MBDA), and 19.7% (high MBDA). Similarly, among those already taking biologics/JAK inhibitor, the proportions were 5.2%, 8.3%, and 13.5%. After multivariable adjustment, referent to those with low disease MBDA scores, the likelihood of switching was 1.51-fold greater for patients with moderate MBDA scores, and 2.62 for patients with high MBDA scores. Among those with high MBDA scores who subsequently added a biologic/JAK inhibitor and were retested, lack of improvement in the MBDA score category was associated with likelihood of future RA treatment failure. The authors concluded that the MBDA score was associated with both biologic and JAK inhibitor medication addition/switching and subsequent treatment outcomes. This study did not compare the MBDA test with other methods of disease activity assessment to determine whether they would have had similar influences on RA patient management.

Johnson et al. (2018) performed a systematic review of the multi-biomarker disease activity (MBDA) and meta-analysis of the correlation between the MBDA and other rheumatoid arthritis (RA) disease activity measures. Twenty-two studies were identified in the systematic review, of which 8 (n = 3,242 assays) reported correlations of the MBDA with RA disease activity measures. Pooling results from these eight studies in the meta-analysis, the MBDA demonstrated modest correlations with DAS28-CRP and DAS28-ESR with weaker correlations observed with SDAI, CDAI, and RAPID3. Correlations between change in

MBDA and change in disease activity measures ranged from r = 0.53 (DAS28-ESR) to r = 0.26 (CDAI). The authors concluded that MBDA demonstrates moderate convergent validity with DAS28-CRP and DAS28-ESR, but weaker correlations with SDAI, CDAI, and RAPID3. While it appears to complement existing RA disease activity measures, further assessment of the MBDA's performance characteristics is warranted.

Hambardzumyan et al. (2017) analyzed data from 157 patients who had an inadequate response to methotrexate monotherapy (MTX-IRs) from the Swedish Pharmacotherapy (SWEFOT) trial who were randomized to receive triple therapy (MTX plus sulfasalazine plus hydroxychloroquine) versus MTX plus infliximab. Among the 157 patients, 12% had a low MBDA score, 32% moderate, and 56% high. Of those with a low MBDA score, 88% responded to subsequent triple therapy, and 18% responded to MTX plus infliximab; for those with a high MBDA score, the response rates were 35% and 58%, respectively. Clinical and inflammatory markers had poorer predictive capacity for response to triple therapy or MTX plus infliximab. The authors concluded that in patients with RA who had an inadequate response to MTX, the MBDA score categories were differentially associated with response to subsequent therapies. Thus, patients with post-MTX biochemical improvements (lower MBDA scores) were more likely to respond to triple therapy than to MTX plus infliximab. According to the authors, if confirmed, these results may help to improve treatment in RA. This study was limited because it was a retrospective analysis. Another limitation is that because of missing data, the authors were unable to analyze 40% of patients who were randomized to second-line therapy causing uncertainty regarding the reliability of the results.

Bouman et al. (2017) evaluated the predictive value of the baseline multi-biomarker disease activity (MBDA) score in long-standing RA patients with low disease activity tapering TNF inhibitors (TNFi) for successful tapering or discontinuation, occurrence of flare and major flare, and radiographic progression. Dose REduction Strategies of Subcutaneous TNF inhibitors (Dutch Trial Register, NTR 3216) is an 18-month non-inferiority randomized controlled trial comparing tapering of TNFi until discontinuation or flaring with usual care (UC) in long-standing RA patients with stable low disease activity. MBDA scores were measured at baseline. Radiographs were scored at baseline and 18 months using the Sharp-van der Heijde score. The area under the receiver operating characteristic (AUROC) curve was used to analyze the capability of baseline MBDA score to predict the above-mentioned outcomes. Serum samples and outcomes were available for 171 of 180 patients from Dose REduction Strategies of Subcutaneous TNF inhibitors (115 tapering; 56 UC). AUROC analyses showed that baseline MBDA score was not predictive for the above-mentioned clinical outcomes in the taper group, but did predict major flare in the UC group. Radiographic progression was minimal and was not predicted by MDBA score. The authors concluded baseline MBDA score was not predictive for successful tapering, discontinuation, flare, major flare or radiographic progression in RA patients who tapered TNFi.

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Code	Description
93702	Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)

The use of bioimpedance spectroscopy for lymphedema assessment is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Lymphedema can occur when the lymph system is damaged or blocked, which can prevent the lymph fluid from returning to the blood, resulting in swelling in the affected body part. Bioimpedance spectroscopy (BIS) is a newer, non-invasive technique for the direct measurement of extracellular fluid volume. The BIS device passes an extremely low-strength electrical current through the area and measures how the flow of the current is slowed by the fluid in the body. It is being explored as a tool to detect early signs of lymphedema when interventions may more effectively prevent progression.

In 2022, Ridner et al. reported results from a stratified, randomized international trial of 1200 newly diagnosed breast cancer patient undergoing mastectomy/partial mastectomy, axillary treatment, radiation therapy, or taxane based chemotherapy. They compared rates of progression to chronic breast cancer related lymphedema following an intervention for subclinical lymphedema (S-BCRL) identified by bioimpedance spectroscopy (BIS) using the L-DexU400 (SOZO) (ImpediMed, Ltd. Brisbane) or by tape measurement (TM). Following post-surgery eligibility reassessment, randomization to prospective surveillance by BIS or TM occurred. A S-BCRL detection then triggered a 4-week, 12-hour per day, compression sleeve, and gauntlet intervention. The primary outcome was the rate of progression to CDP and was assessed over three years. Of the 1200 participants, 963 were randomized, and 879 were included in the analysis. 209 patients had a need for an intervention identified. The results showed a lower proportion of BIS patients triggered an intervention, and the median time from randomization to intervention was longer. 30 of these participants progressed after intervention. Of those patients, no difference between the groups was observed in intervention completion rates. The participants that received BIS were less likely to progress to CDP than the TM group. The median follow-up months were not statistically significant between the groups. The authors concluded that the use of BIS for prospective BCRL surveillance, allows early intervention of CDP and reduces progression to C-BCRL. These results are likely related to the ability of BIS to detect an increase in extracellular fluid, as opposed to TM's ability to only detect an increase in whole arm volume. This study is limited in that it compares BIS to only one diagnostic for BCRL diagnosis and cannot be extrapolated to other well-established diagnostics.

Shah et al. (2021) conducted a systematic review and 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 measurement as compared to the expected incidence. A search, using predetermined terms, was conducted using PUBMED, CINAHL, and Google Scholar. BCRL incidence rates were classified by monitoring method: background (no standardized BIS or circumference assessments), BIS or circumference. A random-effects model was used to calculate a pooled annualized estimate of BCRL incidence while accounting for clinical and methodological heterogeneity. Known risk factors for BCRL were assessed via subgroup analyses. Sufficient data were available on the proportion of patients undergoing axillary lymph node dissection (ALND), sentinel lymph node biopsy (SLNB), and mastectomy. Other known risk factors not included due to a lack of data were body mass index (BMI), taxane chemotherapy, and regional nodal irradiation (RNI). Results were reported without transformation but were square root transformed. A total of 2,259 individual references

were identified and screened and of those, 50 studies were included, representing 67,712 women. The annualized incidence of BCRL was 4.9% (95% CI: 4.3 to 5.5) for background studies (n = 35), 1.5% (95% CI: 0.6 to 2.4) for BIS-monitored studies (n = 7), and 7.7% (95% CI: 5.6 to 9.8) for circumference-monitored studies (n = 11). The cumulative BCRL incidence rate in BIS-monitored patients was 3.1% as compared to 12.9% with background monitoring (69% reduction) and 17.0% with circumference-monitored patients (81% reduction). The authors concluded that monitoring with BIS allows for early intervention and thereby, significantly reduces the relative risk of chronic BCRL with a 69% and 81% reduction compared to the expected incidence and circumference-monitoring, respectively. They also stated that BIS should be considered for BCRL screening in order to detect subclinical BCRL and reduce rates of chronic BCRL, particularly in high-risk patients. However, a notable limitation of this study is that the investigators did not adjust for patient-related BCRL risk factors (e.g., BMI, taxane chemotherapy, and RNI) between the groups, and even after square-root transformation of the data, heterogeneity estimates remained high (> 50%) as related to between-study differences as well as clinical risk factors e.g., ALND, and SLNB. Other differences between cohorts, such as level of BCRL and other confounding factors, significantly limit the conclusion that can be drawn from the indirect comparisons performed in this study. Additional studies evaluating the clinical utility of BIS as a monitoring tool for breast cancer-related lymphedema are still needed.

A Hayes Health Technology Assessment (HTA), Bioelectrical Impedance (Bioimpedance) Analysis for Assessment of Lymphedema states that the clinical performance and accuracy of multiple frequency bioimpedance analysis (MFBIA), also referred to as bioimpedance spectroscopy (BIS) is similar to or somewhat lower than the accuracy of other techniques for lymphedema (LE) diagnosis, prediction of LE development, and guidance of treatment. With regard to guiding management of patients at risk for LE, the evidence does not provide conclusive evidence of clinical utility and additional studies are needed on the clinical role of BIS relative to established techniques (2020; updated 2021).

A 2020 ECRI health technology assessment regarding the SOZO Bioimpedance Spectroscopy™ (ImpediMend, Carlsbad, CA) for Diagnosing and Managing Lymphedema, states that there are too few data on important clinical outcomes and therefore, definitive conclusions cannot be made (2020).

