

OMNIBUS CODES

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Community Plan Policy

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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.

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Code	Description	Conclusion
0061U	Transcutaneous measurement of five biomarkers (tissue oxygenation [StO ₂], oxyhemoglobin [ctHbO ₂], 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
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
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
0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest	Unproven
0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest	Unproven
0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy	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

Code	Description	Conclusion
0268T	Implantation or replacement 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
0330T	Tear film imaging, unilateral or bilateral, with interpretation and report	Unproven
0335T	Insertion of sinus tarsi implant	Unproven
0341T	Quantitative pupillometry with interpretation and report, unilateral or bilateral	Unproven
0355T	Gastrointestinal tract imaging, intraluminal (e.g., capsule endoscopy), colon, with interpretation and report	Unproven
0356T	Insertion of drug-eluting implant (including punctal dilation and implant removal when performed) into lacrimal canaliculus, each	Unproven
0358T	Bioelectrical impedance analysis whole body composition assessment, with interpretation and report	Unproven
0377T	Anoscopy with directed submucosal injection of bulking agent for fecal incontinence	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
0400T	Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia; one to five lesions	Unproven
0401T	Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia; six or more lesions	Unproven
0421T	Transurethral waterjet ablation of prostate, including control of post-operative bleeding, including ultrasound guidance, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included when performed)	Unproven
0424T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)	Unproven
0425T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; sensing lead only	Unproven
0426T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; stimulation lead only	Unproven
0427T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; pulse generator only	Unproven

Code	Description	Conclusion
0428T	Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only	Unproven
0429T	Removal of neurostimulator system for treatment of central sleep apnea; sensing lead only	Unproven
0430T	Removal of neurostimulator system for treatment of central sleep apnea; stimulation lead only	Unproven
0431T	Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only	Unproven
0432T	Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only	Unproven
0433T	Repositioning of neurostimulator system for treatment of central sleep apnea; sensing lead only	Unproven
0434T	Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea	Unproven
0435T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session	Unproven
0436T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study	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
0443T	Real time spectral analysis of prostate tissue by fluorescence spectroscopy, including imaging guidance (List separately in addition to code for primary procedure)	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
0465T	Suprachoroidal delivery of pharmacologic agent (does not include supply of medication)	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
0489T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; adipose tissue harvesting, isolation and preparation of harvested cells including incubation with cell dissociation enzymes, removal of non-viable cells and debris, determination of concentration and dilution of regenerative cells	Unproven
0490T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; multiple injections in one or both hands	Unproven
0493T	Near-infrared spectroscopy studies of lower extremity wounds (e.g., for oxyhemoglobin measurement)	Unproven

Code	Description	Conclusion
0508T	Pulse-echo ultrasound bone density measurement resulting in indicator of axial bone mineral density, tibia	Unproven
0509T	Electroretinography (ERG) with interpretation and report, pattern (PERG)	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
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
0547T	Bone-material quality testing by microindentation(s) of the tibia(s), with results reported as a score	Unproven
0548T	Transperineal periurethral balloon continence device; bilateral placement, including cystoscopy and fluoroscopy	Unproven
0549T	Transperineal periurethral balloon continence device; unilateral placement, including cystoscopy and fluoroscopy	Unproven
0550T	Transperineal periurethral balloon continence device; removal, each balloon	Unproven
0551T	Transperineal periurethral balloon continence device; adjustment of balloon(s) fluid volume	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
19294	Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with partial mastectomy (List separately in addition to code for primary procedure)	Unproven
22899	Unlisted procedure, spine [when used to report cooled radiofrequency ablation]	Unproven
27299	Unlisted procedure, pelvis or hip joint [when used to report cooled radiofrequency ablation]	Unproven
27599	Unlisted procedure, femur or knee [when used to report cooled radiofrequency ablation or LIPOGEMS]	Unproven for cooled radiofrequency ablation ; unproven for LIPOGEMS
29799	Unlisted procedure – Kinesio taping	Unproven
30999	Unlisted procedure, nose [when used to report rhinophototherapy, intranasal application of ultraviolet and visible light, bilateral] [when used to report insertion of an absorbable nasal implant]	Unproven
30999	Unlisted procedure, nose [when used to report Coblation nasal septal swell body reduction]	Unproven

Code	Description	Conclusion
30999	Unlisted procedure, nose [when used to report the insertion of an absorbable nasal implant]	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	Unproven
33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation	Unproven
43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy	Unproven
43252	Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy	Unproven
48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells	Proven
48999	Unlisted procedure, pancreas	Proven in certain circumstances
53855	Insertion of a temporary prostatic urethral stent, including urethral measurement	Unproven
53899	Unlisted procedure, urinary system [when used to report UroCuff]	Unproven
55874	Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed	Proven in certain circumstances
60659	Unlisted laparoscopy procedure, endocrine system	Proven in certain circumstances
63268	Laminectomy for excision or evacuation of intraspinal lesion other than neoplasm, extradural; sacral	Proven in certain circumstances
64999	Unlisted procedure, nervous system [when used to report cooled radiofrequency ablation or surgical treatment of a Tarlov cyst not described by 63268]	Proven in certain circumstances for surgical treatment of a Tarlov cyst ; unproven for cooled radiofrequency ablation
69799	Unlisted procedure, middle ear [when used to report balloon dilation]	Unproven
76120	Cineradiography/videoradiography, except where specifically included	Unproven
76125	Cineradiography/videoradiography to complement routine examination (List separately in addition to code for primary procedure)	Unproven
77424	Intraoperative radiation treatment delivery, x-ray, single treatment session	Unproven
77425	Intraoperative radiation treatment delivery, electrons, single treatment session	Unproven
77469	Intraoperative radiation treatment management	Unproven
80299	Quantitation of therapeutic drug, not elsewhere specified [when used to report therapeutic drug monitoring for inflammatory bowel disease]	Unproven
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score	Unproven
84999	Unlisted chemistry procedure [when used to report therapeutic drug monitoring for inflammatory bowel disease]	Unproven
86849	Unlisted immunology procedure [when used to report antiprothrombin antibody testing for antiphospholipid syndrome]	Unproven

Code	Description	Conclusion
88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session	Unproven
92274	Electroretinography (ERG), with interpretation and report; multifocal (mfERG)	Unproven
93668	Peripheral arterial disease (PAD) rehabilitation, per session [when used to report Supervised Exercise Therapy (SET)]	Unproven
93702	Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)	Unproven
94011	Measurement of spirometric forced expiratory flows in an infant or child through 2 years of age	Unproven
94012	Measurement of spirometric forced expiratory flows, before and after bronchodilator, in an infant or child through 2 years of age	Unproven
94013	Measurement of lung volumes (i.e., functional residual capacity [FRC], forced vital capacity [FVC], and expiratory reserve volume [ERV]) in an infant or child through 2 years of age	Unproven
96902	Microscopic examination of hairs plucked or clipped by the examiner (excluding hair collected by the patient) to determine telogen and anagen counts, or structural hair shaft abnormality	Unproven
97139	Unlisted therapeutic procedure (specify) [when used to report Kinesio Taping]	Unproven
97799	Unlisted physical medicine/rehabilitation service or procedure [when used to report physical medicine/rehabilitation services and/or procedures performed utilizing the robotic lower body exoskeleton device] [when used to report Kinesio taping]	Unproven
99174	Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with remote analysis and report	Proven in certain circumstances
99177	Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with on-site analysis	Proven in certain circumstances
A9999	Miscellaneous DME supply or accessory, not otherwise specified [when used to report Kinesio Taping]	Unproven
B4104	Additive for enteral formula (e.g., fiber)	Unproven
B4105	In-line cartridge containing digestive enzyme(s) for enteral feeding, each	Unproven
B9998	NOC for enteral supplies	Unproven
E1399	Durable medical equipment, miscellaneous [when used to report robotic lower body exoskeleton device]	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
L2999	Lower extremity orthoses, not otherwise specified [when used to report robotic lower body exoskeleton device]	Unproven
L5781	Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system	Unproven
L5782	Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system, heavy duty	Unproven
L8605	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, anal canal	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 three-dimensional (3-D) printed cranial implants] [when used to report an absorbable nasal implant]	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	
S2102	Islet cell tissue transplant from pancreas; allogeneic	Unproven

COVERAGE RATIONALE/CLINICAL EVIDENCE

Code	Description
0061U	Transcutaneous measurement of five biomarkers (tissue oxygenation [StO ₂], oxyhemoglobin [ctHbO ₂], 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

The Ox-Imager CS™ (Modulated Imaging, Inc.) is a 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 Ox-Imager CS™ 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.

Spatial Frequency Domain Imaging (SFDI) technology is an optical technique used to quantitatively characterize turbid (multiple scattering) materials.

The U.S. Food and Drug Administration (FDA) cleared the Ox-Imager CS under its 510(k) premarket notification process as substantially equivalent to predicate devices. For additional information see the following: https://www.accessdata.fda.gov/cdrh_docs/pdf15/k153426.pdf. (Accessed April 2, 2019)

ClinicalTrials.gov lists a pilot study to evaluate multi-spectral imaging and laser speckle imaging during vascular occlusion (NCT01484730), referenced in the FDA approval letter. The estimated completion date was November 2018; however a status of the study was not identified.

Also included on ClinicalTrials.gov is NCT03563105 (Assessment of Circulatory Compromise with Ox-Imager Using a Vascular Occlusion Test Protocol). The estimated study completion date has passed, and current status was not identified.

References:

ClinicalTrials.gov. A pilot study to evaluate multi-spectral imaging and laser speckle imaging during vascular occlusion. NCT01484730. Available at: Available at: <https://www.clinicaltrials.gov/ct2/show/NCT01484730?term=NCT01484730&rank=1>. Accessed April 2, 2019.

ClinicalTrials.gov. Assessment of circulatory compromise with Ox-Imager using a vascular occlusion test protocol. Available at: <https://clinicaltrials.gov/ct2/show/NCT03563105>. Accessed April 2, 2019.

Code	Description
0100T	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy

Code	Description
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 treating retinal disease 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; with bare light or no light perception in both eyes; a previous history of useful form vision; aphakic or pseudophakic eyes; and who are willing and able to receive the recommended postimplant clinical follow-up, device fitting, and visual rehabilitation. Eligibility determination requires that patients with no residual light perception undergo testing for evidence of intact inner-layer retinal function. The procedure description indicates that patients with phakic eyes have their natural lens removed during the implant procedure. 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. See the following website for more information: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H110002>. (Accessed May 6, 2019)

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).

Health Quality Ontario (2016) performed a systematic search of the literature for studies examining 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. One multicentre 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. However, the sight-threatening surgical complication rate was substantial. Retinitis pigmentosa significantly affects people's ability to navigate physical and virtual environments. Argus II was described as enabling the fundamental elements of sight. As such, it had a positive impact on QOL for people with retinitis pigmentosa. 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, but there were complications associated with the surgery that could be managed through standard ophthalmologic treatments.

In a systematic review, Chuang et al. (2014) compared selected retinal implant models by examining publications describing five representative retinal prostheses: Argus II, Boston Retinal Implant Project, Epi-Ret 3, Intelligent Medical Implants (IMI) and Alpha-IMS (Retina Implant AG). Publications were analyzed using three criteria for interim success: clinical availability, vision restoration potential and long-term biocompatibility. Clinical availability: Argus II is the only device with FDA approval. Argus II and Alpha-IMS have both received the European CE Marking. All others are in clinical trials, except the Boston Retinal Implant, which is in animal studies. Vision restoration: resolution theoretically correlates with electrode number. Among devices with external cameras, the Boston Retinal Implant leads with 100 electrodes, followed by Argus II with 60 electrodes and visual acuity of 20/1262. Instead of an external camera, Alpha-IMS uses a photodiode system dependent on natural eye movements and can deliver visual acuity up to 20/546. Long-term compatibility: IMI offers iterative learning; Epi-Ret 3 is a fully intraocular device; Alpha-IMS uses intraocular photosensitive elements. The authors concluded that based on the review of these three criteria, Alpha-IMS is the most likely to achieve long-term success decades later, beyond current clinical availability.

da Cruz et al. (2016) reported the clinical trial 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 difficult to complete a robust statistical analysis of the safety results because of limited power.

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. In each of the four domains, patients' performances were significantly better with the device ON versus OFF, ranging from 19 to 38 per cent improvement. The authors concluded that patients with an Argus II Retinal Prosthesis implanted for 18 to 44 months, demonstrated significantly improved completion of vision-related tasks with the device ON versus OFF. These findings require confirmation in a larger study.

Dagnelie et al. (2017) conducted a 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. These findings require confirmation in a larger study.

Clinical trials of artificial retinal devices are currently ongoing including a 3-year observational study of a larger group of patients implanted with the Argus II Retinal Prosthesis System than was available in the premarket approval study. This study will gather information on the nature and rate of AEs and, secondarily, visual function. See the following website for more information: <http://www.clinicaltrials.gov/ct2/show/NCT01490827>. (Accessed May 6, 2019)

Reference(s)

- Chuang AT, Margo CE, Greenberg PB. Retinal implants: a systematic review. *Br J Ophthalmol*. 2014 Jan 8.
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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 x-rays is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Computer aided detection (CAD) systems are diagnostic tools that purportedly assist radiologists in the detection of subtle findings to facilitate early cancer detection. Used as an adjunct to radiographic or computed tomographic (CT) images of the chest, it analyzes and highlights areas in the image that appear to be solid nodules, alerting the radiologist to the need for additional analysis.

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.

Detterbeck 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.

American College of Radiology (ACR) Appropriateness Criteria® for Screening for Pulmonary Metastases states that CAD for pulmonary metastatic disease has been adapted to chest CT from applications for mammography. Although these programs are in their developmental phases, it has been suggested that CAD can be used as a second look after the radiologist has completed reviewing the study. These programs require more development and currently can only be used when there is limited breathing artifact and stable lung expansion. CAD is still in the experimental phase and currently has limited use in evaluating patients with pulmonary metastatic disease (Mohammed et al., 2010).

The American College of Chest Physicians (ACCP) does not address the use of CAD of chest x-rays for detection of lung cancer and/or lung cancer screenings in their guidelines on the diagnosis and management of lung cancer (2018).

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Code	Description
0207T	Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral

The use of automated evacuation of meibomian glands using heat and intermittent pressure is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

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. These findings require confirmation in randomized controlled trials with larger patient populations.

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 meibomian gland dysfunction (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. This study was funded by the manufacturer of Lipiflow (TearScience, Inc).

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 meibomian gland dysfunction (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. 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.

Blackie et al. (2016) evaluated the sustained effect (up to 1 year) of a single, 12-minute vectored thermal pulsation (VTP) treatment in improving meibomian gland function 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 meibomian gland dysfunction 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 ± 23.2 . Greater mean improvement in MGS was associated with less severe baseline MGS and shorter duration of time between diagnosis and treatment. The authors concluded that a single VTP treatment can deliver a sustained mean improvement in meibomian gland function and mean reduction in dry eye symptoms, over 12 months. 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. Early VTP intervention for meibomian gland dysfunction is associated with improved treatment outcomes. According to the authors, a significant limitation of this study is that the investigators were not masked. This study was funded by the manufacturer of LipiFlow (TearScience, Inc) and the lead authors are affiliated with TearScience, Inc.

Zhao et al. (2016) conducted a hospital-based interventional study comparing thermal pulsation (LipiFlow) to warm compresses for meibomian gland dysfunction (MGD) treatment in 50 patients. The ocular surface and symptom were evaluated before treatment, and one and three months after treatment. Twenty-five patients underwent thermal pulsation (single session), whereas 25 patients underwent warm compresses (twice daily) for 3 months. Meibomian gland loss was graded using infrared meibography, whereas function was graded using the number of glands with liquid secretion. The mean age (SD) of participants was 56.4 (11.4) years in the warm compress group and 55.6 (12.7) years in the thermal pulsation group. Seventy-six percent of the participants were female. Irritation symptom significantly improved over 3 months in both groups, whereas tear breakup time (TBUT) was modestly improved at 1 month in only the thermal pulsation group, without significant difference between both groups over the 3 months. There was also no significant difference in irritation symptom, TBUT, Schirmer test, and gland secretion variables between patients with different grades of gland loss or function at follow-ups. The authors concluded that a single session of thermal pulsation was similar in its efficacy and safety profile to 3 months of twice daily warm compresses. Treatment efficacy was not affected by pretreatment gland loss. According to the authors, the limitations of this study were nonrandomization of interventions, nonblinding of assessors and participants, and lack of meibomian gland secretion evaluation in the control group. Future studies on long-term efficacy of LipiFlow and cost effectiveness of thermal pulsation treatment are necessary.

In a prospective, cohort, observational, single-center study, Greiner et al. (2016) examined the long-term (3 years) effects of a single (12 min) thermal pulsation system (TPS) treatment on symptomatic patients with evaporative dry eye disease (DED) secondary to meibomian gland dysfunction (MGD). Signs (meibomian gland secretion [MGS] scores and tear film breakup time [TBUT]) and symptoms (Ocular Surface Disease Index [OSDI] and Standard Patient Evaluation of Eye Dryness [SPEED] questionnaires) were determined in 20 patients (40 eyes) with MGD and dry eye symptoms at baseline (BL), 1 month, and 3 years post-TPS treatment using LipiFlow. Meibomian gland secretion scores increased from BL (4.5 ± 0.8) to 1 month (12.0 ± 1.1). Improvement persisted at 3 years (18.4 ± 1.4) relative to BL. Meibomian gland secretion scores in all regions of the lower eyelid were improved over BL at 1 month and 3 years. TBUT increased from BL (4.1 ± 0.4) to 1 month (7.9 ± 1.4) but was not significantly different than BL at 3 years (4.5 ± 0.6). The OSDI scores decreased from BL (26.0 ± 4.6) to 1 month (14.7 ± 4.3) but returned to BL levels at 3 years (22.5 ± 5.4). The SPEED scores decreased from BL (13.4 ± 1.0) to 1 month (6.5 ± 1.3), and this improvement persisted at 3 years (9.5 ± 1.6). The investigators concluded that thermal pulsation may be a uniquely efficacious treatment option for DED secondary to MGD in that a single 12-min procedure is associated with significant improvement in MGS and SPEED scores for up to 3 years. The limitations in this study include a lack of control and small sample size.

In a prospective, randomized, crossover, observer-masked clinical trial, Finis et al. (2014) compared the effectiveness of a single LipiFlow treatment with combined lid warming and massage in patients with meibomian gland dysfunction (MGD). Study participants were randomized to receive either a single 12-min LipiFlow Thermal Pulsation (LTP) system treatment or to perform combined twice-daily lid warming and massage for 3 months. All subjects were examined

before, and 1 and 3 months after initiation of treatments. A total of 31 subjects completed the 3-month follow-up. At 1 and 3 months, patients in the LipiFlow treatment group had a significant reduction in Ocular Surface Disease Index (OSDI) scores compared with those in the lid-margin hygiene group. Both treatments produced a significant improvement in expressible meibomian glands compared to the baseline parameters, but no significant difference was noted between the two groups. The other investigated objective parameters did not show a significant difference. The authors concluded that a single LipiFlow treatment is as least as effective as a 3-month, twice-daily lid margin hygiene regimen for MGD. According to the authors, a limitation of the present study was that it was observer-masked only, i.e., patients were aware of the fact that they received either an established or a new and modern treatment for MGD. Thus, a placebo effect may have confounded any improvements in subjective symptoms and other parameters in both groups. The authors also stated that additional studies using a sham LipiFlow treatment in a double-masked design with larger cohorts and longer follow-up times are warranted.

Lane et al. (2012) evaluated the safety and effectiveness of the LipiFlow System compared to the iHeat Warm Compress (WC) for adults with meibomian gland dysfunction (MGD) in a non-significant risk, prospective, open-label, randomized, crossover multicenter clinical trial. A total of 139 patients were randomized between LipiFlow (n=69) and WC control (n=70). Subjects in the LipiFlow group received a 12-minute LipiFlow treatment and were reexamined at 1 day, 2 weeks and 4 weeks. Control subjects received a 5-minute iHeat treatment with instructions to perform the same treatment daily for 2 weeks. At 2 weeks, they crossed over (LipiFlow Crossover) and received the LipiFlow treatment. LipiFlow resulted in significant improvement in meibomian gland secretion at 2 and 4 weeks and tear break-up time (TBUT) at 2 and 4 weeks. There was no significant change in meibomian gland secretion or TBUT in the control group. LipiFlow resulted in a greater significant reduction in dry eye symptoms than the iHeat WC. The crossover group demonstrated similar significant improvement 2 weeks post-treatment with the LipiFlow. There was no significant difference between groups in the incidence of non-serious, device-related adverse events. The authors concluded that the LipiFlow System was significantly more effective than iHeat WC. The significance of this study is limited by the short follow-up period.

A Hayes report for LipiFlow Thermal Pulsation System for Chronic Dry Eye Syndrome and Meibomian Gland Dysfunction indicated that the study abstracts for this technology present conflicting findings and therefore, conclusions about the safety and effectiveness of this technology were not made.

An ECRI report for LipiFlow Thermal Pulsation System for Treating Dry Eye Syndrome indicated that available evidence from controlled trials suggests LipiFlow treatment works for at least 12 months to relieve dry eye symptoms in many patients with meibomian gland dysfunction (MGD). However, the manufacturer conducted most of the identified randomized controlled trials (RCTs) and results from nonrandomized controlled trials may not be generalizable. Therefore, independent RCTs are needed that report longer-term efficacy and compare the device to other MGD therapies

The American Academy of Ophthalmology Preferred Practice Pattern Guidelines on dry eye syndrome (2018b) does not address thermal pulsation.

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 postprocedure. However, there have been no independent, randomized, clinical trials confirming or refuting these industry-sponsored studies.

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Code	Description
0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest
0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest
0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy

Intramuscular autologous bone marrow cell therapy is unproven and not medically necessary for treating peripheral arterial disease due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Peripheral arterial disease (PAD) is a narrowing of the blood vessels outside of the heart caused by a buildup of plaque (atherosclerosis). Standard treatment for severe cases of PAD is surgical or endovascular revascularization; however, not all patients are candidates for these procedures. Intramuscular autologous bone marrow cell therapy is being investigated as a potential new therapeutic option to induce angiogenesis. Early studies show promising results, but further large randomized controlled studies are needed to confirm these findings. Additional studies are needed to evaluate the rate of adverse events and the durability of positive treatment effects before definitive conclusions can be made regarding the safety and efficacy of this treatment. Clinical trials are ongoing.