Ridner et al. (2019) reported interim results from an ongoing RCT to compare the incidence of severe lymphedema using circumference tape measure (TM) or BIS to detect early lymphedema and initiate treatment. This prespecified interim analysis was conducted when at least 500 trial participants had ≥ 12 months of follow-up. Enrolled patients were randomized to either TM or BIS surveillance. Patients requiring early intervention were prescribed a compression sleeve and gauntlet for 4 weeks and then re-evaluated. The primary endpoint was the rate of progression to clinical lymphedema requiring complex decongestive physiotherapy (CDP), with progression defined as a TM volume change in the at-risk arm ≥ 10% above the presurgical baseline. A total of 508 patients were included, with 109 (21.9%) patients triggering prethreshold interventions. Compared with TM, BIS had a lower rate of trigger (15.8% vs. 28.5%, $p<0.001$) and longer times to trigger (9.5 vs. 2.8 months, $p = 0.002$). After a median of 17.8 months (interquartile range, 13-23 months), 12 triggering patients progressed to CDP (10 in the TM group [14.7%] and 2 in the BIS group [4.9%]), representing a 67% relative reduction and a 9.8% absolute reduction ($p = 0.130$). The authors concluded that the interim results demonstrated that post-treatment surveillance with BIS reduced the absolute rates of progression of BCRL requiring CDP by approximately 10%, a clinically meaningful improvement, and that these results support the concept of post-treatment surveillance with BIS to detect subclinical BCRL and initiate early intervention. Limitations of this study are that the authors' conclusions are based on interim results of an ongoing trial, the number of patients that progressed to CDP was very low, and the difference between the rates of progression to CDP in the TM vs. BIS group was not statistically significant. Additional data from this study when completed as well as additional randomized studies may further clarify the clinical utility of BIS as an early intervention to detect BCRL.

Qin et al. (2018) conducted a single-center, retrospective case series study to test the sensitivity, specificity, and diagnostic accuracy of bioimpedance spectroscopy (BIS) in diagnosing lymphedema. In this study, 58 patients had positive indocyanine green lymphography results, which is the most accurate diagnostic modality to diagnosis lymphedema. When tested with BIS, 21/58 had normal BIS readings, which represents a 36% false positive rate. The 21 patients with false-negative results were patients with early-stage disease. The BIS sensitivity and specificity were 0.64 and 1, respectively. The authors concluded that BIS carries an excessively high rate of false-negative results to be dependably used as a diagnostic modality for lymphedema.

Whitworth and Cooper (2018- included in Hayes health technology assessment)) conducted a single-center, case series analysis to evaluate the use of BIS to facilitate early detection and treatment of breast cancer-related lymphedema (BCRL). From April 2010 through November 2016, patients enrolled in the center's BCRL surveillance program and were followed prospectively using a standard protocol, which included BCRL education and preoperative and postoperative L-Dex U400

measurements. An elevated L-Dex score was defined as an increase of greater than 10 points from baseline. If an elevated was noted, the intervention was initiated, which consisted of complete decongestive physiotherapy (CDP) for 4 weeks and then, an L-Dex score re-evaluation. The study group was comprised of 596 participants (79.6% considered to be high risk), with a mean follow-up period of 17 months (range 0.2-80.4). Overall, 73 patients (12%) had an abnormal L-Dex score at some point during surveillance. Of the 73 patients, 55 (75%) patients' L-Dex scores returned to normal while 18 had L-Dex scores that did not return to baseline and required CDP. The authors concluded that the results (which represent the largest group of patients monitored in a structured program for early detection of BCRL using BIS) support the concept that prospective surveillance using BIS can detect subclinical BCRL, facilitating simple preemptive intervention and resulting in very low rates of chronic BCRL. Additional randomized controlled trials evaluating BIS to other detection modalities e.g., arm circumference measurement alone are underway and are still needed to determine the efficacy of BIS. This study was included in the Shah (2021) study.

Bundred et al. (2015-included in Hayes health technology assessment) conducted a multi-center, case series study comparing multi-frequency BIS with perometry in the prediction of lymphedema. Women who were undergoing axillary node clearance had preoperative and postoperative measurements of arm volume by both methods. The primary outcome measure was the incidence of lymphedema (defined as a ≥ 10% arm volume increase compared to the contralateral arm by perometer) at 2- and 5-years following node clearance. A total of 612 women had 6 months of follow-up data, and the 1-month postoperative measurement was used as the baseline measurement. At 6 months, the perometer detected 31 patients with lymphedema vs. 53 patients detected with BIS. By 6 months, 89% of those with no lymphedema reported at least one symptom. There was moderate correlation between perometer and BIS at 3 months (R^2 = 0.40) and 6 months (R^2 = 0.60), with a sensitivity of 73% and specificity of 84%. Univariate and multivariate analyses showed a threshold for early intervention of ≥ 5 to < 10% (p = 0.03). The authors concluded that even though the threshold for early intervention was ≥ 5 to < 10% symptoms alone do not predict lymphedema and that a modest correlation between methods at 6 months indicates that arm volume measurement remains the gold standard, although longer follow-up is also needed.

Erdogan et al. (2015) conducted a single-center, case series analysis of patients with breast cancer who underwent surgical procedures to evaluate the efficacy of BIS for detection of lymphedema. Thirty-seven patients were evaluated using BIS and other clinical measurements every 3 months for up to 1 year. A total of 8 patients (21.6%) developed lymphedema; 4 with Stage 2, 1 with Stage 1, and 3 with Stage 0. With BIS, there was an association between the occurrence of lymphedema and the number of extracted lymph nodes, remaining lymph nodes and region of radiotherapy (p = 0.042, p = 0.024, p = 0.040, respectively). The authors concluded that preliminary results indicate that bioimpedance may be a reasonable method regular monitoring to detect lymphedema. However, additional randomized controlled trials with larger samples are still needed. This study was included in the Shah (2021) study.

Barrio et al. (2015-included in Hayes health technology assessment) performed a prospective validation study of bioimpedance with volume displacement (VD) in early-stage breast cancer patients at risk for lymphedema. Analyzing 186 patients at 3-6 months intervals for 3 years, VD and bioimpedance demonstrated poor correlation with inconsistent overlap of measurements considered abnormal. The authors concluded that further studies are needed to understand the clinical significance of bioimpedance.

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer recommend educating patients on lymphedema, monitoring for the condition, and referring for management as needed. The use of BIS is not specifically mentioned.

The 2011 National Lymphedema Network practice guideline, states that all patients have pretreatment measurements of both arms. Post treatment measurements should be done on both arms at each visit with symptoms assessment for swelling, heaviness, and/or tightness in the affected arm/arms, and at-risk chest and truncal areas using consistent measurement methods. Circumferential tape measurements are acceptable when made with a flexible, non-elastic Gulick II (or similar) tape measure, and bioelectrical spectroscopy (BIS) or infrared perometry are suggested as alternative or adjunct methods.
The U.S. Food and Drug Administration (FDA) cleared the SOZO™ Impedance Plethysmograph (ImpediMed, Carlsbad, CA) under its 510(k) premarket notification process on August 11, 2017. The device is indicated for use on adults and utilizes impedance ratios that are displayed as an L-Dex ratio as an aid to the clinical assessment of unilateral lymphedema of the arm and leg in women and the leg in men. It is only indicated for patients who will have or who have had lymph nodes, from the axillary and pelvic regions, either removed, damaged or irradiated. For additional information, refer to the following website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K180126. (Accessed May 16, 2022)

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Code	Description
K1007	Bilateral hip, knee, ankle, foot (HKAFO) device, powered, includes pelvic component, single or double upright(s), knee joints any type, with or without ankle joints any type, includes all components and accessories, motors, microprocessors, sensors

The use of the robotic lower body exoskeleton device is unproven and not medically necessary for ambulation assistance in all settings/levels of care in patients with conditions which impair the ability to ambulate (e.g., spinal cord injury, stroke, Parkinson's disease, etc.) due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Robotic lower body exoskeletons (also referred to as reciprocating gait orthoses, powered orthoses, robotic orthoses, robotic gait assist devices, wearable exoskeletons, bionic legs, and computerized walking systems) are intended to assist some patients with paraplegia as a result of spinal cord injury (SCI) to stand and move to improve their independence and QOL. Some early clinical trials have also evaluated versions of this technology in patients with other conditions including quadriplegia, stroke, multiple sclerosis, and Parkinson's disease.

Zhang et al. (2022) performed a systematic review and meta-analysis to assess locomotor abilities in patients with spinal cord injuries (SCI) with two different types of robotic-assisted gait training (RAGT) programs, Lokomat and wearable exoskeleton-assisted walking (EAW) training. From 319 studies identified, 12 studies published between 2013 and 2021 were included in this review. The study included evaluation of locomotor abilities with a 10-meter walk test (10-MWT), 6- minute walk test (6-MWT), time up and go (TUG) test, and walking index for spinal cord injury (WISCI-II) in patients with SCI. The authors findings concluded wearable EAW showed notable increase in distance and speed in the 10-MWT [distance: 0.85 (95% ci = 0.35, 1.34); speed: −1.76 (95% ci = −2.79, −0.73)]. In findings for the 6-MWT and TUG test, they also concluded notable increase; 6-MWT distance [−1.39 (95% ci = −2.01, −0.77)] and TUG test [(1.19 (95% ci = 0.74, 1.64)]. However, the WISCI-II did not have a notable distinction [−0.33 (95% ci = −0.79, 0.13)]. In the authors findings for Lokomat, the 10-MWT and WISCI-II revealed notable increases. The 10-MWT distance was [−0.08 (95% ci = −0.14, −0.03)] and WISCI-II was [1.77 (95% ci = 0.23, 3.31)]. Overall, the two types of RAGT had beneficial effects on locomotion abilities but EAW had better outcomes in speed compared to Lokomat. However, there were limitations in the study based on the small sample size of articles. According to the authors, further studies are necessary to understand if the intensity of training affects RAGT success, and by which RAGT techniques enhanced walking recovery capabilities.

Yip et al. (2022) performed a scope review on overground exoskeleton effectiveness, preclusions on secondary health complications, quality of life (QOL) changes, and the outcomes on the independence of individuals with spinal cord injury (SCI) in community settings. The purpose of the review was to identify gaps in the current literature, and to make recommendations on future study areas and research methods. In this systematic review, an initial search 654 articles were identified, and 50 articles met the inclusion criteria. The authors concluded that overground exoskeletons show promise in health benefits, pragmatic outcomes in secondary health complications, enhancing QOL in individuals with SCI and favorable probability of regaining their previous roles in the community. There were limitations identified which include limited types of exoskeletons, variability on study design, distinct study populations, and diverse training programs, which future studies can address. The authors also recommend future studies in cardiovascular health, body mass density, body composition changes and applicability of exoskeleton toward independence and functional gain.

In Duddy et al. (2021), a systematic review of studies was conducted to examine the effects of powered exoskeleton training on cardiovascular function and gait performance. Out of a 65-article search conducted between April 2020 to February 2021, 23 studies were included in this review. The researchers examined cardiovascular function variables which included volume of oxygen (VO2), heart rate (HR), rate of perceived exertion (RPE), metabolic equivalent of task (MET), physiological cost index (PCI), respiratory exchange ratio (RER), energy expenditure and blood pressure (BP). In gait performance the researchers evaluated a variety of assessment protocols which include 6-minute walk test (6 MWT), 10-meter walk test (10 MWT), time up and go test (TUG), 25-foot walk test (25 FWT), 2-minute walk test (2 MWT), 30-minute walk test (30 MWT), total steps, distance and walking speed. The researchers concluded that powered exoskeleton assisted training may increase oxygen and HR when compared to non-exoskeleton walking. In comparison to non-exoskeleton walking and wheelchair propulsion, the MET and PCI of exoskeleton assisted walking demonstrated three to four times greater. In addition, carbohydrate utilization in RER was higher during exoskeleton walking. As for energy expenditure with exoskeleton assisted walking it was slightly less than non-exoskeleton walking and the RPE was equivalent to moderate intensity. When evaluating gait performance, the studies indicated improvements in all gait assessment protocols except for the 30 MWT. The 30 MWT identified that between ReWalk exoskeleton assistance and an unpowered KAFO the KAFO showed greater distance than the ReWalk. In conclusion, the researchers identified that powered exoskeleton training is a safe and effective way to improve cardiovascular function and gait performance. However, there were limitations in the study which include the limited sample size from some of the selected studies. According to the researchers, future studies are warranted with larger sample sizes, exploration of studies with control groups for further comparisons and to explore longitudinal effects of cardiovascular function with exoskeleton gait training, walking capabilities and secondary health conditions with longer durations.

In a clinical evidence assessment, ECRI (2021) evaluated wearable powered exoskeletons for personal use after a spinal cord injury (SCI) in the home and community settings. The analysis included 19 individuals from two case series and one case report. The authors concluded the studies contained a high risk of bias along with a small number of participants and that additional comparative studies with larger sample sizes assessing long-term outcomes and adverse effects were warranted to determine the benefit of these devices.

Rodríguez-Fernández et al. (2021) completed a systematic review of 87 clinical studies that gathered information and measured the outcomes of wearable lower-limb exoskeletons while gait training overground for individuals with neuromuscular impairments. There were 25 exoskeletons included with only 6 containing FDA approval and/or commercially available. The results of the literature survey revealed that wearable exoskeletons have potential for a number of applications including early rehabilitation, promoting physical exercise, and carrying out daily living activities both at home and the community. Likewise, wearable exoskeletons may improve mobility and independence in non-ambulatory people and may reduce secondary health conditions related to sedentariness. However, the use of this technology is still limited by heavy and bulky devices, which require supervision and the use of walking aids. In addition, evidence supporting their benefits is still limited to short-intervention trials with few participants and diversity amongst clinical protocols. Wearable lower-limb exoskeletons for gait rehabilitation are still in the early stages of development and RCTs are needed to demonstrate their clinical efficacy.
Awad et al. (2020) conducted a multi-site clinical trial that included 44 patients with post-stroke hemiparesis to study the safety, reliability and feasibility of the ReWalk Restore soft robotic exosuit for post-stroke gait rehabilitation. The patients trained for five days with the Restore soft exosuit and 16 patients required an assistive device (Ankle foot orthosis (AF0), cane, ankle brace, walker) on the treadmill and overground. During the five days of training, each visit consisted of 20 minutes of overground and 20 minutes treadmill walking practice while wearing the Restore exosuit motor at the waist as it transmitted mechanical forces to points located proximally attached around the calf and distally to a shoe insole. During the study eight patients dropped out for various reasons. Of the 36 patients that finished the study, they found the Restore soft exosuit clinically feasible, less than

10% had safety issues ranging from mild to severe, no falls, and the device malfunctioned for 11.6%. After five days of training 61% of the patients increased their maximum walking speed. The authors concluded that the ReStore soft exosuit is safe and reliable for using in post-stroke gait rehabilitation with the supervision of licensed physical therapist for support. These findings are motivation for further efficacy trials of soft robotic exosuits.

The exoskeleton hybrid assistive limb (HAL) is controlled voluntarily by the patient's own muscle signals detected by surface electrodes. Sczesny-Kaiser et al. (2019) conducted a monocentric, controlled, randomized, two-period crossover study to test the efficacy of HAL-assisted body weight supported treadmill training (BWSTT) compared to conventional physiotherapy (CPT) on walking parameters in chronic stroke patients. A total of 18 chronic stroke patients participated in this study. Treatment consisted of 30 CPT sessions and of 30 sessions of BWSTT with a double leg type HAL exoskeleton successively in a randomized, crossover study design. Primary outcome parameters were walking time and speed in 10-meter walk test (10MWT), time in timed-up-and-go test (TUG) and distance in 6-min walk test (6MWT). Secondary outcome parameters were the functional ambulatory categories (FAC) and the Berg-Balance Scale (BBS). Data were assessed at baseline, at crossover and at the end of the study, all without using and wearing HAL. The study demonstrated neither a significant difference in walking parameters nor in functional and balance parameters. When HAL-BWSTT was applied to naïve patients it led to an improvement in walking parameters and in balance abilities. Pooling all data, we could show a significant effect in 10MWT, 6MWT, FAC and BBS, both therapies sequentially applied over 12 weeks. Thereby, FAC improve from dependent to independent category (3 to 4). One patient dropped out of the study due to intensive fatigue after each training session. The authors concluded that HAL-BWSTT and mixed-approach CPT were effective therapies in chronic stroke patients. However, compared with CPT, HAL training with 30 sessions over 6 weeks was not more effective. The combination of both therapies led to an improvement of walking and balance functions. Robotic rehabilitation of walking disorders alone still lacks the proof of superiority in chronic stroke. Robotic treatment therapies and classical CPT rehabilitation concepts should be applied in an individualized therapy program.

Hayes and colleagues et al. (2018) conducted a systematic search of the literature investigating over ground and treadmill robotic assisted gait training (RAGT) in SCIs. Twelve studies met all inclusion criteria. Case-studies and case series were excluded. Participant numbers ranged from 5-130 with injury levels from C2 to T12, American Spinal Injuries Association A-D. Three studies used over ground RAGT systems and the remaining nine focused on treadmill based RAGT systems. Primary outcome measures were walking speed and walking distance. The use of treadmill or over ground based RAGT did not result in an increase in walking speed beyond that of conventional gait training and no studies reviewed enabled a large enough improvement to facilitate community ambulation. The authors concluded that use of RAGT in SCI individuals has the potential to benefit upright locomotion of SCI individuals. Its use should not replace other therapies but be incorporated into a multi-modality rehabilitation approach.

Cheung et al. (2017) completed a systematic review and meta-analysis to investigate the effects of robot-assisted training on the recovery of people with SCI. The survey considered all randomized controlled trials (RCTs) and quasi-RCTs. Only studies involving people with SCIs were considered. Studies were included if the intervention involved robot-assisted training, including both upper limb robotic training and robot-assisted body-weight–supported treadmill training (BWSTT). 11 articles met the inclusion criteria. Four articles were identified as reporting investigations of the effect of robotic training on walking speed and walking endurance. Two studies provided sufficient data for analysis. Together they involved 158 participants. The robotic group showed no significant improvement in walking speed. The pooled mean difference (fixed effects model) was only .08 seconds. The robot-trained group showed improvements in endurance, which were highly significant in both statistical and practical terms. The pooled mean difference (fixed effects model) was 53.32m (95% CI, −73.15 to −33.48; p ≤.00001; I^2 = 0%). Two articles reporting the effect of robotic training on walking independence were identified. A total of 158 participants were included. The robotic group showed better improvement in walking independence compared with the control group. The pooled mean difference (fixed effects model) was 3.73 (95% CI, −4.92 to −2.53; p < .00001; I^2 = 38%). Lower limb robot-assisted training was also found to be as effective as other types of BWSTT. The authors concluded that robot-assisted training is an adjunct therapy for physical and functional recovery for patients with SCI. Future high-quality studies are warranted to investigate the effects of robot-assisted training on functional and cardiopulmonary recovery of patients with SCI.

Fisahn et al. (2016) completed a systematic review to determine if powered exoskeletons are effective as assistive and rehabilitation devices in improving locomotion in patients with SCI. Eleven publications were included in the review, 10 utilized the robotic exoskeleton Lokomat and the remaining study utilized the robotic exoskeleton MBZ-CPM1 (ManBuZhe [TianJin] Rehabilitation Equipment Co. Ltd., PR China). Nine of the included randomized trials were of parallel design, and 2 were of crossover design. Most studies were of moderately high risk of bias. The authors of the review identified no comparison studies

evaluating exoskeletons as an assistive device. Nine comparison studies (11 publications) evaluated the use of exoskeletons as a rehabilitative device. The 10-meter walk test velocity and Spinal Cord Independence Measure scores showed no difference in change from baseline among patients undergoing exoskeleton training compared with various comparator therapies. The remaining primary outcome measures of 6-minute walk test distance and Walking Index for Spinal Cord Injury I and II and Functional Independence Measure–Locomotor scores showed mixed results, with some studies indicating no difference in change from baseline between exoskeleton training and comparator therapies, some indicating benefit of exoskeleton over comparator therapies, and some indicating benefit of comparator therapies over exoskeleton. The authors of this review concluded that there is no data to compare locomotion assistance with exoskeleton versus conventional knee-ankle-foot orthoses (KAFOs). The authors also concluded that there is no consistent benefit from rehabilitation using an exoskeleton versus a variety of conventional methods in patients with chronic spinal cord injury and that trials comparing later-generation exoskeletons are needed.