In a double-blinded randomized placebo-controlled phase 3 trial, Lindeman et al. (2018) try and resolve a controversy with regard to cell therapy for peripheral artery disease (PAD). Inclusion criteria for participants included stable or progressive disabling PAD, no imminent need for amputation, absent accepted options for revascularization; diabetic disease was excluded. Bone marrow (500-700mL) was harvested and bone marrow-derived mononuclear cells were concentrated to 40 mL. Concentrated cells or placebo (diluted blood) were intramuscularly injected at 40 locations of the calf muscle. Fifty-four patients were randomized; twenty-eight of these patients received bone marrow -derived mononuclear cells and 26 received a placebo. No significant differences were observed for the primary (number of amputations, (pain free) walking distance) and secondary outcome parameters (ankle brachial index, pain scores, quality of life (SF-36)). The authors concluded this trial failed to confirm that bone marrow-derived mononuclear cell therapy was beneficial for patients with PAD and therefore should not be offered as a clinical treatment.

Rigato et al. (2017) conducted a systematic review of the literature and a meta-analysis of studies evaluating safety and efficacy of autologous bone marrow cell therapy for intractable peripheral arterial disease/critical limb ischemia. They assessed 19 randomized controlled trials (837 patients), 7 nonrandomized trials (338 patients), and 41 noncontrolled studies (1177 patients). The cell therapy reduced the risk of amputation by 37%, improved amputation-free survival by 18%, and improved wound healing by 59%. Cell therapy increased ankle brachial index, increased transcutaneous oxygen tension, and reduced rest pain. The authors concluded that cell therapy was found to be safe, being associated with mild and mostly transient adverse events related to local implantation/infusion. Some limitations of the study were low-moderate quality, high heterogeneity, and publication bias, and possible lack of statistical power.

MOBILE is a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of intramuscular injections of concentrated bone marrow aspirate (cBMA) in promoting amputation-free survival in patients with critical limb ischemia (CLI) due to severe peripheral arterial disease (PAD). Patients with critical limb ischemia were randomized to intramuscular injection of autologous bone marrow derived stem cells (n=119) versus placebo injection (n=36). Patients with rest pain or tissue loss resulting from advanced peripheral arterial disease, as

characterized by ankle brachial index (<0.6), toe-brachial index (<0.4), or transcutaneous pressure of oxygen (<50 mm Hg), were eligible for inclusion if surgical revascularization was not possible secondary to advanced disease. Treatment and 1-year follow-up of 155 patients enrolled in MOBILE are completed. Long-term follow-up is ongoing. (Clinical Trial- NCT02474121). Wang et al. (2017).

A prospective case series with interventions occurring between December 2007 and September 2012 and a 3-month minimum follow-up was conducted by Franz et al. (2015) to determine if intramuscular and intra-arterial stem cell injections delay or prevent major limb amputations. Forty-nine patients with severe limb-threatening peripheral arterial disease, without other options for revascularization enrolled. Dual intramuscular and intra-arterial injection of bone marrow mononuclear cells harvested from the iliac crest was performed. Major limb amputation at 3 months was the primary outcome measure. No complications related to the procedure were reported. Of 49 patients enrolled, two patients died, but had not undergone major amputation, and five patients underwent major amputation within the first 3 months. Three-month follow-up evaluations were conducted on the remaining 42 patients. After 3 months, seven patients died but had not undergone major amputation, and seven underwent major amputation. At a mean follow-up of 18.2 months, the remaining 29 patients had not undergone a major amputation. Freedom from major adverse limb events was 91.1% at 3 months and 75.6% at 12 months. The authors concluded that the results of this analysis indicate that autologous bone marrow mononuclear cell implantation therapy is an effective strategy for limb salvage for patients with severe peripheral arterial disease. Further research with randomized controlled trials is needed to validate these findings.

Moazzami et al. (2014) conducted a systematic review to evaluate the effectiveness and safety of local intramuscular autologous mononuclear cells to treat lower limb ischemia. Study results of two randomized controlled trials (total n=57) indicated positive treatment effects in terms of significantly reduced number of amputations and significantly increased in pain-free walking distance when compared with controls. However, study authors concluded that the evidence base is currently insufficient to support the use of this treatment and larger randomized controlled trials with sufficient power are needed to assess the role of intramuscular mononuclear cell implantation in patients with lower limb ischemia.

A European Society of Cardiology (ESC) guideline addresses novel therapies to stimulate neovascularization, known as therapeutic angiogenesis. These therapies promote revascularization and remodeling of collateral vessels to reduce the symptoms of peripheral vascular disease and prevent amputation. For autologous cell transplantation in humans, bone marrow and peripheral blood are rich sources of stem and progenitor cells. Bone marrow is currently the most frequent source of cells used for clinical repair trials, because it is easy to obtain and no complex purification steps are required. Another advantage is that it contains a variety of stem and progenitor cells. At present angiogenic gene and stem cell therapy are still being investigated, and it is too early to give firm recommendations (Tendera et al., 2011).

Fadini et al. (2010) conducted a meta-analysis to determine whether autologous cell therapy is effective in the treatment of peripheral arterial disease (PAD). The authors included 37 controlled and non-controlled, randomized and non-randomized trials using autologous bone marrow or granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood cells to treat PAD. Autologous cell therapy was effective in improving surrogate indexes of ischemia, subjective symptoms and hard endpoints (ulcer healing and amputation). G-CSF monotherapy was not associated with significant improvement in the same endpoints. Patients with thromboangiitis obliterans showed some larger benefits than patients with atherosclerotic PAD. The intramuscular route of administration and the use of bone marrow cells seemed somehow more effective than intraarterial administration and the use of mobilized peripheral blood cells. The authors concluded that intramuscular autologous bone marrow cell therapy is a feasible, relatively safe and potentially effective therapeutic strategy for PAD patients, who are not candidates for traditional revascularization. Larger, placebo-controlled, randomized multicenter trials are needed to confirm these findings.

In the Therapeutic Angiogenesis using Cell Transplantation (TACT) Study, Tateishi-Yuyama et al. (2002) investigated efficacy and safety of autologous implantation of bone marrow mononuclear cells in patients with ischemic limbs because of peripheral arterial disease. In the initial pilot study, 25 patients (group A) with unilateral ischemia of the leg were injected with bone marrow mononuclear cells into the gastrocnemius of the ischemic limb and with saline into the less ischemic limb. The authors then recruited 22 patients (group B) with bilateral leg ischemia, who were randomly injected with bone marrow mononuclear cells in one leg and peripheral blood-mononuclear cells in the other as a control. Primary outcomes were safety and feasibility of treatment, based on ankle-brachial index (ABI) and rest pain. Two patients were excluded from group B after randomization. At 4 weeks in group B patients, ABI was significantly improved in legs injected with bone marrow mononuclear cells compared with those injected with peripheral blood mononuclear cells. Similar improvements were seen for transcutaneous oxygen pressure, rest pain and pain-free walking time. These improvements were sustained at 24 weeks. Similar improvements were seen in group A patients. Two patients in group A died after myocardial infarction unrelated to treatment. The authors concluded that autologous implantation of bone marrow mononuclear cells could be safe and effective for achievement of therapeutic angiogenesis, because of the natural ability of marrow cells to supply endothelial progenitor cells and to secrete various angiogenic factors or cytokines.

Matoba et al. (2008) reported 3-year follow-up results for the TACT trial. The study assessed the 3-year safety and clinical outcomes of angiogenic cell therapy by investigating the mortality and leg amputation-free interval as primary end points. The median follow-up time for surviving patients was 25.3 months (range, 0.8-69.0 months), and 3-year overall survival rates were 80% in patients with atherosclerotic peripheral arterial disease and 100% in 41 patients with thromboangiitis obliterans (TAO). Three-year amputation-free rate was 60% in PAD and 91% in patients with TAO. The multivariate analysis revealed that the severity of rest pain and repeated experience of bypass surgery were the prognostic factors negatively affecting amputation-free interval. The significant improvement in the leg pain scale, ulcer size and pain-free walking distance was maintained during at least 2 years after the therapy, although the ankle brachial index and transcutaneous oxygen pressure value did not significantly change. The authors concluded that angiogenic cell therapy using bone marrow mononuclear cells can induce a long-term improvement in limb ischemia, leading to extension of amputation-free interval. Larger, placebo-controlled, randomized multicenter trials are needed to confirm these findings.

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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)
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)
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.

Note: 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. The HDE does not apply for treatment of heart failure. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf13/h130007c.pdf. (Accessed April 24, 2019)

Coverage for revision or removal of carotid sinus baroreflex activation devices may be addressed in the complication section of the benefit document. See 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 2019 review on device-based neuromodulation for resistant hypertension therapy, authors cited that U.S. randomized, multicenter Barostim neo HTN Pivotal trial (NCT01679132) was suspended “as company resources will only allow adequate oversight for one pivotal trial at a time.” At this time, the role of BA in management of resistant hypertension still awaits findings of randomized controlled trials (RCT) (Lohmeier and Hall).

Springer et al. (2017) conducted a prospective, first-in-human, proof-of-principle, open-label trial 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).

Recruiting is in progress for the new, 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. For more information, go to www.clinicaltrials.gov. (Accessed April 24, 2019)

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.

Reuter et al. (2017) investigated the effects of the MobiusHD device on office systolic BP (SBP) and on 24-hour ambulatory BP (ABPM) in patients with high pulse pressure (PP). A total of 40 patients participated in the observational study, receiving the MobiusHD implant for therapy-resistant hypertension and having BP measured at discharge, 1, 3, and 6 months. For analyses, patients were grouped according to baseline PP (high PP: >70 mmHg, n = 25; low PP: <70 mmHg, n = 15). Responsiveness at 6 months was defined as decrease in SBP of more than 10 mmHg, and also as decrease in ABPM of more than 5 mmHg. At 6 months, SBP, PP, and ABPM were significantly reduced. SBP and ABPM responses were similar between subjects with high or low PP. The authors concluded that the MobiusHD device effectively reduced SBP, PP, and ABPM in patients with therapy-resistant hypertension. Limitations included small sample size and study design.

Wallbach et al. (2016) conducted a prospective study 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.

Hoppe et al. (2012) evaluated the Barostim neo™, a second-generation BAT, in 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 randomization and 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 no longer includes any reference to BAT for the treatment of resistant hypertension (Whelton et al., 2018).

Heart Failure

ECRI states that reported clinical trial data suggests BAT for the treatment of heart failure (HF) may modestly improve New York Heart Association (NYHA) functional class, exercise capacity and QOL through 6 months and slightly reduce medication use. Data from larger trials that measure outcomes such as mortality, hospitalizations and device longevity are needed to better estimate the technology's potential health impact, especially compared with potential competing technologies and drug therapy alone (ECRI, 2013; updated 2018).

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.

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.

The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America's report on the management of HF do not include recommendations for BAT (Yancy et al., 2017).

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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.

Tong and Teng (2018) performed a review of the literature to determine the effectiveness of portable tear film instruments such as the Tearscope. The review included 22 reports related to non-invasive tear break up times (NIBUTs), 18 reports concerning tear film lipid morphology (LM) based on classification of interference patterns, and 8 reports on tear meniscal height (TMH). While publication of these reports indicates an acceptance of the reliability of portable instruments, the authors interrogated these studies further to evaluate the results obtained from portable devices and found that there was no equivalent measurements in fixed devices (LM) or measurements differ considerably from fixed devices (NIBUT). In the case of TMH, portable measurements were similar to those by traditional slit-lamp microscopy. There were relatively few studies on TMH measured using handheld devices, but it was found to be correlated to NIBUT but not the Schirmer test values. The authors concluded that imaging algorithms in portable tear film instruments should be further standardized to facilitate wider adoption and evaluation.

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.

In a retrospective analysis, Finis et al. (2013) evaluated the LipiView interferometer by assessing if there is a correlation between the tear-film lipid layer thickness (LLT) and other diagnostic criteria for meibomian gland dysfunction (MGD) in 110 patients (199 eyes). Subjective symptoms, break-up time (BUT), expressible Meibomian glands, and LLT were measured. There was a significant correlation between expressible Meibomian glands and LLT. Also, a possible trend of inverse correlation between subjective symptoms (standard patient evaluation of eye dryness) and the LLT was observed; however, this was not significant. Analysis of the whole study collective revealed no correlation between the BUT and the LLT. For a cut-off value of ≤ 75 -nm LLT, the authors found a sensitivity of 65.8% and a specificity of 63.4% for the detection of an MGD. For a cut-off value of ≤ 60 , the sensitivity was 47.9%, and the specificity was 90.2%. The authors concluded that the positive correlation between the LLT and expressible meibomian glands found in this study suggests a higher probability of MGD in patients with a low LLT. According to the authors, the LipiView interferometer might be a suitable screening test for detecting MGD. The authors stated that further prospective studies are needed to confirm these results and to identify potential confounders.

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

Reference(s)

American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern® Guidelines. Dry Eye Syndrome. San Francisco, CA: American Academy of Ophthalmology; 2018.

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Code	Description
0335T	Insertion of sinus tarsi implant

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 is a common disorder, anatomically described as excessive pronation during weight bearing due to anterior and medial displacement of the talus. It may be congenital in nature, or it may be acquired in adulthood due to posterior tibial tendon dysfunction, which in turn may be caused by trauma, overuse, and inflammatory disorders, among others. Symptoms include dull, aching and throbbing cramping pain, which in children may be described as growing pains. Additional symptoms include refusal to participate in athletics or walking long distances. Conservative treatments include orthotics or shoe modifications. Surgical approaches for painful flatfoot deformities include tendon transfers, osteotomy, and arthrodesis. Arthroereisis with a variety of implant designs has also been investigated.

Subtalar arthroereisis (SA) is a surgical procedure designed to correct the excessive talar displacement and calcaneal eversion by placing an implant in the sinus tarsi, a canal located between the talus and the calcaneus.

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.

Tao et al. (2019) evaluated the efficacy of surgical treatments for adult acquired flatfoot disorder (AAFD) through meta-analysis. A search of eligible studies conducted through November 2018 identified 21 studies for analysis (N = 498 patients). Examining surgical strategies and pooled outcomes, the list of best surgical approaches identified for AAFD treatment by these researchers does not include SA.

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 removed after 2-3 years. Giannini et al. 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 (2017).

A recent controlled study compared SA with lateral column calcaneal lengthening for the treatment of painful flatfeet (n=24 feet) (Chong et al., 2015). Compared with baseline values, patients in both groups experienced significant improvements in various outcomes pertaining to functionality of the foot; however, there were no significant differences between treatment and controls. Two additional studies were also identified that reported similar results from poor quality studies (De Pellegrain et al., 2014; Zhu and Xu, 2015).

To determine the current practice among orthopaedic foot and ankle specialists regarding SA, Shah et al. polled members of the AOFAS. There were 572 respondents to the web-based questionnaire (32% of AOFAS members) which was sent via e-mail. A total of 273 respondents (48%) have performed SA. Of this group, 187 respondents (69%) still perform the procedure. Of the respondents, 401 (70%) practice in the United States (US), 40% of the US practitioners have performed SA, and 60% of those still do. Of non-US respondents, 66% have performed SA, and 80% of those still perform it. The most common US indications are painful congenital flatfoot, posterior tibial tendon dysfunction, and flatfoot associated with accessory navicular. The authors concluded that while many doctors have performed SA, a significant number no longer perform the procedure for various reasons. A greater percentage of non-US practitioners have performed and still perform SA versus their US counterparts. Most doctors who still perform this procedure have removed the implants, commonly for pain (2015).

There is currently no published evidence from RCTs on SA. Numerous implant systems have received FDA approval through the 510(k) process. See the following website for more information (use product codes HWC): <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. (Accessed March 25, 2019)

While the American Association of Orthopaedic Surgeons (AAOS) states on their website that treatment ranges from nonsurgical to surgical methods, they have not taken a formal position with regard to the use of surgically placed implants as a treatment option for adult (acquired) flatfoot, flexible flatfoot in children, or in combination with other comprehensive surgical procedures for ankle and foot conditions (2017, 2018).

The American Orthopaedic Foot & Ankle Society (AOFAS) does not mention SA in their list of possible surgical treatments for adult flatfoot disorder. They are silent regarding surgical correction of flatfoot in children.

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Tao X, Chen W, Tang K. Surgical procedures for treatment of adult acquired flatfoot deformity: a network meta-analysis. J Orthop Surg Res. 2019 Feb 21;14(1):62.

Zhu Y, Xu XY. Treatment of stage II adult acquired flatfoot deformity with subtalar arthroereises. Foot Ankle Spec. 2015; 8(3):194-202.

Code	Description
0341T	Quantitative pupillometry with interpretation and report, unilateral or bilateral

Pupillometry is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Najjar et al. (2018) evaluated the ability of chromatic pupillometry to reveal abnormal pupillary responses to light in patients with early-stage primary open-angle glaucoma (POAG) and to identify if pupillometric impairment correlates with signs of optic nerve damage in the disease. In a cross-sectional study, 46 participants with early-stage POAG underwent a monocular 2-minute exposure to blue light (462 nm) followed by another 2-minute exposure to red light (638 nm) using a modified Ganzfeld dome equipped with a light-emitting diode lighting system. Light-induced changes in horizontal pupil diameter were assessed monocularly using infrared pupillography. The authors concluded that early-stage POAG is associated with altered pupillary responses to full-field light stimulations, and there is a close relationship between pupillary constriction amplitude under high irradiances of light and thinning of the retinal nerve in this patient group. While findings show promise for early detection of POAG, further improvements are required to render this approach more viable in a clinical setting.

Sabourdin et al. conducted a single-blinded, prospective, parallel-arm study to evaluate the impact of intraoperative pupillometry monitoring on perioperative opioid consumption during major gynecologic surgery. Participants (n=55) were randomly assigned into 2 groups. In the pupillometry group, remifentanyl administration was guided by pupillary diameter changes. In the standard group, remifentanyl administration was left to the discretion of the anesthesiologist. Remifentanyl consumption was markedly decreased and cumulative morphine consumption was reduced in the pupillometry group versus the standard group. A telephone survey at 3 months post-surgery revealed that 15 of 29 patients in the standard group still experienced procedure-related pain versus 3 of 23 in the pupillometry group. AEs associated with pupillometry were not observed. Authors concluded that while using pupillometry to guide intraoperative analgesia reduced intraoperative remifentanyl consumption and postoperative morphine requirements, the possible consequences of decreasing intraoperative remifentanyl in terms of chronic pain require further investigation (2017).

In a double-blind observational study, Couret et al. compared automated quantitative pupillometry with the standard clinical pupillary examination currently used for brain-injured patients (n=200 with 400 healthy eyes). Results demonstrated that pupillary evaluations obtained subjectively at the patient's bedside were inaccurate compared with those obtained with an automatic quantitative pupillometer device. This device can record reliable pupillary measurements. The significant error rate in detection of anisocoria by the current standard examination suggests inclusion of the automated pupil measurements in the routine health care of brain-injured patients. However, the impact of a pupillometer use on patients' outcome would need to be evaluated through further prospective studies (2016).

Suys et al. (2015) evaluated the accuracy of quantitative pupillary light reactivity to predict health outcomes of patients who experienced a coma following cardiac arrest (n=50). Results showed that prognostic accuracy of pupillometry was comparable to conventional measures using EEG and SSEP.

Tatham et al. (2014) evaluated the ability of pupillometry to differentiate between healthy subjects and patients with glaucoma (n=116; 66 glaucoma patients; 50 healthy patients). Study results indicate that pupillometry performed poorly in patients with symmetric glaucoma, although results were acceptable in asymmetric disease. Pupillometry has been used in a research setting to evaluate the autonomic function, pain response, psychological processes, sleep disorders, and drug metabolism.

In a cross-sectional cohort study, Kantor et al. (2014) studied the association between postoperative pain numerical rating scale (NRS) and pupillary diameter or pupillary light reflex amplitude (PLRA) using pupillometry in post-anesthesia care unit (PACU) patients after routine anesthetic care. One hundred and forty-five patients undergoing planned surgery under general anesthesia were included in the study. NRS, pupillary diameter and PLRA were measured on arrival in the PACU. When NRS was more than 4, intravenous morphine titration was started and a second measurement performed. Mean NRS was 4.7, and was more than 4 in 79 patients (55%). Twenty-seven patients (19%) received morphine titration with significant decreases in NRS, pupillary diameter and PLRA afterwards. No association was observed between NRS changes and pupillary diameter or PLRA changes. The authors concluded that acute postoperative pain is not associated with pupillary diameter or PLRA. Further research is required to develop tools to assess pain in the PACU.

Other clinical trials have also assessed the usefulness of automated pupillometry (Rouche et al., 2013; Kardon et al., 2011; Ferrari et al., 2010; Guglielminotti et al., 2013; Isnardon et al., 2013; Suys et al., 2014). These studies were limited by small sample sizes or did not validate pupillometry findings with improved patient care.

A 2017 Preferred Practice Pattern by the American Academy of Ophthalmology states that data from published studies fail to demonstrate a relationship between pupil size and the quality of postoperative vision. Therefore, the importance of pupillometry in the preoperative workup remains controversial. For more information, go to: <https://www.aaopt.org/preferred-practice-pattern/refractive-errors-refractive-surgery-ppp-2017>. (Accessed April 5, 2019)

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Code	Description
0355T	Gastrointestinal tract imaging, intraluminal (e.g., capsule endoscopy), colon, with interpretation and report

Pillcam Colon2 capsule endoscopy system is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The Pillcam Colon2 capsule endoscopy system is a device the size of a pill, equipped with two miniature color video cameras (one on each end), a battery, and LED light source. The device is designed to be swallowed by the patient and transmit video images back to a recording device worn by the patient. The device is set to record video as it travels throughout the patient's body for approximately 10 hours, until the pill is excreted.

The U.S. Food and Drug Administration (FDA) approved Pillcam Colon2 on January 29, 2014 under the de novo classification utilized for devices with low to moderate risk, for use in patients who have had an incomplete optical colonoscopy with adequate preparation, and a complete evaluation of the colon was not technically possible. On March 31, 2016, the FDA approved an expanded indication for detection of polyps in patients with evidence of gastrointestinal (GI) bleeding of lower GI origin. This applies only to patients with major risks for colonoscopy or moderate sedation but who could tolerate colonoscopy and moderate sedation in the event a clinically significant colon abnormality was identified on capsule endoscopy. See the following websites for more information:

- www.accessdata.fda.gov/cdrh_docs/reviews/k123666.pdf
- www.accessdata.fda.gov/cdrh_docs/pdf15/k153466.pdf

Accessed April 2, 2019)

Kobaek-Larsen et al. (2018) evaluated results of back-to-back capsule colon endoscopy (CCE) and colonoscopy in 253 individuals to determine the polyp detection rate and per-patient sensitivity for polyps > 9 mm. All participants had a positive immunochemical fecal occult blood test during screening. The polyp detection rate was significantly higher in CCE compared with colonoscopy (P = 0.02). The per-patient sensitivity for > 9 mm polyps for CCE and colonoscopy was 87% (95% CI: 83-91%) and 88% (95% CI: 84-92%) respectively. In participants with complete CCE and colonoscopy examinations (N = 126), per-patient sensitivity of > 9 mm polyps in CCE (97%; 95% CI: 94-100%) was superior to colonoscopy (89%; 95% CI: 84-94%). A complete CCE examination (N = 134) could detect patients with intermediate or greater risk (according to the European guidelines) with an accuracy, sensitivity, specificity and positivity rate of 79%, 93%, 69% and 58% respectively, using a cut-off of at least one polyp > 10 mm or more than two polyps. The authors concluded that CCE is superior to colonoscopy in polyp detection rate and per-patient

sensitivity to > 9 mm polyps, but only in complete CCE examinations. The rate of incomplete CCE examinations must be improved to validate these findings.