In 2016, Miller et al. completed a systematic review with meta-analysis on the clinical effectiveness and safety of powered exoskeletons in SCI patients. A total of 14 studies (eight ReWalk™, three Ekso™, two Indego®, and one unspecified exoskeleton) representing 111 patients were included in the analysis. Training programs were typically conducted three times per week, 60–120 minutes per session, for 1–24 weeks. Ten studies utilized flat indoor surfaces for training and four studies incorporated complex training, including walking outdoors, navigating obstacles, climbing and descending stairs, and performing activities of daily living. Following the exoskeleton training program, 76% of patients were able to ambulate with no physical assistance. The weighted mean distance for the 6-minute walk test was 98 m. The physiologic demand of powered exoskeleton-assisted walking was 3.3 metabolic equivalents and rating of perceived exertion was 10 on the Borg 6–20 scale, comparable to self-reported exertion of an able-bodied person walking at 3 miles per hour. Improvements in spasticity and bowel movement regularity were reported in 38% and 61% of patients, respectively. No serious adverse events occurred. The incidence of fall at any time during training was 4.4%, all occurring while tethered using a first-generation exoskeleton and none resulting in injury. The incidence of bone fracture during training was 3.4%. Limitations to the meta-analysis included considerable variation in the consistency of outcome reporting among studies. It is also noted that the research for this analysis was supported by ReWalk Robotics, Inc. the manufacturer of the ReWalk™ exoskeleton.

Louie and Eng (2016) completed a literature review surrounding the use of robotic exoskeletons for gait rehabilitation in adults' post-stroke. Articles were included if they utilized a robotic exoskeleton as a gait training intervention for adult stroke survivors and reported walking outcome measures. Of 441 records identified, 11 studies involving 216 participants met the inclusion criteria. The study designs ranged from pre-post clinical studies (n = 7) to controlled trials (n = 4); five of the studies utilized a robotic exoskeleton device unilaterally, while six used a bilateral design. Participants ranged from sub-acute (< 7 weeks) to chronic (> 6 months) stroke. Training periods ranged from single-session to 8-week interventions. Meaningful improvement with exoskeleton-based gait training was more apparent in sub-acute stroke compared to chronic stroke. Two of the four controlled trials showed no greater improvement in any walking outcomes compared to a control group in chronic stroke. The authors concluded that clinical trials demonstrate powered robotic exoskeletons can be used safely as a gait training intervention for stroke. Preliminary findings suggest that exoskeletal gait training is equivalent to traditional therapy for chronic stroke patients, while sub-acute patients may experience added benefit from exoskeletal gait training. According to the authors of this review, efforts should be invested in designing rigorous, appropriately powered controlled trials before powered exoskeletons can be translated into a clinical tool for gait rehabilitation post-stroke.

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Code	Description
G0429	Dermal Filler injection(s) for the treatment of facial lipodystrophy syndrome (LDS) (e.g., as a result of highly active antiretroviral therapy)
L8607	Injectable bulking agent for vocal cord medialization, 0.1 ml, includes shipping and necessary supplies
Q2026	Injection, Radiesse, 0.1ml
Q2028	Injection, sculptra, 0.5 mg

Radiesse is proven and medically necessary and reconstructive for treating facial defects due to facial lipidatrophy in persons with human immunodeficiency virus (HIV). Other uses of this device may be cosmetic.

Sculptra is proven and medically necessary and reconstructive for treating facial defects due to facial lipidatrophy in persons with human immunodeficiency virus (HIV). Other uses of this device may be cosmetic.

Prolaryn and Prolaryn Plus (formerly the Radiesse Laryngeal Implant) are proven and medically necessary and reconstructive for treatment of vocal fold insufficiency.

Clinical Evidence

Human Immunodeficiency Virus

It is estimated that approximately 50% of patients with human immunodeficiency virus (HIV) infection who are treated with highly active antiretroviral therapy (HAART) develop significant loss of facial fatty tissue (lipoatrophy). This feature carries a negative social stigma and imparts such a poor body image that many individuals develop body dysmorphic features so severe that they become non-compliant with HAART, discontinue visits to the infectious disease clinics and stop taking their medications. Injectable fillers have been approved by the FDA to treat this facial lipoatrophy in HIV patients and include poly-L-lactic acid (Sculptra), calcium hydroxylapatite microspheres and carboxymethylcellulose (Radiesse) (Guzman and Al Aboud, 2018).

On December 22, 2006, the FDA approved Radiesse, an injectable (under the skin) implant to restore or correct signs of facial lipidatrophy, or fat loss, in people with human immunodeficiency virus (HIV). For additional information, refer to the following website: https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050052b.pdf. (Accessed April 20, 2022)

On August 3, 2004, the FDA approved Sculptra, an injectable filler to correct facial fat loss in people with HIV) (FDA, 2004). Sculptra is an injectable form of poly-L-lactic acid, a biodegradable, biocompatible synthetic polymer from the alpha-hydroxy-acid family. For additional information, refer to the following: https://www.accessdata.fda.gov/cdrh_docs/pdf3/p030050b.pdf. (Accessed April 20, 2022)

Vallejo et al. (2018) conducted a clinical trial including 147 patients with HIV-induced lipoatrophy treated with Sculptra (poly-L-lactic acid), Radiesse (calcium hydroxylapatite), Aquamid (polyacrylamide), or autologous fat. Objective and subjective changes were evaluated during a 24-month follow-up period. Number of sessions, total volume injected, and overall costs of treatment were also analyzed. Objective improvement in facial lipoatrophy, assessed by the surgeon in terms of changes from baseline using an established classification system, was reported in 53 percent of the cases. Patient self-evaluation showed a general improvement after the use of facial fillers. Patients reported being satisfied with the treatment and with the reduced impact of lipodystrophy on their quality of life. Despite the nonsignificant differences observed in the number of sessions and volume, autologous fat showed significantly lower costs than all synthetic fillers ($p < 0.05$). The authors concluded that surgical treatment of HIV-associated facial lipoatrophy using dermal fillers is a safe and effective procedure that improves the aesthetic appearance and the quality of life of patients. Permanent fillers and autologous fat achieve the most consistent results over time.

Kraus et al. (2016) reported that the QOL outcomes associated with treatment of HIV facial lipoatrophy (FLA) with poly-L-lactic acid and similar agents appears to improve QOL as assessed by various QOL instruments. Additional studies are required to identify a unifying QOL instrument to effectively assess longitudinal QOL outcomes and to compare treatment modalities. Ho and Jagdeo (2016) found similar QOL results in 19 patients that completed a 12-month follow-up. The authors recommend use of the Facial Appearance Inventory (FAI) and FACE-Q in future studies for HA filler treatment of HIV FLA.

Jagdeo et al. (2015) conducted a systematic review of filler agents for aesthetic treatment of HIV facial lipoatrophy (FLA). A search, using predetermined criteria, was conducted in Medline. A total of 321 articles were identified and after screening, 76 original articles were deemed suitable for the review. Of those, 29 articles evaluated poly-L-lactic acid (PLLA; Sculptra) and 6 evaluated calcium hydroxylapatite (CaHA; Radiesse). Based on 3 randomized controlled trials with 2 follow-up studies, 20 observational studies and 4 case reports, PLLA for the treatment of HIV FLA was assigned a B-level recommendation. Six studies evaluated the efficacy and safety of CaHA for treatment of HIV FLA and of those, two showed that CaHA improvement of FLA severity was maintained for 12 months. Based on 6 observational studies, CaHA was assigned a C-level recommendation. The authors concluded that current literature suggests that filler agents for treatment of HIV FLA are an effective and generally safe option for aesthetic improvement and help improve patients' quality of life.

Vocal Fold Insufficiency

Vocal fold insufficiency, also known as vocal cord dysfunction or glottal insufficiency, is characterized as an incomplete closure of one (unilateral) or both (bilateral) of the vocal fold(s). When the glottis does not close properly, vocal fatigue, poor voice quality or tone and difficulty speaking, swallowing or coughing may occur. Individuals with vocal fold insufficiency are at greater risk for larynx penetration, aspiration and pneumonia (Rajaei, 2014). Treatment options include voice therapy, thyroplasty or vocal fold injection. Thyroplasty involves altering the position of the vocal cords by inserting a permanent implant that pushes inward on the vocal folds assisting them to open and close properly. Vocal fold injection involves injecting a bulking agent into the affected fold to assist it in sufficiently aligning with the opposing fold (Zhang 2015).

On March 7, 2007, the U.S. Food and Drug Administration (FDA) approved the Radiesse Laryngeal Implant, a sterile, non-pyrogenic injectable material consisting of calcium hydroxylapatite (CaHA) suspended in an aqueous formulation of USP grade pharmaceutical excipients consisting of sterile water, glycerin, and sodium carboxymethylcellulose, stabilized with a phosphate buffer. It is indicated for vocal fold medialization and vocal fold insufficiency that may be improved by injection of a soft tissue hulking agent. For additional information, refer to: https://www.accessdata.fda.gov/cdrh_docs/pdf7/K070090.pdf. (Accessed April 20, 2022).

Additionally, the U.S. Food and Drug Administration (FDA) 510(k) documents refer to Prolaryn products above using their original product names. Prolaryn Plus was originally cleared as the Radiesse Laryngeal Implant (Bioform Medical, Inc., Franksville, WI, USA), and Prolaryn Gel was originally cleared for marketing as the Laryngeal Augmentation Implant (Bioform, Inc.).

In a single-center prospective study, Mohammed et al. (2016) evaluated 43 patients with unilateral vocal cord palsy undergoing Radiesse vocal cord augmentation. Ten-item voice handicap index (VHI-10) scores were analyzed before and after the procedure. Results suggest a sustained improvement before and after the intervention (pre-injection versus 3 months post-injection $p < 0.01$; pre-injection versus 6 months post-injection $p < 0.033$).