Nogales et al. (2017) conducted a prospective, multicenter study to determine the frequency of complete colonoscopy after incomplete colonoscopy (IC), the diagnostic yield of CCE, the therapeutic impact of lesions found in CCE, the level of colon cleanliness and the safety of the procedure. Consecutive outpatients aged ≥ 18 years with previous IC were invited to participate (n=96). Complete visualization of the colon was obtained with CCE-2 in 69 patients (71.9%). Of the 27 patients in whom the CCE-2 did not reach the hemorrhoidal plexus, it passed the colonic segment explored with the previous colonoscopy in 20 cases; therefore, it could be inferred that a combined approach (CCE-2 plus colonoscopy) enabled complete visualization of the colonic mucosa in 92.7% of patients. CCE-2 revealed new lesions in 58 patients (60.4%). Polyps were the most frequent finding (41 patients; 42.7% of the total number of patients). In 43 of the 58 patients (44.8% of the total number of patients), the new lesions observed led to modification of therapy, which included a new colonoscopy for polyp resection or surgery in patients with colonic neoplasm. The authors concluded that CCE is a suitable diagnostic procedure that can lead to more frequent diagnosis of significant colonic lesions after IC. Randomized controlled studies with larger patient populations are needed to further evaluate CCE.

In a prospective multicenter study, Alvarez-Urturi et al. (2017) assessed the diagnostic yield of CCE in a cohort of asymptomatic individuals (n=53) with a family history of colorectal cancer. CCE and colonoscopy were performed on the same day by 2 endoscopists who were blinded to the results of the other procedure. The sensitivity, specificity, PPV, and NPV of CCE for detecting advanced adenomas were 100%, 98%, 67%, and 100%. Sensitivity, specificity, PPV, and NPV of CCE for the diagnosis of individuals with polyps were 87%, 97%, 93%, and 88%, respectively. CCE identify 100% of individuals with significant or advanced lesions. *The authors* concluded that capsule colon endoscopy is a promising tool, but it has to be considered as an alternative technique in this population in order to reduce the number of colonoscopies performed. More studies are needed to understand appropriate screening follow-up intervals and optimize the bowel preparation regimen.

In a prospective, multi-center study, Morgan et al. (2016) evaluated the performance of the second generation capsule colonoscopy (CC2) in the detection of polyps in symptomatic and screening patients (n=50). The main outcome measurement was accuracy of CC2 for the detection of colorectal polyps ≥ 6 mm and ≥ 10 mm as compared with conventional colonoscopy. For lesions ≥ 10 mm identified on conventional colonoscopy, CC2 sensitivity was 100% (95% CI 56.1% to 100%) with a specificity of 93.0% (79.9% to 98.2%). For polyps ≥ 6 mm, the CC2 sensitivity was 93.3% (66.0% to 99.7%) and the specificity was 80.0% (62.5% to 90.9%). There was a 61% adequate cleansing rate with 64% of CC2 procedures being complete. Randomized controlled-trials with larger patient populations are needed to further evaluate CC2.

Rex et al. (2015) performed a prospective study of asymptomatic patients (n = 884) who underwent capsule colonoscopy followed by conventional colonoscopy (the reference) several weeks later, with an endoscopist blinded to capsule results, at 10 centers in the United States and 6 centers in Israel from June 2011 through April 2012. An unblinded colonoscopy was performed on subjects found to have lesions 6 mm or larger by capsule but not conventional colonoscopy. They concluded that in an average-risk screening population, technically adequate capsule colonoscopy identified individuals with 1 or more conventional adenomas 6 mm or larger with 88% sensitivity and 82% specificity. Capsule performance seems adequate for patients who cannot undergo colonoscopy or who had incomplete colonoscopies; however the authors recommend additional studies to improve capsule detection of serrated lesions.

A case-controlled study was performed by Hagel et al. (2014) to provide a side by side evaluation of optical colonoscopy and the Pillcam Colon2 also known as the CCE. The objective of the study was to test the feasibility, sensitivity and specificity for the detection of colonic pathologies and additional recorded extracolonic findings. Colon Capsule Endoscopy was performed before optical colonoscopy in 24 patients who were already known or suspected of having colonic disease. The tests were then compared with regard to polyp detection. The finding showed visualization of the colon was complete in 23 CCs and 17 CCEs. No AEs or major technical failures occurred. Optical colonoscopy detected 47 polyps and CCE detected 43 polyps of any size (per-finding sensitivity 90.9%, specificity 67.6%). The accuracy of CCE in detecting polyp carriers was 81.5% (per-patient analysis). On average, the colon was adequately cleansed in 90.1% of patients. CCE identified esophageal, gastric and small bowel pathologies in seven (24%), nine (38%) and 14 (58%) patients, respectively. The authors concluded CCE proved to be technically feasible and safe. Acceptable sensitivity and moderate specificity levels in polyp detection were recorded. Bowel preparation was adequate in most patients. Because extracolonic pathologies were effectively visualized, new indications for the PillCam Colon 2 may be defined. Limitations of this study are the small sample size and study methodology, i.e., case controlled.

In a case controlled study Rondonotti et al. (2014) assessed the accuracy of the colon capsule (Pillcam2 [cc2]) and a computed tomographic colonography (CTC) in those patients who are unable or unwilling to undergo optical

colonoscopy (OC). 50 individuals who had been prior identified to have at least one polyp 6mm or larger. The combination of OC, CTC, and CC2 identified 16 cases with at least 1 polyp 6 mm or larger (reference standard). CTC identified the polyps with 88.2% sensitivity, 84.8% specificity, a 3.0 positive likelihood ratio, and a 0.07 negative likelihood ratio. CC2 identified the polyps with 88.2% sensitivity, 87.8% specificity, a 3.75 positive likelihood ratio, and a 0.06 negative likelihood ratio. Thirty-nine subjects (78%) said they preferred CC2 to CTC. The authors concluded that CC2 and CTC detect polyps 6 mm and larger with high levels of accuracy; these techniques are effective in selecting iFOBT-positive individuals who do not need to be referred for optical colonoscopy. CC2 seems to be better tolerated than CTC, and could be a reliable alternative to CTC for iFOBT-positive individuals who are unable or unwilling to undergo OC. Limitations of this study are the small sample size and study methodology, i.e., case controlled.

In a prospective single center study, Negreanu et al. (2013) assessed the feasibility, accuracy and acceptability of PillCam Colon2 in detection of significant lesions in colorectal cancer risk patients, unable or unwilling to perform colonoscopy. A total of 70 patients at risk of colorectal cancer were enrolled in the study. In three patients the procedure failed because the capsule was not functioning when entered the colon. PillCam Colon2 showed positive findings in 23 (34%, 95%CI: 21.6%-44.1%) of the remaining 67 patients. Six patients were diagnosed with tumors: 4 with colon cancers, 1 with gastric cancer and 1 with a small bowel cancer. The capsule findings were confirmed after surgery in all these patients. The capsule excretion rate in twelve hours was 77% with 54 patients having a complete examination. The rectum was not explored during CCE procedure, in 16 patients (23%, 95%CI: 13.7%-34.1%). Every patient accepted CCE as an alternative exploration tool and 65/70 (93%) agreed to have another future control by CCE. No complications were reported during or after CCE examination. The authors concluded that the PillCam Colon 2 capsule was effective in detecting significant lesions and might be considered an adequate alternative diagnostic tool in patients unable or unwilling to undergo colonoscopy. Interpretation of the findings is limited due to the small sample size studied in this uncontrolled prospective single center study.

In a prospective multicenter trial, Spada et al. (2011) assessed the feasibility, accuracy, and safety of the PillCam Colon2 (CCE-2) in a head-to-head comparison with colonoscopy. The study included 117 patients (mean age 60 years). Data from 109 patients were analyzed. CCE-2 was prospectively compared with conventional colonoscopy as the criterion standard for the detection of colorectal polyps that are ≥ 6 mm or masses in a cohort of patients at average or increased risk of colorectal neoplasia. Colonoscopy was independently performed within 10 hours after capsule ingestion or on the next day. Per-patient CCE-2 sensitivity for polyps ≥ 6 mm and ≥ 10 mm was 84% and 88%, with specificities of 64% and 95%, respectively. All 3 invasive carcinomas were detected by CCE-2. The capsule excretion rate was 88% within 10 hours. Overall colon cleanliness for CCE-2 was adequate in 81% of patients. The authors concluded that CCE-2 appears to have a high sensitivity for the detection of clinically relevant polypoid lesions, and it might be considered an adequate tool for colorectal imaging. Study limitations included a relatively small patient population of nonconsecutive patients.

In a five-center feasibility study, Eliakim et al. (2009) prospectively compared the second-generation capsule endoscopy (PillCam Colon2) with conventional colonoscopy as gold standard for the detection of colorectal polyps and other colonic disease, in a cohort of patients scheduled for colonoscopy and having known or suspected colonic disease. Colonoscopy was independently performed within 10 hours after capsule ingestion. A total of 104 patients (mean age 49.8 years) were enrolled; data from 98 were analyzed. Patient rate for polyps of any size was 44%, 53% of these patients having adenomas. No AEs related to either procedure were reported. The capsule sensitivity for the detection of patients with polyps ≥ 6 mm was 89% and for those with polyps ≥ 10 mm it was 88%, with specificities of 76% and 89%, respectively. Both polyps missed by colonoscopy and mismatch in polyp size by study definition lowered specificity. Overall colon cleanliness for capsule endoscopy was adequate in 78% of patients. The authors concluded that the new second-generation colon capsule endoscopy is a safe and effective method for visualizing the colon and detecting colonic lesions. Sensitivity and specificity for detecting colorectal polyps appear to be very good, suggesting a potential for improved accuracy compared with the first-generation system. The authors note further prospective and comparative studies are needed.

In a meta-analysis and systematic review, Spada et al. (2016) evaluated the accuracy of the first and second generation colon capsules in the detection of colorectal polyps, in comparison to a complete colonoscopy. Online databases such as Cochrane, MEDLINE were searched to identify studies that compared accuracy of colonoscopy with histologic evaluation with colon capsule endoscopy. Fourteen studies met the inclusion criteria and provided data from 2420 patients (1128 for CCE-1 and 1292 for CCE-2). The authors report that the sensitivity in detection of polyps >6 mm and >10 mm increased substantially between development of first-generation and second-generation colon capsules and that high specificity values for detection of polyps by CCE-2 seem to be achievable with a 10-mm cutoff and in a screening setting.

Yung et al. (2016) reviewed the current clinical evidence of CCE in comparison with a complete colonoscopy for detection of polyps. In the authors' opinion, further software and hardware development is required to enable CCE to

fulfill its potential as a minimally-invasive and reliable method of colonoscopy. Significant limitations noted in their review include the need for aggressive bowel preparation and the labor-intensiveness of CCE reading.

Han and Im (2016) reviewed the characteristics of CCE in comparison to conventional methods such as conventional colonoscopy or computed tomographic colonography. The authors note one shortcoming of CCE to be the inability of CCE to take biopsy samples and to predict histology during the examination. As such, the authors consider CCE to be a complementary test because its diagnostic accuracy is still less than that of conventional colonoscopy in colorectal cancer (CRC) screening. In the authors' opinion, because CCE is well-tolerated by patients, and can be performed on an outpatient basis it could increase patient compliance with colorectal cancer screening. Considering the rapidly developing technologies, they concluded that the future of CCE is promising in the area of CRC screening.

Health Quality Ontario (2015) performed a literature search for studies on Pillcam Colon2 (PCC2) published between 2006 and 2014, to evaluate the diagnostic accuracy and safety of colon capsule endoscopy for the detection of colorectal polyps among adult patients with signs or symptoms of colorectal cancer or with increased risk of colorectal cancer, and to compare colon capsule endoscopy with alternative procedures. Five studies met the inclusion criteria. The available evidence did not show a difference between the accuracy of colon capsule endoscopy with computed tomography (CT) scan of the colon (colonography). The authors commented that compared with conventional colonoscopy, the colon capsule endoscopy cannot be a replacement. If polyps are found, a colonoscopy or other procedure may be needed to further investigate and remove precancerous polyps. The reviewers concluded that in adult patients with signs, symptoms, or increased risk of colorectal cancer, there is low-quality evidence that colon capsule endoscopy using the PCC2 device has good sensitivity and specificity for detecting colorectal polyps. Low-quality evidence does not show a difference in accuracy between colon capsule endoscopy and CT colonography. There is very low-quality evidence that PCC2 has a good safety profile with few AEs; capsule retention is the most serious complication.

The National Institute for Health and Care Excellence (NICE) 2016 guideline on the diagnosis and management of colorectal cancer includes colonoscopy, flexible sigmoidoscopy, computed tomographic (CT) colonoscopy, and/or barium enema, depending on the patient's medical condition. The Pillcam Colon2 is not mentioned in their guideline as a diagnostic tool for colorectal cancer screening.

In 2013, the American Society for Gastrointestinal Endoscopy (ASGE) published a technology status evaluation report for wireless capsule endoscopy (WCE). The report states that WCE applications still remain limited within the colon (Wang et al., 2013).

Guidelines issued by the European Society for Gastrointestinal Endoscopy (ESGE) (Spada et al., 2012) indicate that cCCE is feasible and safe for patients with incomplete colonoscopy and without stenosis [Evidence level 3 (Nonanalytic studies, e.g., case reports, case series), Recommendation grade D]. According to the guidelines, randomized studies comparing CCE with radiological imaging or conventional endoscopic procedure are needed to confirm the efficacy of CCE in this setting and to better define the patients for whom CCE is most suitable. The guidelines also indicate that there is a lack of specific studies based in the setting of screening for CCE. The authors of the guideline indicate that the average sensitivity of the first generation of CCE (CCE-1) devices for significant findings (≥ 6 mm size, or ≥ 3 polyps irrespective of size) was 58% substantially improving to 86% with the second generation CCE (CCE-2) devices (Eliakim, 2009; Spada, 2011).

The United States Preventive Services Task Force (USPSTF) 2016 final recommendation statement on colorectal cancer screening (an update to the 2008 USPSTF recommendation) does not include a statement related to the use of the Pillcam Colon2 as a preventive service for colorectal cancer screening. The USPSTF recommends screening for colorectal cancer in adults, beginning at age 50 years and continuing until age 75 years.

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Code	Description
0356T	Insertion of drug-eluting implant (including punctal dilation and implant removal when performed) into lacrimal canaliculus, each

The use of drug eluting punctal plugs or implants into the lacrimal canaliculus is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The use of drug-eluting plugs is a new approach to treating patients with various eye conditions including glaucoma, dry eye, and eye inflammation. The drug-eluting implant or plug is placed within the lacrimal canaliculus to deliver precise drug doses for a predetermined period.

In a prospective multicenter randomized parallel-arm double-masked vehicle-controlled phase 3 study, Tyson et al. (2019) assessed the efficacy and safety of a sustained-release intracanalicular dexamethasone insert for the treatment of postoperative ocular inflammation and pain in patients having cataract surgery. Patients with planned clear corneal cataract surgery were randomized (1:1) to receive dexamethasone insert or placebo, and the treatment was placed in the canaliculus of the eye immediately after surgery (Day 1). The primary efficacy endpoints were complete absence of anterior chamber cells at Day 14 and complete absence of pain at Day 8. The study comprised 438 adult patients (216 in the treatment arm and 222 in the placebo arm). At Day 14, significantly more patients had an absence of anterior chamber cells in the dexamethasone insert arm compared with placebo. At Day 8, significantly more patients had an absence of ocular pain in the dexamethasone insert arm compared with placebo. The dexamethasone insert arm showed no increase compared with placebo in incidence of all adverse events or ocular adverse events. Twice as many placebo patients required rescue therapy, compared with treated patients at Day 14. According to the authors both primary endpoints of the study were successfully met. Evidence is lacking regarding the risks and benefits of the dexamethasone insert compared to standard dexamethasone eye drops for the treatment of postoperative ocular inflammation and pain. Randomized trials that directly compare the dexamethasone insert with an active control such as standard dexamethasone eye drops are needed to demonstrate a clinical advantage with the dexamethasone insert.

Torkildsen et al. (2017) conducted a randomized, double-masked, vehicle-controlled, Phase 2 study evaluate the efficacy and safety of a sustained-release dexamethasone intracanalicular insert (Dextenza™) for treating allergic conjunctivitis. The subjects included in the study had to have a positive conjunctival allergen challenge (CAC) reaction to allergen at Visit 1, and for 2 of 3 time points on subsequent visits. Subjects who met entry criteria were randomized to receive Dextenza or PV (vehicle insert). Challenges occurred over 42 days, with efficacy assessed at 14 (primary endpoint visit), 28, and 40 days postinsertion. Outcome measures included the evaluation of ocular itching,

redness, tearing, chemosis, eyelid swelling, rhinorrhea, and congestion. Twenty-eight subjects completed the study in the Dextenza group and 31 in the vehicle group. At 14 days postinsertion, Dextenza was statistically superior to PV. Clinical significance, defined as a 1-U decrease from PV, was not met for primary efficacy. Secondary endpoints, including number of subjects reporting itching and conjunctival redness, indicated superior performance of Dextenza compared with vehicle. Eleven Dextenza-treated (35.5%) and 10 vehicle-treated (30.3%) subjects each experienced a single AE. The authors concluded that this Phase 2 study demonstrated preliminary efficacy and safety data of Dextenza for treatment of allergic conjunctivitis. Well-designed randomized clinical trials with extended follow-up are necessary to evaluate the long-term efficacy and late complications of these intracanalicular inserts.

Walters et al. (2016) evaluated the safety and efficacy of OTXDP, a sustained-release dexamethasone punctum plug when placed in the canaliculus of the eyelid for the treatment of post-surgical pain and inflammation in patients who had undergone cataract surgery. Two prospective, Phase 3, multicenter, randomized, parallel-arm, double-masked, vehicle-controlled studies (referred to as Study 1 and Study 2) were conducted across 32 private practice sites in the United States. Patients were randomized (2:1) on Day 1 to receive a sustained release dexamethasone depot, (0.4 mg; Study 1, n=164; Study 2, n=161) or placebo vehicle depot (Study 1, n=83; Study 2, n=80) in the inferior canaliculus. The primary endpoint for ocular pain was met in both studies; statistically higher proportions of patients in OTX-DP groups, compared with placebo groups, had no ocular pain at day 8. However the inflammation endpoint was met only in Study 1. The authors suggest that this endpoint failed to reach statistical significance in Study 2 because of an unusually high percentage of placebo group patients without anterior chamber cells at day 14. Significantly fewer OTX-DP group than placebo group patients required rescue medications on study days 8 and 14; this endpoint did not statistically differ on study days 1, 2, and 4. No treatment-related AEs were reported. OXTDP is currently undergoing US Food and Drug Administration (FDA) review.

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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 it’s 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.

Fonseca et al. (2018) performed a study to investigate the validity of an eight-contact electrode bioelectrical impedance analysis (BIA) system within a household scale for assessing whole body composition in COPD patients. Seventeen patients with COPD underwent dual-energy X-ray absorptiometry (DEXA) 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 DEXA 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. This is an uncontrolled study with a small sample size.

The aim of a study by Thivel et al. (2018) was to assess the sensitivity of bio-impedance (BIA) in tracking body composition changes in adolescents with various degrees of obesity. Whole-body and segmental body composition were assessed by bio-impedance analysis (BIA) and dual x-ray absorptiometry (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, 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 bioelectrical impedance analysis (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.

Johnston et al. (2014) conducted this 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 $+1.8 \pm 4.8$ kg and $+2.3 \pm 6.4$ kg, respectively. The measurement error was consistently larger in the fasting group and the magnitude of the bias is greater with greater weight loss.

In this study, Widen et al. (2014) was attempting 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), $p = 0.35$; Δ 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
0377T	Anoscopy with directed submucosal injection of bulking agent for fecal incontinence
L8605	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, anal canal

The use of an injectable bulking agent such as Solesta® is unproven and not medically necessary for treating fecal incontinence due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Solesta Injectable Gel (Salix Pharmaceuticals, Inc.) is a sterile gel that is injected into the anal canal to treat the symptoms of fecal incontinence (FI). It is composed of naturally-made materials, dextranomer and sodium hyaluronate. Solesta is classified by the U.S. Food and Drug Administration (FDA) as a medical device (injectable bulking agent for gastro urology use) and not a drug. Solesta Injectable Gel (Salix Pharmaceuticals Inc.) received FDA premarket approval (PMA) on May 27, 2011 (P100014; product code LNM). See the following website for more information: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>. (Accessed April 2, 2019)

Franklin et al. (2016) conducted a randomized, double-blind, sham-controlled multi-center clinical trial in patients with fecal incontinence (FI). A total of 206 adult patients with a Cleveland Clinic Florida fecal incontinence score (CCFIS) ≥ 10 were randomized to receive NASHA Dx or sham treatment. Post hoc subgroup analyses were performed for baseline and demographic characteristics and prior FI treatments. Results showed that injection with NASHA Dx decreased the number of FI episodes by at least 50% in 52.7% of patients at 6 months compared with 32.1% of patients receiving sham treatment. The authors noted that while all patients were required to fail at least some form of previous therapy, in general, patients who had not received prior FI treatment via antidiarrheal medications, bowel habit training, biofeedback, or surgery were significantly more likely to respond to NASHA Dx versus sham treatment.

Graf et al. (2011) conducted a randomized double-blind, sham-controlled trial to assess the efficacy of injection of dextranomer in stabilized hyaluronic acid (NASHA Dx) for treatment of fecal incontinence. A total of 206 adults were randomized and assigned to receive NASHA Dx (n=136) or sham treatment (n=70). Of the NASHA Dx group, 132 were analyzed at six months, and 125 analyzed at 12 months. In the sham group, 65 were analyzed at six months. Seventy-one patients (52%) who received NASHA Dx had a 50% or more reduction in the number of incontinence episode, compared with 22 (31%) patients who received sham treatment. However, the median decrease in number of incontinence episodes was not significantly greater in the active treatment group than in the sham treatment group at both three months and six months. A total of 128 treatment-related AEs were recorded, of which two were serious (one rectal abscess and one prostatic abscess). Study limitations include small sample size and short term follow-up.