Carroll and Rosen (2011) evaluated the long-term effectiveness of CaHA as a vocal fold injectable by accessing data from a cohort of patients who underwent injection for glottal insufficiency. The change in Voice Handicap Index (VHI)-10 scores between pre injection scores and best post injection scores as well as between the pre injection and the most recent VHI-10 scores were used as primary outcome measures to determine the persistence of benefit or the time to loss of benefit. Ninety patients who underwent 108 vocal fold injections with CaHA were evaluated for inclusion. Twenty patients with 22 injections met the criteria for inclusion. Fourteen of 22 (64%) subjects showed loss of benefit of the CaHA material. The average length of benefit was 18.6 months, with a range of 8 to 36 months. Three complications were identified among the original cohort of 108 injections. The authors concluded that CaHA remains a safe and effective long-term vocal fold injectable with an average length of benefit of 18.6 months.

Rosen et al. (2009) evaluated the long-term effectiveness of calcium hydroxylapatite (CaHA) vocal fold injection for patients with glottal insufficiency in a multicenter, open-label, prospective clinical study (n = 63). Voice-related outcome measures were collected for pre-injection, 1, 3, 6, and 12 months. Utilizing the Voice Handicap Index-10, visual analog scale (vocal effort), Consensus Assessment Perceptual Evaluation V (judgments of voice severity), and objective voice measures of glottal closure (maximum phonation time and S:Z ratio), paired t tests showed significant improvements after treatment. A 22% further treatment rate was found at the 12-month time point. The authors concluded that the one-year results in this cohort of patients with glottal incompetence treated with CaHA vocal fold injection demonstrate that excellent clinical results were achieved.

In a multi-center prospective study, Rosen et al. (2007) evaluated the effectiveness of CaHA injection for patients with glottal incompetence. Voice-related outcome measures were collected for pre-injection and at one, three and six months. Sixty-eight patients were available for evaluation. Fifty percent of the injection procedures were done in the office setting. Fifty-seven percent were diagnosed with unilateral paralysis and 42% with glottal incompetence with mobile vocal folds. Patient satisfaction at six months post-procedure showed 56% had significantly improved voice, and 38% reported moderately improved voice.

In a 2013 clinical practice guideline on improving voice outcomes after thyroid surgery, the American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS) made a strong recommendation for identifying the recurrent laryngeal nerve(s) during thyroid surgery, and recommendations to examine and document voice and vocal fold mobility both before and after surgery. AAOHNS recommended that if patients have voice change or abnormal vocal fold mobility after surgery, surgeons should provide counsel on options for rehabilitation. Vocal fold injection medialization is described as a temporary intervention that may reduce the need for later surgical reconstruction.

In a 2018 practice guideline on dysphonia (hoarseness), the AAOHNS states that clinicians should advocate for surgery as a therapeutic option for patients with dysphonia with conditions amenable to surgical intervention, such as suspected malignancy, symptomatic benign vocal fold lesions that do not respond to conservative management, or glottic insufficiency. This surgery includes vocal fold injection medialization using bulking agents.

The U.K.'s National Institute for Health and Care Excellence (NICE) provided guidance in 2005 on collagen injection for vocal cord augmentation. NICE concluded that the current evidence suggests collagen injection is efficacious for short-term symptom relief and there were no major safety concerns, and that patients should be fully informed of the long-term efficacy and the alternative treatment options.

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Code	Description
K1006	Suction pump, home model, portable or stationary, electric, any type, for use with external urine management system.

PureWick™ Female External Catheter and the PureWick™ Urine Collection System are unproven and not medically necessary for managing urinary incontinence due to insufficient evidence of efficacy.

Clinical Evidence

The PureWick system is an external urine collection system for managing urinary incontinence.

A Hayes Evolving Evidence Review (2022) examined external female catheters for managing urinary incontinence (UI). Five clinical studies were identified but authors concluded they were of poor quality due to lack of simultaneous comparison groups and comparison to historical data. No systematic reviews were identified. Therefore, the report states that there is a minimal level of support for using female external urinary catheters (FEUCs) for managing UI. (Authors Eckert 2020, Warren 2021, and Zavodnick 2020 which are discussed in this policy, are included in this Evolving Evidence Review.)

In a Clinical Evidence Assessment, ECRI (2018; updated 2021) concluded that the evidence for reducing catheter-associated urinary tract infections (CAUTI) via use of the Purewick Female External Catheter was inconclusive due to very low-quality studies. The evidence identified suggests that Purewick may reduce CAUTI, however, due to retrospective design, lack of randomization, nonconcurrent controls, and single-center focus, further prospective, controlled studies which compare Purewick to standard care are needed to address these gaps. (Authors Eckert 2020, Warren 2021, and Zavodnick 2020 which are discussed in this policy, are included in this Clinical Evidence Assessment.)

Warren et al. (2021) conducted a retrospective study analyzing the impact of a hospital-wide implementation of an external female urinary catheter. The investigators compared a 12-month period before and after device implementation to assess the impact on indwelling urinary catheter utilization and CAUTI rate. The study included female patients with a combined patient stay of 220,000 days,10,000 external urinary catheter days and 33,000 indwelling urinary catheter days. The authors concluded that an increase in external female urinary catheter utilization coincided with a decline in patient CAUTI rate, but only in intensive care units (ICUs). Limitations of this study included lack of documentation regarding the catheter type used by the patients and lack of direct correlation of CAUTI decline with use of FEUCs, especially outside of the ICU setting. Further studies are needed to correlate usage of FEUCs versus indwelling catheters (IDCs) and the impact on the CAUTI rate.

Zavodnick et al. (2020) conducted a retrospective, observational study that included nine adult ICUs to investigate CAUTIs rates in adult females. The study compared the use of FEUCs versus IDCs. The participants had a combined total of 89,856 patient stay days. CAUTI rates and indwelling catheter days were obtained before and after the introduction of the devices. The study shows that CAUTI rates decreased from 3.14 per 1000 catheter days to 1.42 per 1000 catheter days ($p = 0.013$). The number of days participants needed an indwelling catheter decreased; however, the ICU days of stay increased. The authors concluded that FEUCs are associated with a significant decrease in the CAUTI rate among female intensive care participant, and they may prevent the need for indwelling catheters. Further studies are needed with a larger sample-size along with equal usage of both FEUCs and IDCs over the same number of patient days of stay.

Eckert et al. (2020) conducted a quality improvement, single center study comparing the use of an FEUC device with wall suction as an alternative to IDC. The outcomes were to determine if FEUCs reduced the risk of CAUTI rates. The FEUC device

was trialed September 2015 through December 2015, using 60 FEUC devices on 30 female patients. Data collection on these patients for one year period after use of FEUC. In 2015, before the use of the FEUC device, the baseline female IDC utilization rate was 31.7% (7181 IDC device-days/22,656 patient stay days) and the female CAUTI rate was 1.11 (8 cases/7181 IDC device-days) per 1000 stay days. After implementing use of the FEUC device both IDC utilization and CAUTI rates declined. In 2016, the IDC utilization rate was 29.7% (p = .000) and the CAUTI rate was 0% (p = .005). In 2017 there was a reduction in IDC utilization rates of 26% (p = .000) but the CAUTI rate of 0.90% was not significantly different from the prior year rate (p = .726). The authors concluded they need to continue to prioritize the use of FEUCs over IDCS. Limitations of this study include lack of consistent sample size, short follow-up and lack of equal comparisons of FEUC and IDC patient usage.

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Code	Description
K1018	External upper limb tremor stimulator of the peripheral nerves of the wrist
K1019	Monthly supplies for use of device coded at K1018

External upper limb tremor stimulators of the peripheral nerves of the wrist and the related monthly supplies to treat essential tremor are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

External upper limb tremor stimulators of the peripheral nerves of the wrist (e.g., the Cala Health, Inc., Cala Trio™) deliver non-invasive electrical stimulation to the peripheral nerves of the wrist (Cala Health, Inc. Cala Trio website). In an ECRI 2022 clinical evidence assessment Cala Trio Wrist-worn Neuromodulation Therapy for Essential tremor was explored. Cala Trio is intended to be used when tremor restricts activities of daily living (ADL). Cala Trio works to decrease the severity of tremor and lasts approximately an hour after the treatment session. The report aims to dissect Cala Trio's safety, effectiveness, and compare the therapy to those of other essential tremor (ET) treatments. Limitations to the evidence reviewed include studies with small patient population, patients with wide variations in tremor severity, lack of follow up past three months, high risk of bias due to lack of parallel group in the before-and-after study, and study findings requiring independent validation in additional multicenter randomized controlled trials (RCTs). Although Cala Trio appears to lessen tremor severity and improve ADLs after treatment, the current evidence available does not support firm conclusions on the clinical benefits of Cala Trio beyond three months. Furthermore, out of two small RCTs, and one before- and-after study, no published studies provide data to compare Cala Trio with other ET treatments (ECRI, 2022).

In a 2022 Hayes evolving evidence review, Cala Trio for treatment for essential tremor was found to have minimal clinical studies, no systematic reviews, and guidelines with a weak support for the treatment. Clinical studies reviewed for the use of Cala Trio found one poor quality RCT which suggests some benefits over sham but no clear benefits or advantages (Pahwa et al., 2019). Another poor quality pre and posttest study suggested benefits after 3 months of treatment, however the evidence does not address whether the device confers incremental gain over pharmacotherapy or whether its performance is inferior, equivalent, or improved versus alternative adjunctive treatment (Isaacson et al. 2020).