Al-Bayati, et al. (2017) evaluated 17 patients who had failed medical therapy for FI, and received a biocompatible bulking agent (Solesta) administered by submucosal injection in the distal rectum. The treatment was considered successful if patients achieved $>50\%$ reduction in FI events during monitoring for up to 12 months. After the first treatment session, 14 patients (82.3%) had a successful outcome. The remaining 3 patients received a second therapy 3 months later to achieve this result. At last follow-up, 7 of the 17 patients (41%) were having no FI events. The remaining patients had reduction in fecal accidents from a mean of 6.4/week baseline to 2.8/week during follow-up. In the authors' opinion, intrarectal injection of an injectable bulking agent is effective for treating FI in patients who had failed standard medical treatments.

La Torre et al. (2013) evaluated the long-term efficacy and safety of dextranomer in stabilized hyaluronic acid (NASHA/Dx) assessed 24 months after treatment. Data on fecal incontinence (FI) episodes and QOL measures were collected from diaries over the 28-day period immediately preceding the 24-month assessment. Eighty-three of 115 fifteen patients completed the 24-month follow-up assessment. At 24 months, 62.7% of patients were considered responders and experienced $\geq 50\%$ reduction in total number of FI episodes. The median number of FI episodes declined by 68.8%. Episodes of both solid and liquid stool incontinence decreased. The mean number of incontinence-free days increased from 14.6 at baseline to 21.7 at 24 months. Incontinence scores and FI QOL scores also showed significant improvements. The most common AEs were proctalgia (13.3%) and pyrexia (9.6%). The majority of AEs were mild to moderate, self-limited, and resolved within 1 month of the injection. The authors concluded that NASHA/Dx is safe, effective, and durable over a 24-month period with a majority of patients experiencing significant improvement in multiple symptoms associated with FI. This study was nonrandomized and not case controlled.

Danielson et al. (2013) assessed the effects of NASHA Dx on continence and QOL and to evaluate the relationship between QOL and efficacy up to 2 years after treatment. Thirty-four patients (5 males, mean age 61) were injected with NASHA Dx in the submucosal layer. The patients were followed for 2 years with registration of incontinence episodes, bowel function and QOL questionnaires. Twenty-six patients reported sustained improvement after 24 months. The median number of incontinence episodes before treatment was 22 and decreased to 10 at 12 months and to 7 at 24 months. There was a clear correlation between the decrease in the number of leak episodes and the increase in the SF-36 Physical Function score but only patients with more than 75% improvement in the number of incontinence episodes had a significant improvement in QOL at 24 months. The authors concluded that anorectal injection of NASHA Dx gel induces improvement of incontinence symptoms for at least 2 years. The authors stated that the treatment has a potential to improve QOL. According to the authors, a 75% decrease in incontinence episodes may be a more accurate threshold to indicate a successful incontinence treatment than the more commonly used 50%. Study limitations include the lack of controls and a small study population.

In an observational study, Dodi et al. (2010) evaluated 86 patients with fecal incontinence (FI) who received 4 injections of 1 mL NASHA/Dx gel. This study demonstrated a $\geq 50\%$ reduction from baseline in the number of FI episodes in 57% of patients at 6 months, and 64% at 12 months. A total of 7% of patients reported pyrexia that was assessed by the investigator as related to treatment. A total of 6 cases of anorectal abscess were reported in the study. All of these events resolved after treatment. According to the authors, NASHA/Dx gel is an efficacious in the treatment of FI. Lack of a comparison group limits the conclusions that can be reached from this study.

In a systematic review and meta-analysis, Hong et al. (2017) investigated the midterm outcomes of treatment with injectable bulking agents and to identify predictive factors for improvement in incontinence. A total of 889 patients in 23 articles were included. The weighted mean follow-up duration was 23.7 months (95% CI 19.3-28.2). Eleven different bulking agents were used. Four validated fecal incontinence scores were used; the Cleveland Clinic Fecal Incontinence score (CC-FIS) was used in 19 studies. The weighted mean difference in CC-FIS between preoperative visit and last follow-up was 4.9 (95% CI 4.0-5.8). The rate of improvement in incontinence was 39.5% based on CC-FIS. Meta-regression revealed that the perianal injection route and implants intact on endoanal ultrasonography were predictive of greater improvement in incontinence. The manometric data revealed that the initial increase in the mean resting pressure following injection was attenuated over time. The pooled rate of AEs was 18.0% (95% CI 10.0-30.1). In most cases, AEs were minor and resolved within a couple of weeks. The authors concluded that administration of injectable bulking agents results in significant midterm improvement in FIS. Perianal injection route and implants intact on EAUS were predictive of higher improvement in incontinence. However, given the paucity of randomized controlled trials in the literature, further research is needed to improve the quality of the evidence.

Forte et al. (2016) assessed the efficacy and comparative effectiveness of surgical and non-surgical treatments for fecal incontinence (FI) in adults. Sixty-three unique studies met inclusion criteria; an additional 53 surgical case series were examined for AEs. Most randomized controlled trials (RCTs) were nonsurgical (n = 38). Meta-analysis was not possible because numerous outcomes were used. Low-strength evidence at 6 months suggests that dextranomer anal bulking injections are more effective than sham injections on the FIQL, the number of FI-free days, and the percent of adults with at least 50-percent reduction from baseline in FI episodes, but no more effective than PFMT-BF with or without electrostimulation on FI severity (PFMT-BF -5.4 vs. dextranomer -4.6 point Vaizey score improvements) and the FIQL, (PFMT-BF -5.4 vs. dextranomer -4.6 point Vaizey score improvements) and the FIQL, and no more effective than sham injection on FI severity (-2.5 vs. -1.7 point sham improvement in Cleveland Clinic FI score [CCFIS]) or FI episode frequency. Moderate-strength evidence suggests that Durasphere[®] (off label) bulking injections reduce FI severity up to 6 months (-4 to -5 points CCFIS), but gains diminish thereafter. Evidence was insufficient for all other surgical and nonsurgical comparisons. Surgical improvements varied. Noninvasive nonsurgical treatments had few minor AEs. Surgical treatments were associated with more frequent and more severe complications than nonsurgical interventions. AEs were most frequent for the artificial bowel sphincter (22–100% of adults).

In a Cochrane review, Maeda et al. (2013) evaluated the effectiveness of perianal injection of bulking agents for the treatment of fecal incontinence in adults. Five eligible randomized trials with a total of 382 patients were included in the review. One of the five studies assessed dextranomer in stabilized hyaluronic acid (NASHA Dx). This study demonstrated that NASHA Dx was more effective than sham injection but with more AEs. Most trials reported a short term benefit from injections regardless of the material used, including placebo saline injection. None of the studies reported patient evaluation of outcomes and thus it is difficult to gauge whether the improvement in incontinence scores matched practical symptom improvements that mattered to the patients. The authors concluded that one large randomized controlled trial has shown that this form of treatment using dextranomer in stabilized hyaluronic acid (NASHA Dx) improves continence for a little over half of patients in the short term. However, the number of identified trials was limited and most had methodological weaknesses.

Alavi et al. (2015) completed a literature review of the etiology, diagnosis, and treatment of fecal incontinence. They identified that newer office-based procedures, such as the Solesta injection, are showing promising results in properly selected patients, and that Solesta is found to be effective with patients experiencing improvement in their fecal

incontinence symptoms at up to 24 months. Common side effects noted in their review include pyrexia and proctalgia that resolved within 1 month of therapy.

In a clinical practice update expert review by the American Gastroenterological Association (AGA), Bharucha et al. (2017) recommend a step-wise approach in the treatment of fecal incontinence. Their best practice recommendations include perianal bulking agents such as intraanal injection of dextranomer as an option when conservative measures (such as diet, fluids, bowel retraining program) and biofeedback therapy fail.

In their 2015 clinical practice guideline for the treatment of fecal incontinence, the American Society of Colon and Rectal Surgeons (ASCRS) states that injection of biocompatible bulking agents into the anal canal may help to decrease episodes of passive fecal incontinence. (Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 2B.) They comment that although some studies showed modest short-term improvements, no study evaluated the long-term benefits of these therapies. The clinical evidence for hyaluronic acid dextranomer gel for submucosal injection is limited, because no comparisons with other treatments are available (Paquette et al., 2015).

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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.

High dose rate electronic brachytherapy may be covered for treating certain facial nonmelanoma skin cancers (i.e., basal cell or squamous cell carcinomas) when location can impact treatment outcomes. Requests for these exceptions will be evaluated on a case-by-case basis.

Clinical Evidence

Electronic brachytherapy is a form of brachytherapy that delivers radiation using miniaturized x-rays instead of radioactive isotopes.

An ECRI product brief on the Axxent[®] electronic brachytherapy system did not identify any studies for determining how the system for adjuvant treatment of breast, skin and gynecologic cancers compares to other treatment options. Data from 13 uncontrolled studies indicates the treatment is well tolerated with low complication rates and high survival rates at short-term follow-up. Data from randomized controlled trials comparing different treatments and longer-term data are needed. Ongoing trials will provide longer-term data, but no comparative data (ECRI, 2017).

The American Society for Radiation Oncology (ASTRO) model policy on brachytherapy states that electronic brachytherapy is an emerging treatment modality but is out of scope for the policy (ASTRO, 2019).

Breast Cancer

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.

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).

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer do not specifically address electronic brachytherapy (NCCN, 2019).

Skin Cancer

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).

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).

Bhatnagar (2013) reported clinical outcomes at 1 year or more after high-dose-rate (HDR) electronic brachytherapy (EBT) using surface applicators for the treatment of nonmelanoma skin cancer (NMSC). A total of 122 patients with 171 NMSC lesions were treated with EBT 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.

Delishaj et al. (2015) retrospectively evaluated 57 lesions in 39 elderly patients affected with NMSC treated with HDR brachytherapy using a Valencia applicator to estimate tumor control, toxicity and cosmetic outcomes. All lesions had a diameter \leq 25 mm (median: 12.5 mm) and a depth \leq 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.

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, 2019a; NCCN 2019b).

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).

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).

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.

Other Indications

There is a lack of clinical evidence evaluating the safety and efficacy of high dose rate electronic brachytherapy for treating other indications.

Reference(s)

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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 2019. For more information, see ClinicalTrials.gov Identifier NCT01827904.

A systematic literature review was conducted by Langford et al. (2018) to identify and analyze evidence supporting the use of the emerging magnetic resonance-guided focused ultrasound (MRgFUS) compared to alternative stimulatory and ablative interventions (ablative interventions included radiofrequency thalamotomy, unilateral deep brain stimulation (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.

Mohammed et al. (2018) conducted a meta-analysis to analyze the overall outcomes and complications of magnetic resonance-guided focused ultrasound (MRgFUS) in the treatment of essential tremor (ET). The change in the Clinical Rating Scale for Tremor (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 paresthesias in 25.1% of the patients. At 12 months posttreatment, the ataxia had significantly recovered and paresthesias 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.

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. Paresthesias 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 nonresponders 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 magnetic resonance-guided focused ultrasound (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 deep brain stimulation (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 MRI-guided focused ultrasound (MRgFUS) thalamotomy concluded that MRgFUS thalamotomy for treatment-resistant essential tremor (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).

A Hayes report for Magnetic Resonance-Guided Focused Ultrasound (MRgFUS) Unilateral Thalamotomy for Essential Tremor indicates that it is difficult to draw conclusions about the efficacy of this treatment because of insufficient, low quality evidence. (Hayes, 2019).

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).

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Code	Description
0400T	Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia; one to five lesions
0401T	Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia; six or more lesions

Multi-spectral digital skin lesion analysis is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

In a review of non-invasive diagnostic strategies for detecting melanoma, 10 different techniques (including computer-aided multi-spectral digital analysis) were compared with regard to applicability, status of development, and resources necessary for introduction into clinical routine. None of the techniques were able to provide a definite and final diagnosis or to completely replace the histopathological examination. The authors concluded that the need for fully automated devices offering a complete skin cancer screening has not been satisfied (Fink and Haenssle, 2017).

To analyze the diagnostic performance of MelaFind in a real-life clinical setting, Fink et al. (2017) conducted an observational study of 360 pigmented skin lesions (PSL) in 111 patients. MelaFind scores ≥ 2 were considered to be suspicious of malignancy, and the decision for surgical excision was left to the discretion of the examining dermatologists. Of the 107 excised lesions with a MelaFind-score ≥ 2 , the diagnosis of melanoma was made in 3 cases; 53 lesions (49.5%) proved to be dysplastic nevi. Among all lesions biopsied (n=113), the sensitivity and specificity of MelaFind was 100% and 5.5%, respectively. While a higher specificity of 68.5% may be assumed with respect to the overall data set (n=360), this assumption is limited by incomplete follow-up data required to confirm that all non-excised lesions with a score < 2 were actually benign. The high sensitivity of MelaFind facilitated the detection of melanoma, and the overall specificity and benign-to-malignant ratio of excised lesions were considered acceptable.

Hauschild et al. (2014) performed a randomized two-armed online reader study to determine the biopsy sensitivity to melanoma of dermatologists in Germany and the impact of MelaFind[®] on their decisions to biopsy melanomas. The study presented case information, clinical/dermatoscopic images of pigmented skin lesions and MelaFind results (Arm 2). Each participant was asked to review 130 pigmented skin lesions. Biopsy decisions of dermatologists without MelaFind versus MelaFind and dermatologists without MelaFind versus dermatologists with MelaFind were compared. Dermatologists without MelaFind had average sensitivity to melanoma of 69.5 % and average specificity of 55.9%. MelaFind had greater sensitivity than dermatologists alone (96.9% vs. 69.5%) and lower specificity (9.2% vs. 55.9%). Dermatologists with MelaFind had higher sensitivity than those without MelaFind (78% vs. 69.5%) and a lower specificity (45.8% vs. 55.9%). The number of dermatologists detecting over 90% of melanomas increased from 3/101 without MelaFind to 22/101 with MelaFind while specificity remained relatively equivalent (23% vs. 21%). The authors noted that the MelaFind information, when incorporated into the final biopsy decision, can improve biopsy sensitivity with modest effect on biopsy specificity.

Monheit et al (2011) conducted a prospective, multicenter, blinded study to demonstrate the safety and effectiveness of MelaFind, a noninvasive and objective computer-vision system designed to aid in detection of early pigmented cutaneous melanoma. The diagnostic performance of MelaFind and of study clinicians was evaluated using the histologic reference standard. Standard images and patient information for a subset of 50 randomly selected lesions (25 melanomas) were used in a reader study of 39 independent dermatologists to estimate biopsy sensitivity to melanoma, participating clinicians representing 3 academic and 4 community practices in the United States with expertise in management of pigmented skin lesions. A total of 1383 patients with 1831 lesions enrolled from January

2007 to July 2008; 1632 lesions (including 127 melanomas-45% in situ-with median Breslow thickness of invasive lesions, 0.36 mm) were eligible and evaluable for the study end points: sensitivity of MelaFind, specificities and biopsy ratios for MelaFind and the study investigators, and biopsy sensitivities of independent dermatologists in the reader study. The measured sensitivity of MelaFind was 98.4% (125/127 melanomas) with a 95% lower confidence bound at 95.6% and a biopsy ratio of 10.8:1; the average biopsy sensitivity of dermatologists was 78% in the reader study. Including borderline lesions (high-grade dysplastic nevi, atypical melanocytic proliferations, or hyperplasias), MelaFind's sensitivity was 98.3% (172/175), with a biopsy ratio of 7.6:1. On lesions biopsied mostly to rule out melanoma, MelaFind's average specificity (9.9%) was superior to that of clinicians (3.7%). The authors concluded that MelaFind is a safe and effective tool to assist in the evaluation of pigmented skin lesions.

In May 2015, FDA issued a Class II device recall of the MelaFind system. According to FDA, "the probability and histogram data within the Melafind's device displayed user interface is not included in the PMA supplement." The manufacturer discontinued the development and sales of the MelaFind product line effective September 30, 2017.

NCCN guidelines on both cutaneous and uveal melanoma do not address multi-spectral digital skin lesion analysis (2018, 2019).

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Code	Description
0421T	Transurethral waterjet ablation of prostate, including control of post-operative bleeding, including ultrasound guidance, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included when performed)

Transurethral waterjet ablation of the prostate, also known as aquablation, is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Benign prostatic hyperplasia (BPH) is a condition that occurs in men when the prostate gland becomes enlarged due to noncancerous proliferation of smooth muscle and epithelial cells of the prostate. Initial treatment for BPH is usually medical therapy, but this often provides only modest relief. Up to 30% of patients require surgical intervention. Aquablation is a medical device that allows rapid removal of prostate tissue without leaving a zone of thermal damage on the treated tissue. It utilizes a waterjet for automated tissue resection as well as for optical energy delivery for cauterization in the treatment of BPH (Hayes, 2018).

A study to compare urodynamic outcomes between aquablation vs transurethral resection of the prostate (TURP) was performed (Pimentel et al., 2019). Patients (n=66) were randomized 2:1 (aquablation:TURP) in the Waterjet Ablation Therapy for Endoscopic Resection of prostate tissue study. Urodynamics were measured at baseline and 6 months. At mean baseline pDet@qmax was 71 and 73cm H2O in the aquablation and TURP groups, respectively. At 6-month follow-up, pDet@qmax decreased by 35 and 34cm H2O, respectively. A large negative shift in bladder outlet obstruction index was observed, consistent with a large reduction in the proportion of subjects with obstruction at follow-up compared to baseline (79% to 22% in aquablation and 96% to 22% in TURP). The authors concluded that in this trial, improvements after aquablation in objective measures of bladder outlet obstruction were similar to those observed after TURP.

Plante et al. (2018) conducted prespecified and post hoc exploratory subgroup analyses from a double-blind, multicenter prospective randomized controlled trial that compared transurethral resection of the prostate (TURP) using either standard electrocautery vs surgery using robotic waterjet (aquablation) to determine whether certain baseline factors predicted more marked responses after aquablation as compared with TURP. The primary efficacy endpoint was reduction in International Prostate Symptom Score (IPSS) at 6 months. The primary safety endpoint was the occurrence of Clavien-Dindo persistent grade 1 or grade ≥2 surgical complications. For men with larger prostates (50-80 g), the mean IPSS reduction was four points greater after aquablation than after TURP, a larger difference than the overall result. The primary safety endpoint difference was greater for men with large prostate compared with the

overall result. Postoperative anejaculation was also less common after aquablation compared with TURP in sexually active men with large prostates vs the overall results. Exploratory analysis showed larger IPSS changes after aquablation in men with enlarged middle lobes, men with severe middle lobe obstruction, men with a low baseline maximum urinary flow rate, and men with elevated post-void residual urine volume. The authors concluded that in men with moderate-to-severe lower urinary tract symptoms attributable to BPH and larger, more complex prostates, aquablation was associated with both superior symptom score improvements and a superior safety profile, with a significantly lower rate of postoperative anejaculation. The standardized, robotically executed, surgical approach with aquablation may overcome the increased outcome variability in more complex anatomy, resulting in superior symptom score reduction. The RCT reported short-term outcomes and included patients with a prostate size 30 to 80 cc. Therefore, results may not be generalizable for all prostate sizes.

Between September and December 2017, 101 men with moderate-to-severe BPH symptoms and prostate volume of 80-150 mL underwent aquablation in a prospective multicenter international clinical trial (Desai et al., 2018). The mean (range) prostate volume was 107 (80-150) mL. The mean (range) operating time was 37 (15-97) min and aquablation resection time was 8 (3-15) min. Adequate adenoma resection was achieved with a single pass in 34 patients and with additional passes in 67 patients (mean 1.8 treatment passes), all in a single operating session. The mean length of stay after the procedure was 1.6 days (range same day to 6 days). The Clavien-Dindo grade ≥ 2 event rate observed at 1 month was 29.7%. Bleeding complications were recorded in 10 patients (9.9%) during the index procedure hospitalization prior to discharge, and included six (5.9%) peri-operative transfusions. The authors concluded that aquablation is feasible and safe in treating men with large prostates (80-150 mL). The 6-month efficacy data is being accrued.

Kasisvisvanathan and Hussain (2018) report on WATER a double-blinded, multicenter prospective randomized controlled trial for patients with moderate-to-severe lower urinary tract symptoms related to benign prostatic hyperplasia (BPH). The purpose of the analysis was to compare Aquablation to transurethral resection of the prostate (TURP) with respect to efficacy and safety at 1 year. Men (n=90) were randomized to TURP or Aquablation. The efficacy objective was reduction in International Prostate Symptom Score (IPSS). The safety objective was the occurrence of Clavien-Dindo persistent grade 1 or grade 2 or higher operative complications. Change in IPSS at 1 year between Aquablation and TURP was similar (14.5 versus 13.8, respectively). The number of subjects experiencing persistent Clavien-Dindo grade 1 or Clavien-Dindo grade 2 or higher adverse events was lower in the Aquablation group compared to the TURP group (20% versus 47%, respectively). Amongst sexually active subjects, the rate of anejaculation was lower in patients treated with Aquablation than TURP (9% versus 45%, respectively). The authors concluded that surgical prostate resection using Aquablation showed improvement in lower urinary tract symptoms at 1 year comparable to TURP, but with a lower risk of adverse events and ejaculatory dysfunction.

An October, 2018 ECRI Custom Product Brief Guidance reports that evidence from one high-quality randomized controlled trial (RCT) found that Aquabeam Robotic System surgical results were not inferior to those of transurethral resection of the prostate (TURP) for improving LUTS and quality of life (QOL) up to one year; fewer adverse events (AEs) were reported with Aquabeam. RCTs comparing Aquabeam with other minimally invasive options and reporting longer-term (more than one year) patient-oriented outcomes are needed, but ongoing studies will not address the evidence gap.

Gilling et al. (2018) conducted a double-blind, multicenter, prospective, randomized, controlled trial to the safety and efficacy of Aquablation and transurethral prostate resection for the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. One hundred and eighty-one patients with moderate to severe lower urinary tract symptoms related to benign prostatic hyperplasia underwent transurethral prostate resection or Aquablation. The primary efficacy end point was the reduction in International Prostate Symptom Score at 6 months. The primary safety end point was the development of Clavien-Dindo persistent grade 1, or 2 or higher operative complications. The results showed the mean total operative time was similar for Aquablation and transurethral prostate resection, but resection time was lower for Aquablation. At month 6 patients treated with Aquablation and transurethral prostate resection experienced large I-PSS improvements. The prespecified study noninferiority hypothesis was satisfied. Of the patients who underwent Aquablation and transurethral prostate resection 26% and 42%, respectively, experienced a primary safety end point, which met the study primary noninferiority safety hypothesis and subsequently demonstrated superiority. Among sexually active men the rate of anejaculation was lower in those treated with Aquablation (10% vs 36%) The authors concluded that surgical prostate resection using Aquablation showed noninferior symptom relief compared to transurethral prostate resection but with a lower risk of sexual dysfunction. Larger prostates (50 to 80 ml) demonstrated a more pronounced superior safety and efficacy benefit. Longer term follow-up would help assess the clinical value of Aquablation. This study was supported by PROCEPT BioRobotics, the manufacturer of the AquaBeam[®] device. Several of the authors indicate a financial interest and/or other relationship with PROCEPT BioRobotics. These conflicts of interest may limit the conclusions that can be drawn from the study.

Gilling et al. (2017) performed a prospective, single arm, multicenter trial at a total of 3 centers in Australia and New Zealand with 1-year follow-up to establish the safety and effectiveness of aquablation, an image guided, robotic assisted, water jet tissue ablation technology, for the treatment of benign prostatic hyperplasia. A total of 21 men with moderate to severe lower urinary tract symptoms (LUTS) were included in the study with in-clinic follow up visits at 1, 3, 6 and 12 months. The visits included a review of AEs, uroflow measurements prostate specific antigen (PSA) measurement (at 6 and 12 months only), completion of study questionnaires, and (at 6 months only) urodynamics and transrectal ultrasound (TRUS). Symptoms related to LUTS had significantly improved from baseline at 1 month and were sustained through month 12. At 12 months, the mean international prostatic symptom score (I-PSS) score had improved by 16.2 points. The I-PSS QOL component improved by 3.3 points. Mean maximum urinary flow improved from 8.7 ml per second at baseline to 18.3 ml per second and post-void residual volume (PVR) improved from 136 to 54 ml. Prostate volume decreased from 57 ml at baseline to 35 ml. The bladder outlet obstruction index decreased from 48 at baseline to 13 at month 6. Mean serum PSA, which was measured in 20 subjects, showed no significant change from 3.15 ng/ml at baseline to 2.56 ng/ml at 12 months. No urinary incontinence developed and sexual function was preserved postoperatively. The authors concluded that this study provides early evidence to support the safety and effectiveness of aquablation for symptomatic benign prostatic hyperplasia by improved symptom scores and other measures of obstruction. The study is of small sample size and lacks a concurrent control group.

An abstract from Research and Reports in Urology (Aoun et al. 2015), addressing minimally invasive devices for treating PBH, including aquablation concludes: "More systematic laboratory research and currently ongoing clinical trials need to be completed to elucidate the potential role of these newer devices for the treatment of LUTS/BPH."

In 2015, PROCEPT Biorobotics received an Investigation Device Exemption (IDE) from the FDA to collect data on safety and effectiveness of the Aquabeam® System in the U.S. In December 2017, the FDA granted a De Novo request for the AquaBeam System for the resection and removal of prostate tissue for the treatment of lower urinary tract symptoms (LUTS) as a result of benign prostatic hyperplasia (BPH), or enlarged prostate. This device is used to deliver aquablation therapy, and is the first FDA granted surgical robot providing autonomous tissue removal for the treatment of BPH. Further information can be found at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm?ID=DEN170024>. (Accessed May 16, 2019)

The 2019 American Urological Association (AUA) guideline on surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia states aquablation may be offered to patients with lower urinary tract symptoms attributed to benign prostatic hyperplasia provided prostate volume >30/<80g, however, patients should be informed that long term evidence of efficacy and retreatment rates, remains limited (Foster et al., 2019).

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Code	Description
0424T	Insertion or replacement of neurostimular system for treatment of central sleep apnea; complete system (transvenous placement of right of left stimulation lead, sensing lead, implantable pulse generator)
0425T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; sensing lead only

Code	Description
0426T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; stimulation lead only
0427T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; pulse generator only
0428T	Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only
0429T	Removal of neurostimulator system for treatment of central sleep apnea; sensing lead only
0430T	Removal of neurostimulator system for treatment of central sleep apnea; stimulation lead only
0431T	Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only
0432T	Repositioning of neurostimulator system for treatment of central sleep apnea; stimulation lead only
0433T	Repositioning of neurostimulator system for treatment of central sleep apnea; sensing lead only
0434T	Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea
0435T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session
0436T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study

Implantable neurostimulation devices for the treatment of central sleep apnea are investigational, unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

For additional information on the treatment of central sleep apnea, refer to the policy titled [Obstructive Sleep Apnea Treatment](#).

Clinical Evidence

Central sleep apnea is distinguished by a temporary interruption of neural output from the respiratory control center, resulting in loss of respiratory stimulation and airflow cessation. The International Classification of Sleep Disorders (ICSD) identifies 6 different forms of CSA. However, the underlying pathophysiology of central sleep apnea is due to either post-hyperventilation central apnea, which may be triggered by a variety of clinical conditions or central apnea secondary to hypoventilation, which has been described with opioid use hypoventilation. This condition occurs predominantly in patients with heart failure and increases the risk for morbidity and mortality. It's estimated that CSA may present in 30% to 50% of heart failure patients. CSA differs from obstructive sleep apnea, which is caused by a blockage or restriction in the airway (Costanzo, 2015). Currently available treatments for central sleep apnea are not widely accepted because of sparse effectiveness data, poor patient adherence, and potential safety risks. The remedē system (Respicaardia Inc, Minnetonka, MN) is an implantable device which transvenously stimulates the phrenic a nerve causing diaphragmatic contraction similar to normal breathing (Aurora, 2016).

An expert analysis on the basics of sleep apnea for the American College of Cardiology recommends treating the underlying cause of CSA first. Research has shown that once heart failure is clinically improved, CSA often improves as well. Both continuous positive airway pressure (CPAP) and nocturnal oxygen supplementation have been shown to reduce episodes of CSA, improve cardiac function and exercise capacity, and reduce sympathetic activity. However, they have not been shown to reduce mortality and adherence to CPAP therapy remains a significant problem (Singh, 2013).

The remedē® System (Respicaardia, Minnetonka Minnesota) received FDA approval on October 6, 2017. Further information can be found at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160039> . (Accessed April 26, 2019)

Costanzo et al (2018) conducted an analysis of all (96) patients randomized in the manufacturer sponsored remedē System Pivotal Trial. Effectiveness data from treatment and former control groups were pooled based on months since therapy activation. Changes from baseline to 6 and 12 months in sleep metrics, Epworth Sleepiness Scale, patient global assessment health-related quality of life, Minnesota Living with Heart Failure Questionnaire (MLHFQ), and echocardiographic parameters are reported. Heart Failure (HF) hospitalization, cardiovascular death, and the composite of HF hospitalization or cardiovascular death within 6 months are reported by the original randomized group assignment for safety assessment. Sleep metrics and quality of life improved from baseline to 6 and 12 months. At 12 months, MLHFQ scores changed by -6.8 ± 20.0 . The 6-month rate of HF hospitalization was 4.7% in treatment patients and 17.0% in control patients. Reported adverse events were as expected for a transvenous implantable system. The authors concluded that phrenic nerve stimulation reduces CSA severity in patients with HF. In parallel, this CSA treatment was associated with benefits on HF quality of life.

In a review of treatment options for sleep disordered breathing (SDB) in patients with heart failure, Oates, et al. (2018) sought to identify therapies for SDB with the best evidence for long-term use in patients with heart failure and to minimize uncertainties in clinical practice. Consistent evidence has demonstrated that the development of SDB in patients with heart failure is a poor prognostic indicator and a risk factor for cardiovascular mortality. However, despite numerous available interventions for obstructive sleep apnea and central sleep apnea, it remains unclear what effect these therapies have on patients with heart failure. To date, all major randomized clinical trials have failed to demonstrate a survival benefit with SDB therapy (one major study investigating the use of adaptive servo-ventilation demonstrated harm). Significant questions persist regarding the management of SDB in patients with heart failure. Until appropriately powered trials identify a treatment modality that increases cardiovascular survival in patients with SDB and heart failure, a patient's heart failure management should remain the priority of medical care.

In a manufacturer sponsored, ongoing, prospective, multicenter randomized clinical trial, Costanzo, et al. (2016) sought to evaluate the safety and effectiveness of unilateral neurostimulation in patients with central sleep apnea. Patients were recruited from 31 hospital-based centers in Germany, Poland, and the USA. Participants had to have been medically stable for at least 30 days, have received appropriate guideline recommended therapy, be aged at least 18 years, be expected to tolerate study procedures, and willing and able to comply with study requirements. Eligible patients with an apnea-hypopnea index (AHI) of at least 20 events per hour, tested by a polysomnography, underwent device implantation and were randomly assigned by a computer-generated method to either stimulation (treatment) or no stimulation (control) for 6 months. The primary effectiveness endpoint in the intention-to-treat population was the comparison of the proportions of patients in the treatment versus control groups achieving a 50% or greater AHI reduction from baseline to 6 months, measured by a full-night polysomnography assessed by masked investigators in a core laboratory. The primary safety endpoint of 12-month freedom from serious adverse events related to the procedure, system, or therapy was evaluated in all patients. 151 eligible patients were randomly assigned to the treatment or control groups. In the analysis of results, significantly more patients in the treatment group had an AHI reduction from baseline of 50% or greater at 6 months. 138 of 151 patients had no serious-related adverse events at 12 months. Seven cases of related-serious adverse events occurred in the control group and six cases were reported in the treatment group. 27 of 73 patients in the treatment group reported non-serious therapy-related discomfort that was resolved with simple system reprogramming in 26 patients, but was unresolved in one patient. According to the authors, this study shows that transvenous neurostimulation can significantly reduce the severity of central sleep apnea, and concluded it may be a promising therapeutic approach. Further research is needed to determine the clinical relevance of these findings.

Costanzo, et al. (2015) examined the current state of knowledge about the mechanisms of CSA in heart failure and reviewed emerging therapies for this disorder. They include investigational transvenous phrenic nerve stimulation as a practical management strategy for CSA management in patients with heart failure, noting that as a totally implantable, device-based therapy, it may be better tolerated than CPAP or adaptive servo-ventilation (ASV) in heart failure patients.

Abraham et al. (2015) conducted a small (57 patients) prospective, multicenter, nonrandomized pilot study to evaluate chronic, transvenous, unilateral phrenic nerve stimulation to treat CSA using the implantable Respicardia remedē System. Results showed improvement in apnea-hypopnea index (AHI), central apnea index, arousals, sleep efficiency, and rapid eye movement sleep after 3 months of treatment. These improvements were sustained at 6 months and were accompanied by alleviation of both sleepiness and heart failure symptoms. Their conclusion was that transvenous, unilateral phrenic nerve stimulation appears safe and effective for treating CSA, but as the study was limited by its size, the lack of a parallel control arm, and the diversity of the patient population, they recommended that findings should be confirmed in a prospective, randomized, controlled trial.

A 2018 ECRI report concluded the following: Limited evidence from two small studies indicates that transvenous neurostimulation improves sleeping quality and quality of life (QOL) for more than half of treated patients for six to 12 months. Although one study reported treatment-related adverse events (AEs) in 26% of patients, these were mostly due to lead repositioning early in the study. Larger studies—ideally multicenter randomized controlled trials (RCTs)—are needed to confirm results and report longer-term safety and efficacy data on broader patient populations. An ongoing postmarket study is expected to report three- to five-year results in 2021.

A 2018 Hayes technology brief concluded there is very-low-quality body of evidence evaluating the use of phrenic nerve stimulation (PNS) with the remedē System in adults with central sleep apnea (CSA). The evidence is insufficient to draw conclusions about the efficacy and safety of PNS due to an evidence base consisting of only 2 studies with small sample sizes and limited follow-up. The clinical impact for patients with CSA, especially those with HF, remains uncertain. While results suggest a statistically significant reduction in apnea-hypopnea index (AHI) events, average AHI scores did not achieve normal-to-mild disease severity. Studies that compare the efficacy, safety, patient acceptance, and cost-effectiveness of PNS with other noninvasive, available therapies for CSA are needed. In addition, studies with longitudinal data are needed to assess the effect of PNS on CSA-related morbidity and mortality.

Reference(s)

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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 is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy.

Clinical Evidence

A Hayes report examined cryoablation (also known as cryoanalgesia or cryoneurolysis) for treatment of peripheral neuropathy. Three abstracts were retrieved, including retrospective and prospective uncontrolled studies (collective n=42) and 1 review article. Due to the limited peer-reviewed literature, there is insufficient published evidence to assess the safety and/or impact of cryoablation on patient management or health outcomes in patients with peripheral neuropathy (2017).

In a 2018 review of available evidence on image-guided percutaneous cryoneurolysis, Bittman and colleagues concluded that the technology is safe and effective, providing a new avenue for the relief of many historically difficult-to-manage pain syndromes. Additional rigorous prospective study is warranted to further define the efficacy and specific role of these interventions.

In a review discussing continuous peripheral nerve blocks, cryoanalgesia with cryoneurolysis was mentioned as one of four techniques considered to be a novel, alternative analgesic modality under development and investigation (Ilfeld, 2017).

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-life" (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.

For information on current clinical trials studying the use of cryoablation with peripheral neuropathy, go to www.clinicaltrials.gov. (Accessed April 9, 2019)

Reference(s)

Bittman RW, Peters GL, Newsome JM, et al. Percutaneous Image-Guided Cryoneurolysis. *AJR Am J Roentgenol*. 2018 Feb;210(2):454-465.

Hayes, Inc. Search and Summary. Cryoablation for Treatment of Peripheral Neuropathy. Lansdale, PA: Hayes, Inc. July 20, 2017. Archived August 20, 2018.

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Code	Description
0443T	Real time spectral analysis of prostate tissue by fluorescence spectroscopy, including imaging guidance (List separately in addition to code for primary procedure)

Real time spectral analysis of prostate tissue by fluorescence spectroscopy is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Crawford et al. (2015) reported that transrectal ultrasound (TRUS) guided prostate biopsy cores have a very low diagnostic yield as 90% cores are histopathologically classified as benign. The authors investigated potential clinical application fluorescence spectroscopy (FS) to increase diagnostic yield of TRUS biopsies. The fluorescence emissions from natural fluorophores (e.g., collagen) in prostate tissue are altered by the presence of prostate cancer. FS is used to distinct malignant locations from benign to aid TRUS biopsies. Thirteen patients were included in the study for a total of 208 in vivo biopsies (29 malignant) and 224 ex vivo biopsies (51 malignant) analyzed. The authors concluded that the optical biopsy needle assisted with FS had a very high negative predictive value (over 90%) to indicate benign tissue while sufficient sensitivity and specificity for real-time diagnosis of prostate cancer and can potentially increase diagnostic yield of prostate biopsies.

Sharma et al. (2014) conducted a study to evaluate the capability of detecting prostate cancer (PCa) using a dual-modal optical device (dMOD), which incorporates dual measurements from auto-fluorescence lifetime spectroscopy (AFLS) and light reflectance spectroscopy (LRS). Patients were selected with an intermediate-to-high grade of disease and a moderate-to-high volume of prostate cancer. Both AFLS and LRS were taken on n = 724 distinct locations from both prostate capsular (nc = 185) and parenchymal (np = 539) tissues, including PCa tissue, benign peripheral zone tissue and benign prostatic hyperplasia of fresh ex vivo radical prostatectomy specimens from 37 patients. The study reported accuracy above 90% in differentiating benign from malignant tissue and a sensitivity and specificity of 75%

and 87.3%, respectively, for PCa detection. The authors concluded that the dMOD approach is able to discriminate prostatic tissue types of ex vivo prostate specimens with excellent classification sensitivity, specificity and accuracy. They did acknowledge that re-evaluation of their methodology under *in vivo* setting may yield different spectral outputs; the sample size was relatively small, and limited to patients with high grade PCa.

Werahera et al. (2015) performed a prospective, single center, non-randomized, feasibility study to investigate clinical feasibility of an optical biopsy needle guided by fluorescence spectroscopy for real-time in vivo prostate cancer diagnosis. The patient population consisted of 13 men with a mean age of 60.9 and a serum PSA of 6.5±2.7 ng/mL (range: 2.5-11.6). Spectral data and corresponding tissue biopsy cores were obtained from different locations within each prostate specimen. Histopathological analysis found cancer in 29/208 in vivo and 51/224 ex vivo viable biopsy cores. The analysis showed 56% sensitivity (SE), 70% specificity (SP), 89% negative predictive value (NPV), and 26% positive predictive value (PPV) for in vivo, and 75% SE, 80% SP, 93% NPV, and 46% PPV for ex vivo malignant versus benign prostate tissue classification. The authors concluded that the optical biopsy needle has a high negative predictive value to indicate benign tissue and sufficient sensitivity for targeting areas suspicious for cancer and can increase the diagnostic yield of prostate biopsies with consequent improvement in patient care. The sample size is too small to prove the usefulness of this test as a diagnostic tool.

The 2019 National Comprehensive Cancer Network Clinical Practice Guidelines for prostate cancer goals of imaging state that imaging techniques can evaluate anatomic or functional parameters. Functional imaging techniques include radionuclide bone scan, PET/CT, and advanced MRI techniques, such as spectroscopy and diffusion weighted imaging (DWI).

The 2016 American College of Radiology (ACR) Appropriateness Criteria® for prostate cancer–pretreatment detection, surveillance, and staging does not list fluorescence spectroscopy as a radiologic procedure utilized for this purpose.

Reference(s)

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Crawford ED, Jasion EA, Liu Y, et al. Fluorescence spectroscopy can increase diagnostic yield of prostate biopsies. *The Journal of Urology*. Vol. 193. No. 4S. May 17, 2015.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology-Prostate Cancer. Version 2.2019.

Sharma Vikrant, Olweny Ephrem, Kapur Payal, et al. Prostate cancer detection using combined autofluorescence and light reflectance spectroscopy:ex vivo study of human prostates. *Biomed Opt Express*. 2014 Apr 14;5(5):1512-29.

Werahera Priya N., Jasion Edward A., Liu Yongjun, et al. Human feasibility study of fluorescence spectroscopy guided optical biopsy needle for prostate cancer diagnosis. *Conf Proc IEEE Eng Med Biol Soc*. 2015 Aug;2015:7358-61.

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.

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, but such studies will require several years of follow-up and currently are not feasible at this stage of development.

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 Mydriasset 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 Mydriasset insert was similar to conventional mydriatic agents. The authors indicated that pupil size was restored to normal faster when using the Mydriasset insert compared with conventional mydriatic agents for pupil dilation. Study limitations included a small study population and the investigators used an additional topical drug (cyclopentolate) in Group 1.

Reference(s)

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.

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
0465T	Suprachoroidal delivery of pharmacologic agent (does not include supply of medication)

The use of suprachoroidal delivery of pharmacologic agents is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Injection into the suprachoroidal space has been proposed as a method to effectively deliver pharmacologic agents to the posterior segment of the eye. The posterior segment of the eye, including the retina, macula and optic nerve, is difficult to access due to the recessed position within the orbital cavity.

In a prospective cohort study within a randomized, controlled phase-II clinical trial, Willoughby and colleagues (2018) evaluated choroidal and supra-choroidal changes following supra-choroidal injections. Enhanced depth imaging optical coherence tomography (EDI-OCT) images were analyzed from 38 eyes of 38 treatment-naive patients with macular edema. Macular choroidal thickness measured to the outer choroidal vessel lumen (vascular choroidal thickness, VCT), outer choroid stroma (stromal choroidal thickness, SCT), or inner scleral border (total choroidal thickness, TCT) showed no significant changes over 3 months in both study arms. The authors concluded that supra-choroidal injection of CLS-TA did not alter choroidal thickness in eyes with macular edema due to RVO, but may result in expansion of the SCS.

Rai and colleagues (2015) stated that the development of safe and convenient drug delivery strategies for treatment of posterior segment eye diseases is challenging. Although intra-vitreous injection has wide acceptance among clinicians, its use is associated with serious side-effects. Recently, the supra-choroidal space (SCS) has attracted the attention of ophthalmologists and pharmaceutical formulators as a potential site for drug administration and delivery to the posterior segment of the eye. These investigators reviewed the major constraints of drug delivery to the posterior eye segment, key anatomical and physiological features of the SCS and drug delivery applications of this route with emphasis on micro-needles along with future perspectives.

Tetz et al. (2012) investigated the safety and feasibility of using a microcatheter for drug delivery in the suprachoroidal space in eyes with advanced, exudative, age-related macular degeneration (AMD) unresponsive to conventional therapy. A unique microcatheter was used to deliver a drug combination consisting of bevacizumab and triamcinolone to the submacular suprachoroidal space. Twenty-one eyes of 21 patients with choroidal neovascularization (CNV) secondary to advanced, exudative AMD were followed over a 6-month postprocedure period. The microcatheter was successfully and atraumatically inserted into the suprachoroidal space of all eyes. No serious intraoperative or postoperative complications including suprachoroidal hemorrhages were encountered. Postsurgically, complications consisted of 1 eye experiencing a transient elevation in intraocular pressure at 3 months, which was medically controlled, and 2 eyes (10.5%) with an apparent increase in nuclear sclerotic cataracts. The authors concluded that suprachoroidal drug administration was achieved without serious complication using a novel microcatheter. According to the authors, direct drug delivery to the choroid can potentially increase local tissue drug levels and drug efficacy for the treatment of AMD and other diseases associated with CNV. However, the study did not confirm the utility of suprachoroidal delivery of pharmacologic agents in improving care and outcome of patients.

In a prospective, interventional pilot study, Rizzo et al. (2012) evaluated the safety, feasibility, and preliminary efficacy of suprachoroidal drug delivery with a microcatheter for the treatment of severe subfoveal hard exudates (SHE) in retinal vasculopathies in six eyes of six patients. Mean follow-up was 12 months. Three eyes had central retinal vein occlusion, one had branch retinal vein occlusion, and two had chronic diabetic macular edema. Best-corrected visual acuity improved by ≥ 2 lines in 4 eyes and remained stable in 2 eyes. At 1 month to 2 months postprocedure, SHE was almost completely resolved in all eyes and macular edema was significantly reduced. There were no surgical or postoperative complications. The authors concluded that suprachoroidal infusion of drugs can be effective in reabsorbing massive SHE. These findings require confirmation in a larger study.

There are no evidence-based clinical practice guidelines that address the use of suprachoroidal drug delivery for drug delivery in the treatment of any indication.

Reference(s)

Rai Udo J, Young SA, Thrimawithana TR, et al. The suprachoroidal pathway: A new drug delivery route to the back of the eye. Drug Discov Today. 2015.

Rizzo S, Ebert FG, Bartolo ED, et al. Suprachoroidal drug infusion for the treatment of severe subfoveal hard exudates. Retina. April 2012.

Tetz M, Rizzo S, Augustin AJ. Safety of Submacular Suprachoroidal Drug Administration via a Microcatheter: Retrospective Analysis of European Treatment Results. Ophthalmologica. February 2012.

Willoughby AS, Vuong VS, Cunefare D, et al. Choroidal changes after suprachoroidal injection of triamcinolone acetonide in eyes with macular edema secondary to retinal vein occlusion. Am J Ophthalmol. 2018;186:144-151.

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 Pediatric Vision Scanner (PVS) by Rebin, are hand held 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) approved PVS on December 13, 2013 under the de novo classification utilized for devices with low to moderate risk as a strabismus detection device. Use of this device is limited. For more information, refer to the following website: https://www.accessdata.fda.gov/cdrh_docs/reviews/den130051.pdf. (Accessed April 17, 2019)

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.