Isaacson et al. (2020, included in the Hayes and ECRI review) performed a prospective, multi-center, open-label, post-clearance, single-arm study to evaluate the efficacy and safety of Transcutaneous Afferent Patterned Stimulation (TAPS) delivered by an

FDA-cleared wrist-worn device (Cala Health, Inc.). A total of 263 subjects were enrolled at 26 study sites. Of those, 205 subjects completed the study. Subjects were instructed to use the wrist-worn device for 40 minutes, twice daily, for three months. The co-primary efficacy endpoints were clinician-rated Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) and (patient-rated Bain & Findley Activities of Daily Living (BF-ADL) dominant hand scores. These endpoints were considered met ($p \ll 0.0001$), with 62% (TETRAS) and 68% (BF-ADL) of "severe" or "moderate" subjects improving to "mild" or "slight." Wrist-worn accelerometer recordings of tremor power showed that 92% of subjects improved and 54% of subjects experienced ≥ 50% improvement. Clinical Global Impression (CGI-I) scores showed that clinicians reported tremor improvement in 68% of patients. Patient Global Impression (PGI-I) scores showed 60% of subjects self-reported tremor improvement. Quality of Life in Essential Tremor (QUEST) surveys completed by subjects also showed improvement ($p = 0.0019$). Device-related adverse events occurred in 18% of subjects and included wrist discomfort, skin irritation, and pain. There were no device-related serious adverse events reported. The authors concluded that non-invasive neuromodulation therapy used at home over three months is safe and effective to treat patients with ET. This study had some limitations including the open-label, single-arm design; clinical raters were unblinded; while there were statistically significant reductions across the TETRAS and BF-ADL ratings, the extent of those reductions varied; and 58 subjects did not complete the study.

The randomized, controlled, multi-center study to evaluate the safety and efficacy of a wrist-worn peripheral nerve stimulation device (Pahwa et al. 2019, included in the Hayes and ECRI report) evaluated the safety and efficacy of a wrist-worn peripheral nerve stimulation device (Cala Health, Inc., Cala ONE) in subjects with ET in a single in-office session. A total of 111 subjects were screened at 4 sites. Of those, 93 subjects were randomized to receive treatment (n = 48) or sham stimulation (n = 45). Treatment consisted of a single 40-minute stimulation session. The primary endpoint was the clinician-rated TETRAS Archimedes spiral score. The study showed that subjects who received treatment did not show significantly larger improvements in Archimedes spiral task scores when compared to sham. However, subjects did show significantly greater improvement in upper limb TETRAS tremor scores ($p = 0.017$). Subject-rated improvements using the BF-ADL scale were significantly greater with treatment (49% reduction) than with sham (27% reduction; $p = 0.001$). CGI-I showed a greater percentage of ET patients (88%) reported improvement in the stimulation group, as compared to the sham group (62%) ($p = 0.019$). The adverse event rate was 3% and included significant and persistent skin irritation, sensation of weakness, or stinging pain. The authors concluded that peripheral nerve stimulation to treat ET may provide safe, well-tolerated, and efficacious treatment for transient relief of hand tremor symptoms. This study had some limitations including the evaluation of only a single in-clinic treatment session and a lack of kinematic measurements.

Lin et al. (2018, included in the ECRI review) conducted a randomized, sham-controlled pilot trial on non-invasive neuromodulation in essential tremor exploring the extent of relief. The study aims to assess the efficacy of median and radial nerve stimulation as a noninvasive, nonpharmacological treatment to support the symptomatic relief of hand tremor for those with ET. All twenty-three blinded Individuals were randomized to treatment or sham groups at a single site under an institution review board approved protocol. To quantify efficacy the Tremor Research Group's Essential Tremor Rating Assessment Scale (TETRAS) was employed. The treatment group had significant outcome differences compared with sham and starting point, with blinded rater scores enhanced after stimulation versus prestimulation. The sham group scores had no noteworthy change following stimulation versus prestimulation. Although the study proposes that noninvasive neuroperipheral therapy may offer clinically meaningful symptomatic relief of hand tremor, it included too few subjects for sub analyses of the influence of age, medication status, and past medical history. Additional studies are necessary with a greater number of test subjects, examination of response, rate and robustness of the therapy, investigation of chronic utilization effects, and evaluation of quality-of-life. Additionally, future studies can characterize the exact mechanism that enables improvements to therapy.

The U.S. Food and Drug Administration (FDA) cleared the Cala Health, Inc. Cala Trio device under its 510(k) premarket notification process as substantially equivalent to predicate devices. For additional information, refer to the following: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K182706. (Accessed April 11, 2022).

For information on current clinical trials studying the use of the Cala Health, Inc. Cala Trio, refer to www.clinicaltrials.gov. (Accessed September 7, 2021).

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Code	Description
L8699	Prosthetic implant, not otherwise specified [when used to report three-dimensional (3-D) printed cranial implants]

Three-dimensional (3-D) printed cranial implants are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Note: 3D printing of implants may be performed with other procedures such as 3D rendering with interpretation and reporting of imaging. For additional information regarding these imaging procedures, refer to the Cardiology and Radiology Imaging Guidelines. (Accessed May 26, 2022).

Clinical Evidence

Custom craniofacial implants are used to repair skull bone defects after trauma or surgery. Cranial implants must fit precisely within all borders of a defect to restrict movement and successfully restore natural cranial shape. Currently, cranial implants are designed and produced by third-party suppliers, which can be time consuming and expensive. Recent advances in additive manufacturing (3-D) make point of care fabrication of personalized implants feasible. (Li et al., 2021)

On February 18, 2013, Oxford Performance Materials (OPM) received Food and Drug Administration (FDA) 510(k) clearance for the OsteoFab™ Patient Specific Cranial Device (OPSCD). OsteoFab is OPM's brand for Additively Manufactured (also called 3D Printing) medical and implant parts produced from polyetheretherketone (PEEK) polymer. Refer to the following for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf12/k121818.pdf. (Accessed May 26, 2022)

On January 19, 2017, the FDA granted OssDsign Cranial Patient-specific Implant (OssDsign AB), (Uppsala, Sweden) 510(k) marketing clearance for its three-dimensional (3-D) printed OssDsign® Cranial PSI (patient-specific implant). The customized implant is indicated for non-load-bearing applications to reconstruct cranial defects in adults for whom cranial growth is complete and with an intact dura with or without duraplasty. The OssDsign Cranial PSI is made from a calcium phosphate–based ceramic material, reinforced by a titanium skeleton. The implant's interconnecting tile design purportedly allows fluid movement through the device. Refer to the following for more information:
https://www.accessdata.fda.gov/cdrh_docs/pdf16/k161090.pdf. (Accessed May 26, 2022)

In a 2021 ECRI Clinical Evidence Assessment on AccuShape PEEK, patient-specific Cranial Implants (MedCAD) for Cranial reconstruction were evaluated. The report focused on determining the product's safety and efficacy for cranial reconstruction. No published studies addressed the technologies safety and efficacy for cranial reconstruction.
In a 2019 ECRI product brief, OssDsign AB for Cranial Reconstruction was assessed. The authors found significant limitations to the body of evidence. Limitations include small sample size, retrospective design, lack of control, randomization, blinding, lack of comparison, single-center studies, and studies conducted in different countries. Longer follow-up times are necessary to determine outcome measures to assess safety and efficacy.

Maricevich et al. (2019) evaluated the symptomatic and aesthetic improvement of patients with cranial defects secondary to decompressive craniectomies after cranial reconstruction with customized polymethyl methacrylate (PMMA) prostheses produced by 3D impression molds. This prospective study included 63 patients who underwent cranioplasties that were performed using customized PMMA prosthesis produced by 3D impression molds. All patients underwent a functional and aesthetic evaluation questionnaire in the preoperative period and in the sixth postoperative month. The mean area of the defect was 147 cm^2. The mean postoperative follow-up of the patients was 21 months, ranging from 6 to 33 months. Fifty-five patients attended the 6-month postoperative consultation. All patients presented symptomatic improvement after reconstruction of the

skull. The infection rate was 3.2%, 4.8% of extrusion, 1.6% of prosthesis fracture, 7.9% of extradural hematoma, 17.4% of reoperation, 5% of wound dehiscence, and 4.8% of removal of the prosthesis. The authors concluded that cranioplasty, with a customized PMMA prosthesis, improved the symptoms and aesthetic appearance of all operated patients. The use of prototypes to customize cranial prostheses facilitated the operative technique and allowed the recovery of a cranial contour very close to normal. Limitations of this study include its case series design, the use of simple direct questions by the team that performed the cranioplasties to assess cognitive, motor, and QOL rather than the use of validated assessment tools, and the short follow-up period. Additional prospective, randomized controlled trials with longer follow-up are needed to examine the safety and efficacy of 3D printed cranial implants.

Francaviglia et al. (2017) conducted a case series analysis to present their preliminary experience with a custom-made cranioplasty, using electron beam melting (EBM) technology, in ten patients. EBM is a new sintering method for shaping titanium powder directly in 3D implants. According to the authors, this is the first report of a skull reconstruction performed by this technique. In a 1-year follow-up, no postoperative complications were observed and good clinical and esthetic outcomes were achieved. According to the authors, a longer production process, and the greater expertise needed for this technique are compensated by the achievement of most complex skull reconstructions with a shorter operative time. This study was limited by its design, a small population and short follow-up period. Additional prospective studies with comparison groups, larger sample sizes and longer follow-up periods are needed.

Park et al. (2016) conducted a case series analysis to evaluate the efficacy of custom-made 3D-printed titanium implants for reconstructing skull defects. From 2013 to 2015, 21 patients (age range, 8-62 years; mean, 28.6 years) with skull defects were treated. Total disease duration ranged from 6 to 168 months. The size of skull defects ranged from 84×104 to 154×193mm. Custom-made implants were manufactured using 3D computed tomography data, Mimics software, and an electron beam melting machine. The team reviewed several different designs and simulated surgery using a 3D skull model. During the operation, the implant was fit to the defect without dead space. Operation times ranged from 85 to 180 minutes. Operative sites healed without any complications except for 1 patient who had red swelling with exudation at the skin defect, which was a skin infection and defect at the center of the scalp flap reoccurring since the initial head injury. This patient underwent reoperation for skin defect revision and replacement of the implant. Twenty-one patients were followed for 6 to 24 months (mean,14.1 months). The patients were satisfied and had no recurrent wound problems. Head computed tomography after operation showed good fixation of titanium implants and satisfactory skull-shape symmetry. According to the authors, for the reconstruction of skull defects, the use of autologous bone grafts has been the treatment of choice. However, bone use depends on availability, defect size, and donor morbidity. The authors stated that as 3D printing techniques are further advanced, it is becoming possible to manufacture custom-made 3D titanium implants for skull reconstruction. This study was limited by a small study population, lack of a comparison group, and short follow-up time.