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.

Loudon, et al (2011) performed a prospective study to investigate whether the PVS could detect anisometric 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. This study was conducted in

the same single, large university facility as the Nassif et.al study. 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 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.

A 3 year, prospective clinical trial evaluating the PVS was completed in January 2019 although the results of the study have not yet been published. ([NCT02536963](#)).

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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.

Code	Description
0489T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; adipose tissue harvesting, isolation and preparation of harvested cells including incubation with cell dissociation enzymes, removal of non-viable cells and debris, determination of concentration and dilution of regenerative cells
0490T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; multiple injections in one or both hands

Autologous adipose-derived regenerative cell therapy for scleroderma of the hands is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Guillaume-Jugnot et al. (2016) reported on the 12 month outcome of patients from an open-label clinical trial assessing injection of autologous adipose-derived stromal vascular fraction (ADSVF) for treatment of systemic sclerosis (SSc) involving the hands. Twelve females, mean age 54.5 years, were assessed 1 year after ADSVF injection. ADSVF was obtained from lipoaspirate using an automated processing system and subsequently injected into the subcutaneous tissue of each finger in a one-time procedure. Endpoints were changes in hand disability and skin fibrosis, vascular manifestations, pain and QOL at the 12 month follow-up. During the visit, patients estimated the benefit of the procedure with a specific self-completed questionnaire. A significant decrease from baseline of 51.3% for Cochin Hand Function Scale score, 63.2% for Raynaud’s phenomenon (RP) severity and 46.8% for QOL (Scleroderma Health Assessment Questionnaire) was observed. A significant improvement of finger edema, skin sclerosis, and motion and strength of the hands was also noted. The reduction in hand pain approached statistical significance. The questionnaire revealed a benefit in daily activities. The authors concluded that ADSVF injection is a promising therapy and may have benefits that extend for at least 1 year. According to the authors, these results should be confirmed by a randomized placebo-controlled trial in a larger population.

Daumas et al. (2017) reported on the longer term outcomes from the same cohort of patients in the above trial conducted by Guillaume-Jugnot et al., 2016. Twelve females who were initially enrolled in the clinical trial were assessed during a scheduled medical care, which took place between 22 and 30 months after ADSVF treatment. Multiple patient-reported outcomes showed sustained improvement, in comparison with the assessment performed just before surgery: 62.5% in the Cochin Hand Function Scale, 51.1% in the Scleroderma Health Assessment Questionnaire, 33.1% in hand pain, and 88.3% in the Raynaud Condition Score. A decrease in the number of digital ulcers number was noted. Mobility, strength and fibrosis of the hand also showed improvement. The authors concluded that despite the limits of an open label study, the results are in favor of the long-term safety of the adipose-derived stromal vascular fraction injection. The lack of a control group limits the conclusions that can be drawn from this study.

Del Papa et al. (2015) treated systemic sclerosis (SSc)-related digital ulcers (DUs) by implantation of autologous adipose tissue-derived cell (ATDC) fractions. Fifteen patients with SSc having a long-lasting DU in one fingertip who were unresponsive to intensive systemic and local treatment were enrolled in the study. The grafting procedure consisted of the injection, at the base of the corresponding finger, of 0.5-1 ml of autologous ATDC fractions, separated by centrifugation of adipose tissue collected through liposuction from subcutaneous abdominal fat. Time to heal after the procedure was the primary end point of the study, while reduction of pain intensity and of analgesic use

represented a secondary end point. Healing of the DUs was reached in all of the enrolled patients (mean time to healing 4.23 weeks; range 2-7 weeks). A significant reduction of pain intensity was observed after a few weeks, while the number of capillaries was significantly increased at the 3- and 6-month nailfold video capillaroscopy (NVC) assessment. Finally, a significant after-treatment reduction of digit artery resistivity was also observed. Even with the limitations related to the small number of patients included and to the open-label design of the study, the observed strongly favorable outcome suggests that local grafting with ATDCs could represent a promising option for the treatment of SSc-related DUs. According to the authors, the positive outcome reported in this trial requires confirmation in larger, controlled studies.

Multiple clinical trials for autologous adipose-derived regenerative cell therapy for scleroderma were found on the www.clinicaltrials.gov website (Accessed May 6, 2019). The STAR trial (NCT02396238) has been completed; however, final results have not yet been published.

Reference(s)

- Daumas A, Magalon J, Jouve E, et al. Long-term follow-up after autologous adipose-derived stromal vascular fraction injection into fingers in systemic sclerosis patients. *Curr Res Transl Med*. 2017 Jan - Mar;65(1):40-43.
- Del Papa N, Di Luca G, Sambataro D, et al. Regional implantation of autologous adipose tissue-derived cells induces a prompt healing of long-lasting indolent digital ulcers in patients with systemic sclerosis. *Cell Transplant*. 2015;24(11):2297-305.
- Guillaume-Jugnot P, Daumas A, Magalon J, et al. Autologous adipose-derived stromal vascular fraction in patients with systemic sclerosis: 12-month follow-up. *Rheumatology (Oxford)*. 2016 Feb;55(2):301-6.

Code	Description
0493T	Near-infrared spectroscopy studies of lower extremity wounds (e.g., for oxyhemoglobin measurement)

Near-infrared spectroscopy (NIRS) is unproven and not medically necessary for assessing tissue oxygenation in lower extremity wounds due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Shuler et al. (2018) evaluated near-infrared spectroscopy (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.

Schmidt et al. (2018) recorded measurements of muscle perfusion using near-infrared spectroscopy (NIRS) and intramuscular pressure (IMP) in a study designed to develop a decision rule for predicting acute compartment syndrome (ACS). One hundred and eighty-five patients with lower-leg injuries had data consisting of continuous NIRS measurement of the O₂ saturation in the anterior compartment of the injured limb and the contralateral (control) limb, and continuous IMP recording in the anterior and deep posterior compartments of the injured leg as part of their participation in an institutional review board-approved multicenter trial. For both types of data, the percentage of valid data capture was defined as the ratio of the minutes of observed data points within a physiological range to the total minutes of expected data points. Clinically useful NIRS data required simultaneous data from the injured and control limbs to calculate the ratio. Statistical tests were used to compare the 2 methods as well as factors associated with the percent of valid NIRS data capture. For the original cohort, clinically useful NIRS data were available a median of 9.1% of the expected time, while IMP data were captured a median of 87.6% of the expected time. Excluding 46 patients who had erroneous NIRS data recorded, the median percentage was 31.6% for NIRS compared with 87.4% for IMP data. Fractures with an associated hematoma were less likely to have valid data points. Gustilo types-I and II open fractures were more likely than Tscherne grades C0 and C1 closed fractures to have valid data points. The authors indicated that NIRS data were not collected reliably in this study. In contrast, IMP measurements were collected during >85% of the expected monitoring period. According to the authors, this study raises questions about the ability of current NIRS technology to reliably measure continuous oxygenation in traumatized limbs, limiting its potential usefulness as a diagnostic tool for ACS.

In a prospective single-center observational study, Laroche et al. (2017) evaluated near-infrared spectroscopy (NIRS) versus transcutaneous oxygen tension (TcPO₂) for microcirculatory assessment of vascular transtibial stumps at the stabilized period of prosthesis fitting, as a preliminary step before exploring its ability to predict stump healing. Thirty

individuals with unilateral transtibial amputation for peripheral artery disease, at the definitive stage of prosthesis fitting, able to perform a 2-minute walk test were included in the trial. Test-retest, with the stump being evaluated in supine and inclined positions, first by NIRS (tissue saturation index [TSI], oxyhemoglobin, deoxyhemoglobin, and total hemoglobin) and second by TcPO₂. Subjects carried out a 2-minute walk test and visual analog scales (wound healing and pain). Feasibility and tolerance of NIRS were satisfactory. The reliability of NIRS and TcPO₂ values was good. No significant relation was found between NIRS and TcPO₂. No responsiveness (inclined vs supine) was reported. A significant relation between TSI and the 2-minute walk test was found. The authors concluded that NIRS is painless, complication-free, and feasible, with good reliability. Further studies with larger patient populations are necessary to determine the long-term safety and efficacy of this technology.

Reference(s)

Laroche D, Barnay JL, Tourlonias B, et al. Microcirculatory Assessment of arterial below-knee stumps: near-infrared spectroscopy versus transcutaneous oxygen tension—a preliminary study in prosthesis users. *Arch Phys Med Rehabil.* 2017 Jun;98(6):1187-1194.

Schmidt AH, Bosse MJ, Obrebsky WT, et al. Major Extremity Trauma Research Consortium (METRC). Continuous near-infrared spectroscopy demonstrates limitations in monitoring the development of acute compartment syndrome in patients with leg injuries. *J Bone Joint Surg Am.* 2018 Oct 3;100(19):1645-1652.

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
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

Bindex[®] a pocket-sized tool for osteoporosis screening and diagnostics. Bindex[®] is used for measuring the cortical thickness of tibia. The results, combined with other patient data, are used to estimate the hip region's bone mineral density.

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 provided 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.

Schousboe et al. (2017) estimated how well a pulse-echo US device discriminated between those who did not have hip osteoporosis and the association of pulse-echo US measurements with prevalent (radiographically confirmed) clinical fractures. Five hundred fifty-five post-menopausal women age 50 to 89 had femoral neck and total hip BMD measured by a DXA, and pulse-echo US measurement of the distal radius, proximal tibia, distal tibia cortical thickness, and multi- and single-site density indices. Using previously published threshold ultrasound values, the authors estimated the proportion of women who would avoid a follow-up DXA after pulse-echo ultrasonometry, and the sensitivity and specificity of this for the detection of hip osteoporosis. Logistic regression models were used to estimate the associations of pulse-echo US measurements with radiographically confirmed clinical fractures within the prior 5 years. Using multi and single-site density indices measures, follow-up DXA could be avoided for 73 and 69 % of individuals, respectively, while detecting hip osteoporosis with 80-82 % sensitivity and 81 % specificity. The authors concluded pulse-echo ultrasonometry could be used as an initial screening test for hip osteoporosis, however additional prospective studies of how well pulse-echo US measurements predict subsequent fractures are warranted.

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.

In a study by Riekkinen et al. (2008), a novel dual-frequency ultrasound (DFUS) pulse-echo technique is introduced for reduction of the errors induced by soft tissues. First, DFUS was validated using elastomer samples. For further validation, twenty-five human trabecular bone samples covered with heterogeneous soft tissues were measured at frequencies of 2.25 MHz and 5.0 MHz. The authors concluded, the DFUS, being the first ultrasound technique capable of determination of the composition and thickness of the soft tissue overlying the bone, may enhance the accuracy of clinical ultrasound measurements thus showing a significant clinical potential. Future studies on long-term efficacy of the pulse-echo technique and cost effectiveness are needed.

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 April 24, 2019)

Reference(s)

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Karjalainen JP, Riekkinen O, Kröger H. Pulse-echo ultrasound method for detection of post-menopausal women with osteoporotic BMD. *Osteoporos Int.* 2018 May;29(5):1193-1199.

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Riekkinen O, Hakulinen MA, Töyräs J, Jurvelin JS. Dual-frequency ultrasound--new pulse-echo technique for bone densitometry. *Ultrasound Med Biol.* 2008 Oct;34(10):1703-8.

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Schousboe JT, Riekkinen O, Karjalainen J. Prediction of hip osteoporosis by DXA using a novel pulse-echo ultrasound device. *Osteoporos Int.* 2017 Jan;28(1):85-93.

Code	Description
0509T	Electroretinography (ERG) with interpretation and report, pattern (PERG)
92274	Electroretinography (ERG), with interpretation and report; multifocal (mfERG)

Multifocal electroretinogram (mfERG) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Pattern electroretinogram (PERG) or pattern electroretinogram optimized for glaucoma screening (PERGLA) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Multifocal electroretinogram (mfERG) is a noninvasive test used to detect the regional functional changes of the central retina by measuring the electrophysiological response. Pattern electroretinogram optimized for glaucoma screening (PERGLA) is a non-invasive, fully automatic version of the pattern ERG.

Park et al. (2017) conducted a retrospective review and comparative study of 74 glaucoma patients (44 early stage and 30 advanced stage cases) and 66 control subjects to determine possible relationships between the N95 amplitude of pattern electroretinogram (PERGamp) and macular ganglion cell/inner plexiform layer thickness (GCIPLT). Macular GCIPLT was measured using Cirrus spectral domain-optical coherence tomography. Standard automated perimetry and pattern ERGs were used in all patient examinations. Three types of regression analysis (broken stick, linear regression, and quadratic regression) were used to evaluate possible relationships between PERGamp and GCIPLT. Correlations between visual field parameters and GCIPLT were evaluated according to glaucoma severity. The best fit model for the relationship between PERGamp and GCIPLT was the linear regression model ($r^2 = 0.22$; $P < 0.001$). The best-fit model for the relationship between visual field parameters and GCIPLT was the broken stick model. During early glaucoma, macular GCIPLT was positively correlated with PERGamp, but not with visual field loss. In advanced glaucoma, macular GCIPLT was positively correlated with both PERGamp and visual field loss. The authors concluded that based on the results of this study, PERGamp is a method to assist clinicians in making an early decision regarding the most suitable treatment plan, especially when GCIPLT is thinning with no change in visual field performance. Study limitations include its retrospective nature, and lack of a standard international reference range for PERG measurements.

Merchant et al. (2017) conducted a cross-sectional analysis of 60 patients using optical coherence tomography (OCT) and electroretinography (ERG), including flash ERG and pattern ERG (PERG) to determine the association of ocular manifestations in beta-thalassemia with patient's age, blood transfusion requirements, average serum ferritin and dose and duration of iron chelation therapy. Routine ophthalmic examination and B scan of the eye was also done. Flash ERG a-waves and b-waves were recorded, however only a-wave amplitude was evaluated. Pattern ERG n35, n95 and p50 waves were recorded and p50 wave amplitude was evaluated. The a-wave on flash and p50 on pattern waves represent retinal photoreceptor epithelium (RPE) photoreceptor response, which is mainly affected in beta-thalassemia. Ocular changes were detected in 38.3% and a significant correlation was noted with increase in age ($p = 0.045$) but not with serum ferritin, transfusion requirements or chelation therapy. Refractive errors were found in 14 cases (23%), such as myopia with astigmatism in 13 (21.7%) and only myopia in 6 subjects (10%). OCT abnormality was noted in 1 patient (1.7%) who had thinning of central retina; right eye 132 μm and left eye 146 μm ($n > 200 \mu\text{m}$). Abnormalities were noted in a-wave amplitude on flash ERG in 20% of cases, while reduced p50 amplitude on PERG was noted in 15%. The authors summarized that a significant correlation was noted between ocular findings and increase in age, but not with serum ferritin, transfusion requirements or chelation therapy. They concluded that ERG appears to be a promising tool for screening patients with beta-thalassemia and can serve as a follow-up test for evaluating retinal function. Randomized controlled trials with larger patient populations are needed to further evaluate this technology.

In a cross-sectional study ($n=34$), Cvenkel et al. (2017) evaluated discrimination ability of PERG and photopic negative response (PhNR) between early glaucoma and healthy controls, and their relationship with structural measurements using spectral-domain optical coherence tomography (SD-OCT). Patients included in the study had ocular hypertension ($n = 7$), suspect glaucoma ($n = 17$), and early glaucoma ($n = 10$), plus 24 age-matched controls. The following parameters were analyzed: P50 and N95 amplitude of the PERG, PhNR amplitude and PhNR/b-wave ratio, peripapillary retinal and macular nerve fiber layer (NFL) thicknesses, and ganglion cell complex (GCC) thickness. Data from only one eye per individual were included in the statistical analysis. Descriptive statistics, ANOVA, receiver operating characteristics (ROC) curves, and correlation tests were used for analysis of the variables. Results showed that PERG N95 and PhNR amplitudes were significantly reduced in suspect and early glaucoma eyes versus controls. Significant differences across ocular hypertensive, suspect, and early glaucoma eyes were found for macular NFL and GCC thickness, but not for any of the ERG parameters. The authors concluded that in eyes with suspect glaucoma, important decrease in PhNR amplitude is associated with small changes in peripapillary retinal and macular NFL thicknesses.

Gonzalez-Garcia et al. (2016) reported 2-years of follow-up data for electrophysiological and clinical tests in dry age-related macular degeneration to determine the more sensitive technique between mfERG and OCT. Fundus photography, OCT (macular thickness and number of drusen), Pattern VEP (P100 wave), Pattern ERG (P50 wave) and multifocal ERG (central rings) were carried out in 30 patients that were diagnosed with dry AMD in both eyes. The tests were repeated 1 and 2 years later. No statistically significant changes were observed in visual acuity or in the severity of the disease throughout the study. OCT showed an increase in the number of drusen, as well as in macular thickness. As for the electrophysiological techniques, no significant changes were observed throughout the study in Pattern VEP or Pattern ERG. mfERG showed significant alterations. The authors reported that the statistical analysis showed that mfERG is more efficient in detecting changes throughout the study period. The authors concluded that both OCT and mfERG are useful in the diagnosis and monitoring of dry AMD patients, however mfERG is the most

sensitive technique to study the progression of this disease in short periods of time. Study limitations include small patient population and short follow-up period.

Browning et al. (2014) conducted a study to determine the relative sensitivity and specificity of 10-2 visual fields (10-2 VFs), multifocal electroretinography (mfERG), and spectral domain optical coherence tomography (SD-OCT) in detecting hydroxychloroquine retinopathy. A total of 121 patients taking hydroxychloroquine (n=119) or chloroquine (n=2) with 10-2 VF, mfERG, and SD-OCT tests were retrospectively reviewed. Rates of test abnormality were determined. Retinopathy was present in 14 and absent in 107. Eleven of 14 (78.6%) patients with retinopathy were overdosed. Twelve (85.7%) had cumulative dosing greater than 1,000 g. The sensitivities of 10-2 VF, mfERG, and SD-OCT in detecting retinopathy were 85.7%, 92.9%, and 78.6%, respectively. The specificities of 10-2 VF, mfERG, and SD-OCT in detecting retinopathy were 92.5%, 86.9%, and 98.1%, respectively. Positive predictive values of 10-2 VF, mfERG, and SD-OCT in detecting retinopathy were less than 30% for all estimates of hydroxychloroquine retinopathy prevalence. Negative predictive values were >99% for all tests. The author concluded that estimates of hydroxychloroquine retinopathy prevalence, all three tests are most reliable when negative, allowing confident exclusion of retinopathy in patients taking ≤ 6.5 mg/kg/day. Each test is less useful in allowing a confident diagnosis of retinopathy when positive, especially in patients taking ≤ 6.5 mg/kg/day. This study is limited by a small study population.

The AAO 2016 revised recommendations for screening of chloroquine and hydroxychloroquine retinopathy state that the primary screening tests are automated visual fields plus spectral-domain optical coherence tomography (SD OCT). The multifocal electroretinogram (mfERG) can provide objective corroboration for visual fields, and fundus autofluorescence (FAF) can show damage topographically. Modern screening should detect retinopathy before it is visible in the fundus (Marmor et al., 2016).

Tsang et al. (2015) determined the validity of mfERG as a screening tool for detecting CQ and HCQ retinal toxicity in patients using these medications. To evaluate the sensitivity and specificity of mfERG when compared with automated visual fields (AVFs), FAF, and OCT. The 2011 AAO recommendations on screening for CQ/HCQ retinopathy recommended a shift toward more objective testing modalities. Multi-focal ERG may be effective in detecting functional change before irreversible structural damage from CQ/HCQ toxicity. These investigators performed a search for records reporting the use of mfERG for screening CQ/HCQ retinopathy in MEDLINE (PubMed and OVID), EMBASE, and Web of Science, and assessed these using the QUADAS-2 risk of bias tool. They conducted an analysis of 23 individual studies and their reported individual patient data (449 eyes of 243 patients) published from January 2000 to December 2014. Multi-focal ERG had the greatest proportion of positive test results, followed by AVF. The pooled sensitivity and specificity of mfERG were 90 % (95 % confidence interval [CI]: 0.62 to 0.98) and 52 % (CI: 0.29 to 0.74), respectively, with AVF as reference standard (13 studies). Sensitivity was high, but specificity was variable when OCT, FAF, and the positivity of 2 of 3 tests was used as the reference standard. When verified against AVF as the reference test, patients with a false-positive mfERG result received higher HCQ cumulative doses (1,068 g) than patients with true-negative (658 g, $p < 0.01$) and false-negative (482 g, $p < 0.01$) results. The authors concluded that mfERG was shown to have a high sensitivity but variable specificity when verified against AVF, OCT, FAF, and a combination of tests. The greater average cumulative dose in the false-positive group compared with the true-negative group when mfERG was verified against AVF suggested that mfERG may have the ability to detect cases of toxicity earlier than other modalities. In addition, they state that there is an unclear risk of bias in the available evidence, and future studies should adhere to Standards for Reporting of Diagnostic Accuracy reporting guidelines.

In a prospective study, Kandel et al. (2012) evaluated the effects of ethambutol therapy in visual functions of both eyes in 44 patients. Parameters evaluated included multifocal electroretinography (ERG) with Roland-RETI scan. Based on the results of the study, the authors concluded that visual acuity, contrast sensitivity, and multifocal ERG are sensitive tests to detect ethambutol toxicity in subclinical stages and hence very useful tools for monitoring patients under ethambutol therapy for ocular toxicity. These findings require confirmation in a larger study.

In a prospective study, Ambrosio et al. (2015) examined the role of mfERG for predicting visual acuity (VA) decline in early age-related macular degeneration (ARMD) with time. A total of 26 early ARMD patients (12 males and 14 females, mean age of 66.9 ± 9.8 ; range of 46 to 82 years) were included in the study. A complete ophthalmic examination and mfERG (Retiscan, Roland Germany, ISCEV standard protocol) were performed at the study entry (baseline), after 20 and 24 months. The first-order kernel mfERG responses were analyzed by ring analysis. The amplitude density (AD) of the first positive peak (P1, nV/deg²), the P1 amplitude (μ V) and P1 implicit time (ms) for Rings 1 (central) to 6 (most peripheral) were evaluated. Data were statistically analyzed by analysis of variance and receiver operating characteristic (ROC) curves. The loss in the mfERG Ring 1 AD from normal control values, recorded at baseline, was correlated with the decrease in ETDRS VA with time ($p = 0.004$); ROC analysis showed that, after 24 months, the average decline in VA was greater (3 letters versus 0.4 letters, $p = 0.0021$) in patients whose Ring 1 P1 AD at baseline was equal to or less than 65.9 nV/deg², compared to those with higher AD values. Both P1 amplitude and AD of Ring 1 had an area under the curve of 0.702 (95% CI: 0.50 to 0.92) with a sensitivity of 64.3% (35.14 to 87.24%) and a specificity of 91.7% (61.52 to 99.79 %). The authors concluded that these results indicate that mfERG

P1 amplitude and AD of Ring 1 may be highly specific to predict visual acuity decline in early AMD. This was a nonrandomized study design without a control group, and small patient sample size.

In a preferred practice pattern for primary open-angle glaucoma, the American Academy of Ophthalmology (AAO) does not specifically mention electroretinography as a diagnostic tool (Prum et al., 2015).

Dale et al. (2010) compared the ability of the multifocal electroretinogram (mfERG) and frequency domain optical coherence tomography (fdOCT) to detect retinal abnormalities. A total of 198 eyes (100 patients) were included in the study to rule out a retinal etiology of visual impairment. All patients were evaluated with static automated perimetry (SAP), mfERG, and fdOCT. Local mfERG and fdOCT abnormalities were compared to local regions of visual field sensitivity loss measured with SAP and categorized as normal/inconclusive or abnormal. 146 eyes were categorized as normal retina on both fdOCT and mfERG. The retina of 52 eyes (36 patients) was categorized as abnormal based upon mfERG and/or fdOCT. Of this group, 25 eyes (20 patients) were abnormal on both tests. However, 20 eyes (13 patients) were abnormal on mfERG, while the fdOCT was normal/inconclusive; and 7 eyes (7 patients) had normal or inconclusive mfERG, but abnormal fdOCT. According to the authors, considerable disagreement exists between these two methods for detection of retinal abnormalities. The authors stated that the mfERG tends to miss small local abnormalities that are detectable on the fdOCT. On the other hand, the fdOCT can appear normal in the face of clearly abnormal mfERG and SAP results. The authors indicated that while improved imaging and analysis may show fdOCT abnormalities in some cases, in others early damage may not appear on structural tests.

Tafreshi et al. (2010) compared the diagnostic accuracy of the pattern ERG to that of standard automated perimetry (SAP), short-wavelength automated perimetry (SWAP), and frequency-doubling technology (FDT) perimetry for discriminating between healthy and glaucomatous eyes in 83 eyes of 42 healthy recruits and 92 eyes of 54 glaucoma patients. The diagnostic accuracy of the pattern ERG amplitude was similar to that of SAP and SWAP, but somewhat worse than that of FDT. Agreement among the tests was characterized as fair to moderate.

Preiser et al. (2013) compared photopic negative response (PhNR) and pattern electroretinogram (PERG) in different stages of the disease. Eleven eyes with preperimetric glaucoma (glaucomatous optic disc with normal field); 18 with manifest glaucoma; and 26 normals were included in the study. Based on the results of the study, the authors concluded that both PhNR and PERG performed similarly to detect glaucoma; for both, ratios performed better than amplitudes. The authors stated that the PhNR has the advantage of not requiring clear optics and refractive correction; the PERG has the advantage of being recorded with natural pupils. This study is limited by a small study population.

Sehi et al. (2009) examined retinal ganglion cell function measured using pattern electroretinogram optimized for glaucoma screening (PERGLA) in 29 normal individuals, 28 glaucoma patients, and 37 glaucoma suspect volunteers. According to the authors, retinal ganglion cell function measured using pattern electroretinogram optimized for glaucoma screening (PERGLA) is reduced in glaucoma but only demonstrates modest correlations with central SAP sensitivity values and structural measures of optic nerve topography and retinal nerve fiber layer thickness.

Banitt et al. (2013) conducted a longitudinal cohort study that included 107 adults (201 eyes) at risk of glaucoma and compared pattern electroretinography (PERG) amplitudes and optical coherence tomography (OCT) imaging of retinal nerve fiber layer (RNFL) over a 4-year period in order to determine the time lag between loss of retinal ganglion cells (RGC) function and loss of RNFL thickness. RNFL thickness did not decrease until the PERG amplitude had lost at least 50% of its normal value for age, indicated by post hoc comparisons showing highly significant differences between RNFL thicknesses of eyes in the stratum with the most severely affected PERG amplitude ($\leq 50\%$ of normal) and the two strata with the least affected PERG amplitudes ($> 70\%$). The authors concluded from the results of the study that there was an approximate time lag of 8 years between a 10% loss in PERG amplitude and a 10% loss in RNFL thickness, which could be used as a window for intervention. The study did not confirm the utility of such findings in improving care and outcome of patients.

Jafarzadehpour et al. (2013) evaluated retinal ganglion cell (RGC) dysfunction in glaucoma suspects and patients with early primary open angle glaucoma (POAG) using pattern electroretinography (PERG). Transient PERG was recorded in response to 0.8° and 16° black and white checkerboard stimuli. Amplitude and peak time (latency) of the P50 and N95 components of the PERG response, and the ratio of N95 amplitude in response to 0.8° and 16° checks were measured. Twenty glaucoma suspects, 15 early POAG and 16 normal controls were enrolled. N95 peak time (latency) was significantly increased in both early manifest POAG and glaucoma suspects as compared to normal controls. In early POAG, N95 amplitude in response to small (0.8°) checks and the small/large check ratio were reduced in comparison to normal eyes. However, in glaucoma suspects no significant N95 amplitude reduction was observed. No significant difference was observed among the study groups in terms of P50 amplitude or peak time. According to the authors, PERG may detect RGC dysfunction (increased latency) before cell death (decreased amplitude) occurs. The sample size in this study is too small to prove the usefulness of PERG as a diagnostic tool.

In a cross-sectional study of 71 patients, Bowd et al. (2009) obtained PERGLA recordings within 6 months of standard automated perimetry (SAP) testing. Dependent variables were PERGLA amplitude, phase, amplitude asymmetry, phase asymmetry, and SAP pattern standard deviation (PSD) and mean deviation (MD). The authors reported that pattern electroretinograms recorded using the PERGLA paradigm can discriminate between healthy and glaucomatous eyes, although this technique performed no better than SAP at this task. Low specificity of the PERGLA normative database suggests that the distribution of recordings included in the database is not ideal.

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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

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 received FDA premarket approval (P150009) on April 9, 2018. The AngelMed Guardian System is indicated for use in patients who have had prior acute coronary syndrome (ACS) events and who remain at high risk for recurrent ACS events. The 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 April 17, 2019)

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.

High-risk ACS subjects (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.

A Hayes report concluded that published evidence is insufficient to determine if the device provides an adjunctive benefit to patient recognition of symptoms predictive of ACS events, and prompts patients to seek emergency care faster than patients who are not implanted with the device. The report also concluded that published evidence is insufficient to determine if, in the absence of symptoms, the AngelMed Guardian System accurately identifies asymptomatic ACS events and prompts patients to seek medical attention (Hayes, 2018).

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.

Reference(s)

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 Cardiol. 2019 April 23; 73(15); 1928-1930.

Hayes, Inc. Hayes Prognosis Overview. AngelMed Guardian System. Lansdale, PA: Hayes, Inc.. May 2018. Archived April 2019.

Code	Description
0547T	Bone-material quality testing by microindentation(s) of the tibia(s), with results reported as a score

Bone microindentation testing (BMT) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Bone microindentation testing (BMT) measures Bone Material Strength Index (BMSi) of cortical bone in living humans. The instrument performs (BMT) by inserting a probe assembly through the skin covering the tibia. This testing allows for the measurement of mechanical properties of bone and other hard tissues, and it is used for estimating the stresses and strains exerted at the cellular level. (Diez-Perez, 2010).

Arnold et al. (2017) performed a systematic review. A total of 1094 abstracts were retrieved and 32 papers were included in the analysis, 20 of which used reference point indentation, and 12 of which used traditional depth-sensing indentation. There are several factors that must be considered when using microindentation, such as tip size, depth and method of analysis. Only two studies validated microindentation against traditional mechanical testing techniques. Both studies used reference point indentation (RPI), with one showing that RPI parameters correlate well with mechanical testing, but the other suggested that they do not. The authors concluded that microindentation has been used in various studies to assess bone stiffness, but only two studies with conflicting results compared microindentation with traditional mechanical testing techniques. Further research, including more studies comparing microindentation with other mechanical testing methods, is needed before microindentation can be used reliably to calculate cortical bone stiffness.

Diez-Perez et al. (2010) assessed the validity results of microindentation technique capable of directly testing the mechanical endurance of bone tissue in patients. The study reviews a device that performs bone microindentation testing (BMT) of bone in vivo in a series of patients with and without osteoporotic fractures. This technique is based on creating microfractures and measuring the overall resistance of bone to the propagation of these microfractures. This represents a direct assessment of bone tissue mechanical strength in patients, an important component of the properties encompassed under the umbrella of "bone quality." More research will be needed to use bone microindentation and other parameters measured by the RPI instrument to quantify the contribution of tissue mechanical properties to bone fracture risk.

Reference(s)

Arnold, S. et al. Microindentation – a tool for measuring cortical bone stiffness? A systematic review. Bone Joint Res 2017.

Diez-Perez A, Güerri R, Nogues X, et al. Microindentation for in vivo measurement of bone tissue mechanical properties in humans. J Bone Miner Res. 2010.

Code	Description
0548T	Transperineal periurethral balloon continence device; bilateral placement, including cystoscopy and fluoroscopy
0549T	Transperineal periurethral balloon continence device; unilateral placement, including cystoscopy and fluoroscopy
0550T	Transperineal periurethral balloon continence device; removal, each balloon
0551T	Transperineal periurethral balloon continence device; 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. For women the ACT® device, the balloons are surgically placed on either side of the bladder neck, providing compression. 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. The ACT device for women is currently in clinical trials and not available in the United States.

Nash et al. (2019) 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 stress urinary incontinence (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 sequelae. 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. The implant procedure is minimally invasive, and complications are generally mild and easily resolvable. Further research with randomized controlled trials is needed to validate these findings.

Nordhoff et al. (2019) conducted a retrospective multicenter study to evaluate the outcome of adjustable continence balloons in the treatment of stress urinary incontinence (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 urinary incontinence 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. Further research with randomized controlled trials is needed to validate these findings.

Nordhoff et al. (2018) evaluated the 10 year outcomes of the adjustable continence balloons ProACT™ for the treatment of male stress urinary incontinence after radical prostatectomy. Between May 2007-August 2016 the ProACT™ was implanted in 143 patients without a history of radiotherapy. Endpoints were patient-reported changes in pad counts and complications. Treatment was considered successful if no pad or just one "security" pad per day sufficed, and improved if daily pad use was reduced by $\geq 50\%$. Incontinence before implantation was mild in 36 (25%), moderate in 57 (40%), and severe in 50 (35%) patients. Complications within 30 days were classified by the Clavien-Dindo classification; eight (5.6%) grade I, three (2.1%) grade II, three (2.1%) grade IIIb, and 129 (90.2%) patients had no complication. Revision was done in 43 (30%) patients. The IPSS quality of life item improved significantly from 5.0 (IQR 4.0-5.0) preoperative to 2.0 (IQR 1.0-4.0) and 1.0 (IQR 0.0-3.0) 6 and 12 months after implantation, respectively. After a median follow up of 56 months (range 28 to 79, $n = 112$), 72 (64%) patients were improved, including 51 (45%) patients were successful. Daily pad use decreased from 3.0 to 1.0 (67% reduction). The median outcome on the Patient Global Impression of Improvement scale was "much better," and 97 (87%) patients perceived improvement. The authors concluded that the minimally invasive ProACT™ device showed a clear beneficial continence outcome in patients with stress urinary incontinence after radical prostatectomy. The majority of the patients were satisfied and perceived improvement $\geq 50\%$ on daily pad use on the long term. Further research with randomized controlled trials is needed to validate these findings.

In a 2017 single-centre, single-surgeon study, Nestler et al. evaluated the success and revision rates of ProACT over long-term follow-up and if repeat ProACT implantation after failure would be a reasonable strategy. In May 2017, follow-up of 134 patients who underwent ProACT implantation between 2003 and 2013 was obtained. Parameters were numbers of pads used, filling volume of balloons, and patient-reported satisfaction. Furthermore, revisions were noted. The median follow-up was 118 months. The results showed 112 implantations were successful (82.6%) and the number of pads used decreased significantly. 63 patients were revised and 49 were successful (77.8%). No differences in success rate, pads used or filling volume were seen. In a second revision, again, no differences in success rate or pads used were noted. Patients' personal satisfaction was high despite the high revision rate. The authors concluded that in the hands of an experienced surgeon, ProACT is a safe and effective therapy for post-prostatectomy incontinence especially if major surgery is to be avoided. Revision rates are high, and the results of ProACT reimplantation are comparable to the results after the first implantation.

Crivellaro et al. (2016) 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 Stress urinary incontinence (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 Invince Sling, 48.8% for Advance Sling, 64.2% for ProACT. The overall complication rate was 19.43% for AUS, 7.4% for Invince 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) conducted a study to evaluate the functional results, morbidity, and quality of life of the adjustable continence balloons ProACT for the treatment of male stress urinary incontinence 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 refills 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 explantation 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 ProACT device appears to be safe and efficacious in the short term. The postoperative readjustment allows the achievement of a short-term continence status. However, on the long term, the ProACT does not appear to be an ideal device for durable continence and patients' satisfaction.

In a 2019 practice guideline, the American Urology Association (AUA)/ Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) states the following: Adjustable balloon devices may be offered to patients with mild stress urinary incontinence after prostate treatment. However clinical experience in the United States with this device remains limited. 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 AUS. Given the limited clinical experience of implanters across the United States, providers should obtain specialty training prior to device implantation.

The International Consultation on Incontinence Surgical Treatment of Urinary Incontinence in Men 2009 states that the proACT™ balloon technique appears to be a feasible procedure to improve the continence in short and median term, with better results occurring with more operator experience. Similar to the male sling procedure, appropriate candidates include those with mild to moderate leakage due to intrinsic sphincter deficiency, and no previous radiation. The benefit of an adjustable system should be weighed against the need for multiple sessions of refilling the balloon, and with reported rate of peri-operative and post-operative complications. Longer follow-up is needed before definitive comparison to male sling or artificial sphincter can be made. No recommendation is possible due to variable data on complication rates (12-58%).

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

Reference(s)

American Urology Association. Incontinence after Prostate Treatment: AUA/SUFU Guideline 2019.

Crivellaro S, Morlacco A, Bodo G, et al. Systematic review of surgical treatment of post radical prostatectomy stress urinary incontinence. *Neurourol Urodyn*. 2016 Nov;35(8):875-881.

Nash S, Abouseif S, Gilling P, et al. Four-year follow-up on 68 patients with a new post-operatively adjustable long-term implant for post-prostatectomy stress urinary incontinence: ProACT™. *Neurourol Urodyn*. 2019 Jan;38(1):248-253.

Nestler S, Thomas C, Neisius A, et al. Long-term results of ProACT primary and repeat implantation for treatment of stress urinary incontinence in men. *World J Urol*. 2018 Sep 17.

Noordhoff TC, Finazzi-Agrò E, Scheepe JR, et al. Outcome and complications of adjustable continence therapy (ProACT(TM)) in the treatment of urinary incontinence after transurethral resection of the prostate: A multicenter study. *Neurourol Urodyn*. 2019 Apr;38(4):1111-1119.

Noordhoff TC, Scheepe JR, Blok BFM. Outcome and complications of adjustable continence therapy (ProACT™) after radical prostatectomy: 10 years' experience in 143 patients. *Neurourol Urodyn*. 2018 Apr;37(4):1419-1425.

The International Consultation on Incontinence Surgical Treatment of Urinary Incontinence in Men 2009.

Venturino L, Dalpiaz O, Pummer K, et al. Adjustable Continence Balloons in Men: Adjustments Do Not Translate Into Long-term Continence. *Urology*. 2015 Jun;85(6):1448-52.

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
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:

- Medical education
- Surgical planning

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). 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.

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.

Bangeas et al. (2019) conducted a randomized controlled trial to compare the educational role of 3D printed models with that of the conventional MRI films in the training of surgical residents. Statistical analysis showed that resident surgeons who studied only the anal fistula printed models, achieved a higher overall score in the fistula assessment test compared to resident surgeons who studied only MRI images. According to the authors, 3D printing technology can lead to improvement in preoperative planning accuracy, followed by efficient optimization of the treatment strategy. This study did not confirm the utility of such findings in improving care and outcome of patients.

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.

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 specialities 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.

Zheng et al. (2018) assessed the feasibility and effectiveness of the three-dimensional (3D) printing technology in the treatment of Pilon fractures in 100 patients. The patients were divided randomly into 3D printing group (n = 50) and conventional group (n = 50). The 3D models were used to simulate the surgery and carry out the surgery according to plan in 3D printing group. Operation time, blood loss, fluoroscopy times, fracture union time, and fracture reduction as well as functional outcomes and complications were recorded. The 3D printing group showed significantly shorter operation time, less blood loss volume and fluoroscopy times, higher rate of anatomic reduction and rate of excellent and good outcome than conventional group. However, the two groups did not differ significantly in functional outcome at the last follow-up period. No significant difference was observed in complications between the two groups. The authors concluded that the use of 3D printing technology to treat Pilon fractures in clinical practice is feasible.

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 randomized controlled trials (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.

An ECRI report for the use of three-dimensional printed anatomic models for cardiovascular and neurologic surgical planning indicates that evidence suggests that 3D-printed models may be advantageous in surgical planning. However, the evidence is currently too limited to determine which clinical fields will benefit most from this technology. More studies are needed to demonstrate the benefits of 3D models in surgical planning and in what clinical situations 3D models provide significant benefits over current surgical planning using 2D imaging (ECRI, 2018).

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Code	Description
22899	Unlisted procedure, spine [when used to report cooled radiofrequency ablation]
27299	Unlisted procedure, pelvis or hip joint [when used to report cooled radiofrequency ablation]
27599	Unlisted procedure, femur or knee [when used to report cooled radiofrequency ablation]
64999	Unlisted procedure, nervous system [when used to report cooled radiofrequency ablation]

Cooled radiofrequency ablation (RFA) is unproven and not medically necessary for the treatment of pain of any etiology due to insufficient evidence of safety and/or efficacy.

Cooled RFA is a minimally-invasive treatment using radiofrequency energy to heat and cool the tissue at the site of pain, e.g., back, hip, knee, to create a treatment area that is larger than with conventional radiofrequency ablation procedures. The purported advantages of cooled-tip probes are the larger heating distance (up to 3 cm from the active tip) and greater depth of lesion creation; also, because needle placement is perpendicular rather than parallel, this technique is considered to be technically easier to perform and less likely to cause tissue trauma. The larger lesion diameter may also ablate more pain nerves (ECRI, 2017).

For FDA approval information on Coolief and other cooled RFA systems, see the following website (use product code GXI): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. (Accessed May 23, 2019)

Clinical Evidence

A Hayes report concluded that there is insufficient published evidence to assess the safety and/or impact of the Coolief Cooled RFA on health outcomes or patient management in patients with hip and/or knee pain (Hayes, 2018).

Patel et al. (2012) conducted a randomized controlled trial to evaluate sacroiliac joint pain in 51 subjects with sacroiliac joint pain randomized on a 2:1 basis to lateral branch neurotomy and sham groups, respectively. The sham procedure was identical to the active treatment, except that radiofrequency energy was not delivered. Subjects and coordinators were blinded to randomization until 3 months and sham subjects were allowed to crossover to lateral branch neurotomy after 3 months. The authors reported that at 3-month follow-up, 47% of treated patients and 12% of sham subjects achieved treatment success, favoring cooled RFA. At 6 and 9 months, respectively, 38% and 59% of treated subjects achieved treatment success. Longer term outcome data is needed.

In a randomized placebo-controlled trial, Cohen et al. (2008) studied 28 patients with injection-diagnosed sacroiliac joint pain who received L4-L5 primary dorsal rami and S1-S3 lateral branch radiofrequency denervation using cooling-probe technology after a local anesthetic block (n=14), or local anesthetic block followed by placebo denervation (n=14). One, 3, and 6 months after the procedure, 11 (79%), 9 (64%), and 8 (57%) radiofrequency-treated patients experienced pain relief of 50% or greater and significant functional improvement. In contrast, only 2 patients (14%) in the placebo group experienced significant improvement at their 1-month follow-up, and none experienced benefit 3 months after the procedure. In the crossover group (n = 11), 7 (64%), 6 (55%), and 4 (36%) experienced improvement 1, 3, and 6 months after the procedure. The authors concluded that cooled RFA technology may provide intermediate-term pain relief and functional benefit in selected patients with suspected sacroiliac joint pain.

Tinnirello et al. (2017) compared two radiofrequency (RF) devices, Simplicity III (conventional RF), and SInergy (cooled RF), which are specifically designed to denervate the sacroiliac joint (SIJ). Forty-three patients with SIJ-derived pain refractory to conservative treatment; 21 and 22 patients, respectively, received Simplicity III or SInergy to denervate the SIJ. Mean numerical rating scale (NRS) and Oswestry Disability Index (ODI) scores were determined for each study group up to 12 months postprocedure. Secondary outcomes included the average amount of time required to complete each RF procedure and the AEs associated with each technique. Average SInergy group NRS and ODI scores were consistently less than those in the Simplicity III cohort at each post-RF denervation follow-up, and such differences were statistically significant at six and 12 months. The authors report that the study results suggest that SInergy safely afforded patients with greater and more durable analgesia and disability relief than Simplicity III for SIJ-derived pain. The Simplicity III procedure may be more conducive than SInergy for bilateral procedures and for patients who have limited tolerance to be in an RF procedure-required prone position. Randomized controlled trials are needed to confirm the implication made in this study that SInergy is the preferred RF denervation option for treating SIJ-derived pain and the disability associated with it.

In an observational study, Karaman et al. (2011) investigated the efficacy and safety of cooled RFA for sacral lateral-branch denervation (n=15). At the final control, while 80% of the patients reported at least a 50% decline in pain scores, 86.7% of those reported at least a ten-point reduction in Oswestry Disability Index (ODI) scores.

The use of cooled RF lateral branch neurotomy (LBN) to treat chronic sacroiliac joint-mediated low back pain in 126 patients was retrospectively reviewed by Stelzer et al. (2013). When stratified by time to final follow-up (4-6, 6-12, and >12 months, respectively): 86%, 71%, and 48% of subjects experienced $\geq 50\%$ reduction in VAS pain scores, 96%, 93%, and 85% reported their QOL as much improved or improved, and 100%, 62%, and 67% of opioid users stopped or decreased use of opioids. The authors concluded that the results show promising, durable improvements in pain, QOL, and medication usage with benefits persisting in some subjects at 20 months after treatment.

In a retrospective review, Ho et al. (2013) evaluated the efficacy of cooled radiofrequency denervation using the SInergy™ cooled radiofrequency system for sacroiliac joint pain. After 2 years, 15 of 20 patients showed a significant reduction in pain (a decrease of at least three points on the Numeric Rating Scale). Mean Numeric Rating Scale for pain decreased from 7.4 ± 1.4 to 3.1 ± 2.5 , mean Patient Global Impression of Change was "improved" (1.4 ± 1.5), and Global Perceived Effect was reported to be positive in 16 patients at two years following the procedure. The authors concluded that cooled radiofrequency denervation showed long-term efficacy for up to two years in the treatment of sacroiliac joint pain.