Choi and Kim (2015) conducted a systematic review to investigate the current status of 3D printing technology and its clinical application. Thirty-five articles were selected for review. In addition, the benefits and possibilities of the clinical application of 3D printing in craniofacial surgery were reviewed, based on personal experiences with more than 500 craniofacial cases conducted using 3D printing tactile prototype models. Based on the review, the authors concluded that the following obstacles need to be addressed: 1) the computer software should be more specific to craniofacial reconstruction; 2) a surgical osteotomy guide should be included to ensure that the preoperative planning and intraoperative defect are in agreement; and 3) accuracy should be approved upon. Although CT scans are made in very thin slices, the imaging modality can only provide the accumulation of the multiple slices. Errors can occur between the slices as the orbital wall is too thin to be reconstructed by only a 3D printing technique and a 3D printed orbit model represents the orbit as vacant fields; and 4) the presence of metal can cause substantial image artifacts and may discourage the use of 3D printing models (e.g., dental models cannot be recreated with CT scanning because of accuracy issues. According to the authors, despite these obstacles, 3D printing technology has potential to be beneficial in terms of precision medicine and personalized treatment. With further technological advances, 3D printing could be very beneficial in craniofacial surgery.

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Code	Description
L8701	Powered upper extremity range of motion assist device, elbow, wrist, hand with single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated
L8702	Powered upper extremity range of motion assist device, elbow, wrist, hand, finger, single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated

The use of the upper limb orthotic known as the MyoPro™ is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

MyoPro™ is a powered orthosis (brace) designed to help restore function to arms and hands paralyzed or weakened by CVA stroke, brachial plexus injury, cerebral palsy or other neurological or neuromuscular disease or injury. It works by reading the faint nerve signals (myoelectric signals) from the surface of the skin (fully noninvasive, no implants) then activating small motors to move the arm and hand as the user intends (no electrical stimulation) (Hayes, 2021).

Pundik et al. (2022) performed a prospective single arm mixed cohort interventional pilot study to evaluate MyoPro as a tool for motor learning-based therapy for individuals with chronic upper limb weakness. The study included thirteen individuals with chronic moderate/severe arm weakness due to either stroke (n = 7) or TBI (n = 6). The study consisting of 2 phases. The in-clinic phase included 18 sessions (2x per week, 27hrs of face-to-face therapy) plus a home exercise program. The home phase included practice of the home exercise program. There was no control group. Outcomes were collected at baseline and at weeks 3, 5, 7, 9, 12, 15, and 18. Improvements were observed on Fugl-Meyer (+ 7.5 points). Gains were seen at week 3, increased further through the in-clinic phase and were maintained during the home phase. Changes in the Modified Ashworth Scale, Range of Motion, and Chedoke Arm and Hand Activity Inventory were seen early during the in-clinic phase. Orthotic and Prosthetic User's Survey demonstrated satisfaction with the device throughout study participation. Both stroke and TBI participants responded to the intervention. The authors concluded that MyoPro might be a useful tool for motor learning in individuals with chronic stroke and TBI. Reduction in impairment, gains in function, and satisfaction with the device were observed in response to the intervention. Further studies using a randomized controlled design is warranted.

A 2021 Hayes Evidence Analysis Research Brief was performed to summarize the volume of publications and to determine whether there was adequate published, peer-reviewed literature to evaluate the evidence related to the use of the MyoPro Orthosis for the treatment of stroke-induced upper extremity paresis or paralysis. Two randomized controlled trials (RCTs), 1 prospective comparative study, and 2 single-arm pretest-posttest studies were identified. Only 1 RCT included more than 20 patients. The authors determined there was insufficient published, peer-reviewed literature to evaluate the evidence related to MyoPro Orthosis for upper extremity post-stroke paresis or paralysis in a full assessment (Hayes, 2021).

A 2020 ECRI Custom Product Brief identified three case series with 28 participants examining the device MyoPro-G, as there were no published studies available on MyoPro2 devices. The report concluded that the evidence is insufficient to determine how well the MyoPro-G works or how it compares with alternative devices intended to improve arm and hand impairment. Controlled studies with larger sample sizes are needed to assess efficacy, provide longer-term results, assess home use and study use of the device in different clinical condition patient populations (ECRI, 2020) (Authors McCabe et al. (2019) and Peters et al. (2017)) which were previously cited in this policy are included in this study).

A single-blinded randomized controlled trial was conducted by Page et al. (2020) to compare the efficacy of myoelectric bracing (Myomo) and/or repetitive task-specific practice (RTP) i]n moderately impaired stroke patients. There were 34 participants all exhibiting chronic, stable, moderate upper extremity impairment. Each participant was selected randomly for therapy consisting of Myomo combined with RTP, RTP only or Myomo therapy only. All three groups were supervised by a therapist and were administered therapies targeting their hemiparetic upper extremities. The primary outcome measure was the upper extremity section of the Fugl-Meyer Impairment Scale (FM); the secondary measurement was the Arm Motor Activity Test (AMAT). The therapies were one hour in duration, occurring 3 days/week for eight weeks. Upon completion of the study, all three groups showed a Fugl-Meyer (FM) score increase of + 2 points. On the secondary outcomes, the two groups that included Myomo had the same FM score increase of + 1 and the group with RTP only had a FM score increase of + 2.6. The authors concluded that outcomes in the group with Myomo and RTP were comparable to the RTP only group. Several limitations were identified by the authors, the device tested in the trial did not always work as expected and was somewhat cumbersome. Future studies would be strengthened by larger sample sizes.

A single-blinded randomized controlled pilot study was conducted by Park et al. (2020) to evaluate the differences in the clinical and kinematic outcomes between active-assistive and passive robotic rehabilitation among stroke survivors. Twenty stroke patients with upper extremity dysfunction were randomly assigned to the active-assistive robotic intervention (using an exoskeletal robot with robotic actuators; ACT) group or passive robotic intervention (using a passive exoskeletal robot without robotic actuators; PSV) group. Both groups completed 20 sessions of 30-minute robotic intervention, five days a week for four weeks. Each group received 30 minutes of conventional therapy of the affected upper limb five days a week for four weeks as well. In both the groups the Wolf Motor Function Test (WMFT) score and -time improved. The PSV group showed better improvement in participation and smoothness than the ACT group. The ACT group exhibited better improvement in mean speed. The authors concluded there was minimal measurable difference in outcomes such as improvement of patient impairments and activity between the ACT group and PSV group. For usability, the patients in the ACT group complained the device was “too heavy” and “bulky.” Further studies with larger populations and longer intervention periods are needed.

Willigenburg and colleagues (2017) examined the efficacy of an 8-week regimen combining repetitive task-specific practice (RTP) with a myoelectric brace (RTP + Myomo) on paretic upper extremity (UE; use in valued activities, perceived recovery, and reaching kinematics) in 12 patients. Seven were administered RTP + Myomo therapy, and 5 were administered RTP only. Both groups participated in individualized, 45-min therapy sessions occurring 3 days/week over an 8-week period. The arm, hand ability, activities of daily living, and perceptions of recovery subscales of the Stroke Impact Scale (SIS), as well as UE reaching kinematics, assessed before and after the intervention. The RTP + Myomo group showed greater improvements on all SIS subscales. Patients in the RTP-only group showed a greater increase in hand velocity in the reach up task, but no changes were observed in the range of shoulder flexion or elbow extension during reaching. None of the changes in kinematic outcome measures significantly correlated with any of the changes in SIS subscales. The authors concluded that RTP integrating myoelectric bracing may be more beneficial than RTP only in improving self-reported function and perceptions of overall recovery. The authors observed no changes in the range of elbow extension, and no relationship between self-reported improvements and changes in reaching kinematics. This study is limited by small sample size and short follow-up period.

A randomized controlled pilot trial was conducted by Page et al. (2013). to compare the efficacy of a RTP in a person with chronic, moderate upper extremity impairment A total of 16 people was utilized (7 males; mean age 57.0 ±11.02 years; mean time post stroke 75.0 ±87.63 months; 5 left-sided strokes) all exhibiting chronic, stable, moderate upper extremity impairment. Each person was given an RTP in which they participated in valued, functional tasks using their paretic upper extremities. Both groups were supervised by a therapist and were administered therapies targeting their paretic upper extremities that were 30 minutes in duration, occurring 3 days/week for eight weeks. One group participated in RTPs entirely while wearing the portable robotic, while the other performed the same activity regimen manually. Upon completion of the study itself each group showed the same Fugl-Meyer score increases of ≈2.1 points; the group using robotics exhibited larger score changes on all but one of the Canadian Occupational Performance Measure and Stroke Impact Scale subscales, including a 12.5-point increase on the Stroke Impact Scale recovery subscale. It was noted that the finding suggest that therapist supervised task- specific practice with an integrated robotic device could be as efficacious as manual practice in some subjects with moderate upper extremity impairment. Additional studies are needed as there is still insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

The U.S. Food and Drug Administration (FDA) cleared the Myomo e100 for marketing through the 510(k) process in April 2007 (K062631). Myomo e100 is a Class II device with Product Code OAL. The indications for use are as follows:

- The Myomo e100 is indicated for use by stroke patients undergoing rehabilitation to facilitate the following:

- Stroke rehabilitation by muscle re-education
- Maintaining or increasing range of motion

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K062631. (Accessed May 3, 2022).

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Code	Description
P2031	Hair analysis (excluding arsenic)

Hair analysis is unproven and not medically necessary for evaluating any disorder or condition due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Hair analysis has been proposed as an aid in the diagnosis of several conditions including but not limited to dietary deficiencies, allergies, hair loss, autism, schizophrenia, mood disorders, and environmental contamination. Hair has also been used as a specimen source for drug testing. Currently, in federally regulated programs, only urine specimens are collected for drug testing (SAMHSA). There are no widely accepted standards that specify how hair samples should be collected, stored, and analyzed, making results unreliable and inconsistent (ATSDR).

Hardy et al. (2021) conducted a pilot cohort study to compare the information obtained from the analysis of urine versus hair for exposure to pesticides. In ninety-three pregnant women, one urine and one hair sample were collected simultaneously. Samples were analyzed using GC-MS/MS analytical methods allowing for the detection of both parent pesticides and metabolites and designed to be as similar as possible between urine and hair for reliable inter-matrix comparison. Fifty-two biomarkers of exposure were targeted, including parents and metabolites of organochlorines, organophosphates, pyrethroids, carbamates, phenylpyrazoles and other pesticides. The results showed the number of different compounds detected ranged from 16 to 27 (median = 22) in hair, and from 3 to 22 (median = 12) in urine. In hair, 24 compounds were found in > 40% of the individuals, whereas only 12 compounds presented the same frequency of detection in urine. Among the chemicals detected in > 80% of both hair and urine samples, only one (pentachlorophenol) showed a signification correlation between hair and urine concentrations. The authors concluded that these results highlight multiple exposures and suggest that hair provides more

comprehensive information on pesticide exposure than urine analysis and supports the relevance of hair analysis in future epidemiological studies investigating association between exposure and adverse health effects.

In a 2019 systematic review and meta-analysis, Huang et al. sought to identify whether magnesium levels are lower in children with ADHD. A total of twelve studies were included. The results showed magnesium levels in the hair of children diagnosed with ADHD were significantly lower than those in controls (k = 4, Hedges' g = -0.713, 95% CI = -1.359 to -0.067, p = .031). In this meta-analysis, the authors found that children diagnosed with ADHD have lower serum and hair magnesium levels than children without ADHD. The authors concluded that further study is needed to investigate the behavioral influence on ADHD due to lower magnesium levels, the association between brain and serum magnesium levels, and the effects brought about by larger longitudinal cohort studies.

Khajuria et al. (2018) conducted a review designed to investigate the efficacy of chromatography for detection of drugs of abuse in hair. A comprehensive review of articles from last two decades on hair analyses via PubMed and similar resources was performed. The results showed a hair sample may be chosen over traditional biological samples such blood, urine, saliva or tissues due to its inimitable ability to provide a longer time frame for drug detection. Its collection is almost non-invasive, less cumbersome and does not involve any specialized training/expertise. Recent advances in analytical technology have resulted in better sensitivity, reproducibility and accuracy, thus providing a new arena of scientific understanding and test interpretation. The authors concluded that although recent studies have yielded insights into drug binding and drug incorporation in hair, the major challenge in hair analysis lies in the interpretation of results, which may be affected by external contamination and thus lead to false positives. Therefore, there is a need for more sensitive and selective analysis methods to be developed.

Mikulewicz et al. (2013) completed a systematic review to investigate the reference values of minerals in human hair. The five studies that met inclusion criteria reported reference ranges for the content of elements in hair: macro elements, microelements, toxic elements and other elements. Reference ranges were elaborated for different populations in the years 2000–2012. The analytical methodology differed, in particular sample preparation, digestion and analysis, as a result, the levels of hair minerals reported as reference values varied. The authors concluded standardization of procedures and detailed methodology are needed to validate hair mineral analysis. Only then it would be possible to provide meaningful reference ranges and take advantage of the potential that lies in Hair Mineral Analysis (HMA) as a medical diagnostic technique.

Wolowiec et al. (2013) conducted a systematic review on the relation between the mineral composition of hair and physical or mental disorders. Sixty-six studies were included in the review. Most of the studies reported that there exists a correlation between deficiency or excess of some elements in hair and occurrence of some diseases, such as: autism, cancer, hypertension, myocardial infarction, kidney disease and diabetes mellitus. However, not all results were consistent. The authors concluded that there is a need to standardize sample preparation procedures, in particular washing and mineralization methods.

A 2011 guideline for food allergy in children and young people from the National Institute for Health and Care Excellence (NICE) recommends against the use of hair analysis in the diagnosis of food allergy.

In their 2010 guidelines, the National Institute of Allergy and Infectious Diseases (NIAID) states that hair analysis for food allergies is non-standard and unproven. Additionally, the utility of these tests has not been validated for the diagnosis of FA and may result in false positive or false negative diagnoses.

In a 2014 joint practice parameter by the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), and the Joint Council of Allergy, Asthma & Immunology (JCAAI), hair analysis is listed as an unproven test for the evaluation of food allergies.

A practice parameter from the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society states that there is insufficient evidence to support the use of hair analysis for the diagnosis and evaluation of autism (Filipek et al., 2000. Reaffirmed August 2014).

In 2013, the American Society of Addiction Medicine (ASAM) published a document titled, Drug Testing: A White Paper of the American Society of Addiction Medicine. This document indicates that hair sample benefits include difficulty in falsifying sampling and a longer period of detection. However, the ASAM noted that recent exposures cannot be detected in hair

samples, and hair coloring can cause modest degradation of drugs in the matrix. The ASAM notes that one distinct disadvantage to hair testing is that some drug classes (e.g., benzodiazepines) are poorly detected in hair.

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Policy History/Revision Information

Date	Summary of Changes
07/01/2023	Coverage Rationale • Added coverage guidelines for: *Transcutaneous Magnetic Stimulation (tMS) for the Treatment of Chronic Pain (CPT codes 0766T, 0767T, 0768T, and 0769T)* (new to policy) ○ Added language to indicate transcutaneous magnetic stimulation (tMS) by focused low-frequency electromagnetic pulse for the treatment of chronic pain is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy *Implantable Wireless Pulmonary Artery Pressure Sensor (e.g., CardioMEMS) (CPT/HCPCS codes 33289, 93264, and C2624)* (new to policy) ○ Added language to indicate:

Date	Summary of Changes
	▪ Implantable wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring (e.g., CardioMEMS) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy ▪ For members with an existing implanted device, monitoring is a covered service ▪ Removal of an implantable wireless pulmonary artery pressure sensor is a covered service in the rare instance when it might be required • Updated list of applicable CPT/HCPCS codes for: *Aquapheresis (Ultrafiltration) (CPT code 0692T)* o Removed CPT codes 37799 and 90999 *Autologous Pancreatic and Allogeneic Islet Cell Transplantation (CPT/HCPCS code 0584T, 0585T, 0586T, 60659, G0341, G0342, and G0343)* o Removed CPT/HCPCS codes 48160, 48999, and S2102 *Balloon Dilation (CPT codes 69705 and 69706)* o Removed CPT code 69799 *Laboratory Measurement of Antibodies and Serum Levels Related to Biologic Agents (CPT codes 80145, 80230, and 80280)* o Removed CPT codes 80299 and 84999 *Radiofrequency (RF) Therapy (CPT codes 0672T and 53860)* o Removed CPT codes 53899 and 58999 *Use of the Robotic Lower Body Exoskeleton Device (HCPCS code K1007)* o Removed CPT/HCPCS codes 97799, E1399, and L2999 • Removed coverage guidelines for: *Ablative Laser Treatment for Wound Healing (CPT code 0491T and 0492T)* o The state of North Carolina does not require clinical review for CPT codes 0491T and 0492T *Antiprothrombin Antibody Testing for Antiphospholipid Syndrome (CPT code 86849)* o The state of North Carolina does not require clinical review for CPT code 86849 *Biomechanical Mapping Using Vaginal Tactile Imaging Techniques (CPT code 0487T)* o The state of North Carolina does not require clinical review for CPT code 0487T *Corticosteroid Drug-Eluting Punctal Plugs or Implants Into the Lacrimal Canaliculus (CPT code 68841)* o The state of North Carolina does not require clinical review for CPT code 68841 *Digestive Enzyme Cartridges (e.g., Relizorb™) for Use with Enteral Tube Feeding (HCPCS code B4105)* o The state of North Carolina does not require clinical review for HCPCS code B4105 *Genicular Nerve Block (GNB) (CPT code 64454)* o The state of North Carolina does not require clinical review for CPT code 64454 *Instrument-Based Ocular Photo Screening (CPT codes 99174 and 99177)* o The state of North Carolina does not require clinical review for CPT codes 99174 and 99177 *Intraoperative Radiation Therapy (CPT codes 19294, 77424, 77425, and 77469)* o The state of North Carolina does not require clinical review for CPT codes 19294, 77424, 77425, and 77469 *Kinesio Taping (CPT/HCPCS codes 29799, 97139, 97799, and A9999)* o The state of North Carolina does not require clinical review for CPT/HCPCS codes 29799, 97139, 97799, and A9999 *Multifocal Electroretinogram (mfERG) and Pattern Electroretinogram (PERG) (CPT codes 0509T and 92274)* o The state of North Carolina does not require clinical review for CPT codes 0509T and 92274 *Posterior Nasal Nerve Ablation (Using Radiofrequency or Cryoablation) (CPT codes 30117 and 30999)*

Date	Summary of Changes
	○ The state of North Carolina does not require clinical review for CPT codes 30117 and 30999 *Radiofrequency Ablation (RFA) (CPT codes 23929, 27299, 27599, 64624, and 64999)* ○ The state of North Carolina does not require clinical review for CPT codes 23929, 27299, 27599, 64624, and 64999 *Rhinophototherapy (CPT code 30999)* ○ The state of North Carolina does not require clinical review for CPT code 30999 *Spheroid Cell Culture Testing for Ovarian Cancer (CPT codes 0324U and 0325U)* ○ CPT codes 0324U and 0325U deleted Apr. 1, 2023 *Spirometry and Other Pulmonary Function Tests (CPT codes 94011, 94012, and 94013)* ○ The state of North Carolina does not require clinical review for CPT codes 94011, 94012, and 94013 *Surgical Treatment (e.g., Laminectomy and Sacral Reconstruction) of a Sacral Perineural Tarlov Cyst (CPT code 63268)* ○ The state of North Carolina does not require clinical review for CPT code 63268 *UroCuff Test for Diagnosing Male Lower Urinary Tract Disorders (CPT codes 53899 and 55899)* ○ The state of North Carolina does not require clinical review for CPT codes 53899 and 55899 Supporting Information • Updated *Clinical Evidence* sections to reflect the most current information • Archived previous policy version CSNCT0535.04

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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