In an update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain, Manchikanti et al. (2013) reported that the evidence for sacroiliac cooled radiofrequency neurotomy is fair, limited for intraarticular steroid injections; limited for periarticular injections with steroids or botulinum toxin; and limited for both pulsed radiofrequency and conventional radiofrequency neurotomy. The authors recommend this procedure after appropriate diagnosis confirmed by diagnostic sacroiliac joint injections.

Sun et al. (2018) conducted a meta-analysis to assess the efficacy and safety of using cooled radiofrequency in treating patients with chronic SIJ pain in terms of pain and disability relief, patients' satisfaction degree as well as complications. A total of 7 studies with 240 eligible patients were enrolled. The overall pooled results demonstrated that pain intensity decreased significantly after cooled radiofrequency procedures compared with that measured before treatment. The authors suggest that high-quality and large-scale RCTs are required to validate their findings.

In a systematic review, Hansen et al. (2012) evaluated the accuracy of therapeutic sacroiliac joint interventions. With the primary outcome measure as pain relief (short-term relief = up to 6 months and long-term > 6 months) and secondary outcome measures being improvement in functional status, psychological status, return to work, and reduction in opioid intake, the authors concluded that the evidence was fair in favor of cooled radiofrequency neurotomy and poor for short-term and long-term relief from intraarticular steroid injections, periarticular injections with steroids or botulin toxin, pulsed radiofrequency, and conventional radiofrequency neurotomy. They noted study limitations to be paucity of literature on therapeutic interventions, variations in technique, and variable diagnostic standards for sacroiliac joint pain.

Kapur et al. (2008) reviewed electronic records of 27 patients with chronic low back pain (median 5 years) who underwent cooled RFA of S1, S2, and S3 lateral branches and of dorsal ramus (DR) L5 following two diagnostic SI joint blocks. The authors observed that the majority of patients with chronic SI joint pain experienced a clinically relevant degree of pain relief and improved function following cooled RF of sacral lateral branches and DR of L5 at 3-4 months follow-up.

The American Society of Anesthesiologists (ASA) Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine practice guideline for chronic pain management states that consultants, ASA and members are equivocal as to whether water-cooled radiofrequency ablation should be used for chronic sacroiliac joint pain. Based on one supporting clinical trial (category A3), and equivocal literature (category C2), their recommendation is that water-cooled radiofrequency ablation may be used for chronic sacroiliac joint pain (Rosenquist et al., 2010).

Davis et al. (2018) conducted a prospective, multicenter, randomized clinical trial comparing the safety and effectiveness of Coolief System (Halyard Health Inc, Alpharetta, Georgia) cooled RFA (CRFA) with corticosteroid injection (IAS) in the management of knee pain from osteoarthritis. One hundred fifty-one patients with at least a 36-month history of knee pain due to osteoarthritis (via radiographic confirmation) was required, with no other etiology demonstrated as the source of knee pain. All patients were unresponsive to conservative modalities. Knee pain (Numeric Rating Scale [NRS]), Oxford Knee Score, overall treatment effect (Global Perceived Effect), analgesic drug use, and AEs were compared between CRFA and IAS cohorts at 1, 3, and 6 months after intervention. At 6 months, the CRFA group had more favorable outcomes in NRS: pain reduction 50% or greater: 74.1% versus 16.2%, $P < 0.0001$ (25.9% and 83.8% of these study cohorts, respectively, were nonresponders). Mean NRS score reduction was 4.9 ± 2.4 versus 1.3 ± 2.2 , $P < 0.0001$; mean Oxford Knee Score was 35.7 ± 8.8 vs 22.4 ± 8.5 , $P < 0.0001$; mean improved Global Perceived Effect was 91.4% vs 23.9%, $P < 0.0001$; and mean change in nonopioid medication use was CRFA > IAS ($P = 0.02$). There were no procedure-related serious AEs. At 12 months, 65% of the original CRFA group had pain reduction 50% or greater, and the mean overall drop was 4.3 points on the NRS. Seventy-five per cent reported 'improved' effects. The cross-over group demonstrated improvements in pain and functional capacity (Davis et al., 2019). Additional randomized clinical trials with longer reported outcomes are needed to further evaluate CRFA for the treatment of knee pain due to osteoarthritis.

McCormick et al. (2017) reported 6 month outcomes from thirty-three patients (52 discrete knees) who met inclusion criteria for genicular nerve cooled radiofrequency ablation (C-RFA). Patients were surveyed 6 or more months after C-RFA and numeric rating scale (NRS), Medication Quantification Scale III (MQSIII), Patient Global Impression of Change (PGIC), and total knee arthroplasty (TKA) data were collected. Logistic regression was used to identify factors that predicted treatment success. Thirty-five percent (95% confidence interval [CI] = 22-48) of procedures resulted in the combined outcome of 50% or greater reduction in NRS score, reduction of 3.4 or more points in MQSIII score, and PGIC score consistent with "very much improved/improved." Nineteen percent (95% CI = 10-33) of procedures resulted in complete pain relief. Greater duration of pain and greater than 80% pain relief from diagnostic blocks were identified as predictors of treatment success. The accuracy of the model was 0.88 (95% CI = 0.78-0.97, $P < 0.001$). The authors concluded that genicular C-RFA demonstrated a success rate of 35% based on a robust combination of outcome measures, and 19% of procedures resulted in complete relief of pain at a minimum of six months of follow-up. Further prospective well-designed studies are needed to optimize the patient selection protocol and success rate of this procedure.

In a systematic review of published studies investigating conventional, pulsed, or cooled radiofrequency ablation in the setting of chronic knee pain, Gupta et al. (2017) provided an overview of the current knowledge regarding variations in procedures, nerve targets, AEs, and temporal extent of clinical benefit. The authors reported that while

the wide search strategy included a variety of articles, broad conclusions and pooled data could not be obtained based on the studies analyzed. These included small randomized controlled trials, retrospective reviews or case studies. The authors reported that there is a low level of certainty in supporting the superiority of any specific RFA procedure modality. The majority of the studies report positive patient outcomes, but the inconsistent procedural methodology, inconsistent patient assessment measures, and small study sizes limit the applicability of any specific study to clinical practice.

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Code	Description
27599	Unlisted procedure, femur or knee (when used to report LIPOGEMS)

Refined autologous adipose cell transfer is unproven and not medically necessary to treat conditions of the knee due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Mesenchymal stromal cells (MSCs) have the ability to differentiate into many cell types, making them valuable for a variety of clinical applications, including tissue repair. They are easily isolated and harvested from several organs, including human adipose tissue. The LIPOGEMS® System is a sterile, single-use device designed to harvest, process,

and transfer refined autologous adipose tissue . Fat tissue is microfragmented and washed of proinflammatory oil and blood residues, and transplanted to the surgical site (Tremolada et al. 2016).

Schiavone et al. (2019) reported the preliminary clinical and functional results of a series of patients with early knee osteoarthritis (KOA) treated with the intra-articular injection of autologous adipose-derived stem cells (aASCs) plus arthroscopic debridement. The hypothesis was that protocol would significantly improve the clinical and functional outcomes in patients with early KOA. Fifty-two patients with early KOA, who received arthroscopic debridement followed by percutaneous injection of aASCs, were enrolled into the study and retrospectively analyzed with an average follow-up of 15.3 months. Patients were assessed through the IKS knee and function scores and VAS pain scale. The results showed the mean IKS knee score improved from 37.4 points pre-operatively to 62.6 points at the latest follow-up, and the mean IKS function score improved from 57.2 points pre-operatively to 83.0 points at the latest follow-up. The mean VAS score decreased from 8.5 pre-operatively to 5.1 at the latest follow-up. Additionally, patients with a pre-operative VAS score greater than 8 were found to show greater clinical and functional benefits compared with patients with VAS score lower than 8. The authors concluded that the knee injection of aASCs associated to arthroscopic debridement increased significantly the clinical and functional scores in patients with early KOA at a mid-term follow-up, especially those with higher pre-operative VAS scores. These results should be confirmed by randomized controlled studies.

Panchal et al. (2018) conducted a study to evaluate the safety and efficacy of using autologous, micro-fractured, minimally manipulated adipose tissue in patients with refractory knee osteoarthritis (OA). A total of 17 subjects (26 knees) with a median age of 72 years (range: 54-78 years) and a history of knee OA (Kellgren-Lawrence, grade of 3 or 4) underwent treatment with ultrasound-guided injection of micro-fractured adipose tissue. Micro-fractured fat was obtained using a minimal manipulation technique in a closed system (Lipogems), without the addition of enzymes or any other additives. The study subjects were clinically evaluated using the numerical pain rating scale (NPRS), the 100-point Knee Society Score (KSS) with its functional component (FXN), and the lower extremity activity scale (LEAS) at 6 weeks, 6 months, and 12 months following this procedure. When compared with baseline, significant improvements were noted in the mean values of NPRS, FXN, and LEAS at 6 weeks, 6 months, and 12 months. The mean KSS significantly improved at 6 weeks and 12 months. In particular, the average KSS score improved from 74 to 82, the FXN score improved from 65 to 76, and the LEAS score improved from 36 to 47. These values were significantly greater than the previously published minimal clinically important difference described for KSS and FXN in patients who underwent total knee arthroplasty for primary OA. No serious adverse events were reported. The injection of autologous, micro-fractured, minimally manipulated adipose tissue appears to be a safe and effective treatment option for patients with refractory, severe (grade 3 or 4) knee OA. This study demonstrated significant improvements in pain, quality of life, and function for at least 12 months in this study population. This intervention may represent a nonsurgical treatment option to avoid knee joint replacement in this population; however, further investigation is needed.

Russo et al. (2017) conducted a retrospective study on the 1-year safety and outcome of a single intra-articular injection of autologous and micro-fragmented adipose tissue in 30 patients affected by diffuse degenerative chondral lesions. The safety of the procedure was evaluated by recording type and incidence of any adverse event. The clinical outcomes were determined using the KOOS, IKDC-subjective, Tegner Lysholm Knee, and VAS pain scales taken pre-operatively and at 12 months follow-up. A level of at least 10 points of improvement in the scores was selected as the cut-off representing a clinically significant difference. The results showed no relevant complications or clinical worsening was recorded. A total median improvement of 20 points was observed in IKDC-subjective and total KOOS, and a higher percentage of success was found in VAS pain and Tegner Lysholm Knee, where the total median improvement was 24 and 31 points, respectively. The authors concluded that the results of this study show the safety and feasibility of using autologous and micro-fragmented adipose tissue in patients affected by diffuse degenerative chondral lesions, and that the technique is safe, minimally invasive, simple, one-step, with low percentage of complications. Although it is not possible to draw a clear conclusion about the efficacy because 80% of the patients had an associated surgery, the results of this study are satisfactory, with the majority of patients significantly improved in terms of clinical outcomes with respect to baseline. This study is limited by a small patient population and lack of randomization. Further high quality studies with larger populations are needed before clinical usefulness of this procedure is proven.

A 2017 ECRI custom product brief concluded that the available evidence for the LIPOGEMS® System has major limitations. The included studies are at high risk of bias due to a lack of randomization, blinding, reporting on subjective outcomes, and single-center patient recruiting. Outcomes from the case report study, reporting on patients with degenerative chondral lesions, are not generalizable because of a small patient population. Moreover, studies do not report on important patient-oriented outcomes. Additional studies comparing the effectiveness of Lipogems-processed autologous adipose tissue reinjections with that of other processing methods, with that of no adipose tissue grafting (placebo), and with that of unprocessed autologous adipose tissue grafting are necessary for determining the comparative effectiveness of Lipogems-processed adipose tissue.

Several clinical trials were identified regarding The LIPOGEMS System for a variety of clinical applications. Further information can be found at: <https://clinicaltrials.gov/ct2/results?cond=&term=Lipogems&cntry=&state=&city=&dist=>. (Accessed April 24, 2019)

On May 18, 2017, the FDA granted 510(k) clearance for the LIPOGEMS® System with the classification code MUU. Further information can be found at: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171135.pdf. (Accessed April 24, 2019)

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Code	Description
30999	Unlisted procedure, nose (when used for coblation nasal septal swell body reduction)

Coblation nasal septal swell body reduction for the treatment of nasal obstruction is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Turbinates are small structures inside the nose that cleanse and humidify air that passes through the nostrils into the lungs. They are made by a bony structure surrounded by vascular tissue and a mucous membrane outside, and can become swollen and inflamed by allergies, irritation or infection, causing nasal obstruction and producing an excessive amount of mucous which leads to congestion.

Coblation is a new surgical method for removing soft tissue of the 'nasal septal swell body' (NSB). This is a term used to describe the thickened mucosa of the anterior nasal septum superior to the inferior turbinate and anterior to the middle turbinate. It is claimed that the NSB can contribute towards nasal resistance due to its location in the internal valve area. (Kim, 2016).

In a retrospective, case-series study, Kim and associates (2016) presented the results of Coblation nasal septal swell body (NSB) reduction for the treatment of nasal obstruction in patients with abnormally thickened NSB. The study was conducted at a single tertiary medical center; 8 patients underwent Coblation NSB reduction. Pre- and post-operative nasal functions were evaluated by acoustic rhinometry and subjective symptom scales, as well as pre-operative CT scan images and nasal endoscopic findings. The post-procedure follow up period was 3, 6, and 12 months. The mean maximal NSB width was 16.4 ± 2.2 mm on pre-operative coronal CT scan images. The mean visual analog scale score for nasal obstruction was decreased from preoperative 7.63 (± 0.99) points to 3.88, 4.16, and 4.63 points at 3, 6, and 12 months, respectively. Clinical satisfaction at 1 year was reported by 75% of participants. The authors concluded that coblation can be an effective treatment modality for nasal valve narrowing in patients with abnormally thickened NSB. Limitations to this study include small sample size and study design.

Yu and colleagues (2015) conducted a prospective randomized study to evaluate the efficacy of septal body volume reduction (SBVR) for the treatment of septal body hypertrophy. Fifty one subjects with nasal obstruction associated with septal body and inferior turbinate hypertrophy refractory to medical therapy were included. Conventional inferior turbinoplasty (ITR) was performed on 25 subjects (control group). A combination of ITR plus concurrent bilateral microdebrider-assisted SBVR was performed on 26 patients (study group). All were followed postoperatively for 3 months. The nasal symptoms, including nasal obstruction, rhinorrhea, itching, and sneezing, had significantly improved at 3 months in both groups. However, a greater improvement in nasal obstruction and a more significant increase in nasal volume were demonstrated in the study group with no AEs encountered. The researchers concluded that combined SBVR and turbinoplasty appears to be more effective than turbinoplasty alone for the treatment of nasal obstruction in patients with inferior turbinate and septal body hypertrophy.

Reference(s)

Kim SJ, Kim HT, Park YH, et al. Coblation nasal septal swell body reduction for treatment of nasal obstruction: a preliminary report. Eur Arch Otorhinolaryngol. 2016 Sep;273(9):2575-8.

Code	Description
30999	Unlisted procedure, nose (when used to report rhinophototherapy, intranasal application of ultraviolet and visible light, bilateral)

Rhinophototherapy is unproven and not medically necessary for treating allergies due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Jiang et al. (2018) evaluated the effect of red light rhinophototherapy (RLRPT) on nasal patency in patients with a clinical diagnosis of allergic rhinitis. Subjects were randomly divided into 2 groups, with patients in one group given one treatment session of RLRPT, followed by medical treatment. Those in the second group were treated with medical treatment only. The rhinitis symptoms were evaluated both before and 30 minutes after RLRPT and 2 days later. The nasal patency was objectively measured through the use of both active anterior rhinomanometry and acoustic rhinometry before and 30 minutes after RLRPT. All rhinitis symptoms, including nasal congestion, significantly improved 30 minutes after a single RLRPT treatment, but worsened again, particularly for sneezing, 2 days later. Nasal resistance slightly decreased 30 minutes after RLRPT. The first minimal cross-sectional area did not change after RLRPT, but the second minimal cross-sectional area with the volume of the nasal cavity between 2.0 and 5.0 cm from the tip of the nosepiece significantly lessened. The authors concluded that RLRPT treatment did not objectively improve patient's nasal patency, but the actual effect of RLRPT on nasal patency still requires further investigation.

In a randomized double-blind, placebo-controlled trial, Dulguerov et al. (2017) evaluated the efficacy of rhinophototherapy in patients with chronic rhinosinusitis (CRS) without nasal polyps. The study included 50 CRS patients who received either mixed visible and ultraviolet (UVA and UVB) light source application (mUV/VIS) or visible light alone that served as placebo. Both groups were treated for 3 weeks. Results in the rhinophototherapy and placebo group were not significantly different and failed to reduce patient-reported outcomes measures (Rhinosinusitis Disability Index, Visual Analogic Scale of symptom severity) and objective scores (rhinomanometry, olfactory thresholds, nasal Nitric Oxide concentrations), immediately and one month after treatment. The investigators concluded that the present data suggest that rhinophototherapy is not an efficient treatment for chronic rhinosinusitis without nasal polyps.

Alyasin et al. (2016) conducted a randomized single-blind study to investigate the effect of low-dose phototherapy in allergic rhinitis (AR) patients. Among AR patients who did not respond to local and systemic therapy, the authors chose 62 allergic patients all above 25 years of age with moderate to severe AR whose disease was verified by allergy skin test or specific IgE to allergens; then, they were randomly divided into 31 patients as treatment group and 31 patients as control group. In the treatment group, a mixture of UVA, UVB and visible light were used. Visible light alone as placebo was used in the control group. The level of response to treatment were evaluated and compared in both groups according to Total Nasal Symptom scores (TNSS) and Global Severity Scores (GSS) and Rhinoconjunctivitis Quality of Life Questionnaires (RQLQ) symptom scores. The authors concluded that phototherapy was an efficient therapeutic procedure for the treatment of patients with AR. However, the authors recommend that for substantiation of the claim, further investigations are still required. A limitation of the study is that intranasal phototherapy was not compared with standard treatment (intranasal/ oral corticosteroids and intranasal antihistamines).

The National Institute for Health and Care Excellence (NICE) interventional procedures guidance on intranasal phototherapy for allergic rhinitis indicates that the current evidence on the efficacy and safety of intranasal phototherapy for allergic rhinitis is limited in quantity and quality. NICE recommends that this procedure should only be used in the context of research (NICE 2018).

Reference(s)

Alyasin S, Nabavizadeh SH, Houshmand H, et al. Short time efficiency of rhinophototherapy in management of patients with allergic rhinitis resistant to medical therapy. Iran J Allergy Asthma Immunol. 2016 Aug;15(4):317-327.

Dulguerov N, Guinand N, Courvoisier D, et al. Rhinophototherapy in chronic rhinosinusitis: a double blind randomized placebo-controlled trial. Rhinology. 2017 Jun 1;55(2):106-112.

Jiang RS, Wang JJ. Effect of Red Light Rhinophototherapy on nasal patency in patients with allergic rhinitis. Int J Otolaryngol. 2018 Dec 17;2018:6270614.

National Institute for Health and Care Excellence (NICE). Interventional procedures guidance. Intranasal phototherapy for allergic rhinitis. London (UK): Published June 2018.

Code	Description
30999	Unlisted procedure, nose [when used to report the insertion of an absorbable nasal implant]
L8699	Prosthetic implant, not otherwise specified [when used to report an absorbable nasal implant]

Absorbable nasal implants (e.g., Latera Absorbable Nasal Implant [Stryker]) are unproven and not medically necessary for supporting nasal upper and lower lateral cartilage due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The Latera Absorbable Nasal Implant (Stryker) received U.S. Food and Drug Administration (FDA) clearance through the 510(k) premarket notification pathway on June 23, 2016) and is indicated for supporting nasal upper and lower lateral cartilage. The System consists of the Latera Absorbable Nasal Implant (Implant) and Accessory Delivery Device (Delivery Device) and is composed of a PLLA-PDLA copolymer.

The predicate device, INEX Absorbable Nasal Implant (Spirox®), was cleared by the FDA on December 4, 2015.

For additional information, see:

- https://www.accessdata.fda.gov/cdrh_docs/pdf16/k161191.pdf
 - <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K161191>
- (Accessed April 2, 2019)

According to the manufacturer's website, the Latera is used to support upper and lower lateral cartilage in the nose, reinforcing the nasal wall like traditional cartilage and polymer grafts. Supporting the cartilage in this manner may reduce nasal airway obstruction symptoms and help patients breathe better. The Latera implant supports the upper and lower lateral cartilage by anchoring above the maxilla to provide cantilever support. Through a minimally invasive procedure, the nasal implant is inserted through a small incision made inside a patient's nose. (Stryker, 2019).

Stolovitzky et al. (2018) reported 6-month outcomes from a prospective, multicenter, nonrandomized, single-blinded study for treatment of nasal valve collapse due to lateral wall insufficiency. One hundred and one patients with severe-to-extreme class of Nasal Obstruction Symptom Evaluation (NOSE) scores were enrolled at 14 U.S. clinics. Patients were treated with a bioabsorbable implant designed to support lateral wall, with or without concurrent septoplasty and/or turbinate reduction procedure(s). NOSE scores and visual analog scale (VAS) were measured at baseline and month 1, 3, and 6 postoperatively. The Lateral Wall Insufficiency (LWI) score was determined by independent physicians observing the lateral wall motion video. Forty-three patients were treated with implant alone, whereas 58 had adjunctive procedures. Seventeen patients reported 19 AEs, all of which resolved with no clinical sequelae. Patients showed significant reduction in NOSE scores at 1, 3, and 6 months postoperatively (79.5 ± 13.5 preoperatively, 34.6 ± 25.0 at 1 month, 32.0 ± 28.4 at 3 months, and 30.6 ± 25.8 at 6 months postoperatively; $P < 0.01$ for all). They also showed significant reduction in VAS scores postoperatively (71.9 ± 18.8 preoperatively, 32.7 ± 27.1 at 1 month, 30.1 ± 28.3 at 3 months, and 30.7 ± 29.6 at 6 months postoperatively; $P < 0.01$ for all). These results were similar in patients treated with the implant alone compared to those treated with the implant and adjunctive procedures. Consistent with patient-reported outcomes, postoperative LWI scores were demonstrably lower (1.83 ± 0.10 and 1.30 ± 0.11 pre- and postoperatively; $P < 0.01$). The authors concluded that stabilization of the lateral nasal wall with a bioabsorbable implant improves patients' nasal obstructive symptoms over 6 months. Longer-term outcomes are needed to validate the efficacy of a bioabsorbable implant for the treatment of nasal valve collapse.

San Nicolo et al. (2017) conducted a prospective study to evaluate the safety and effectiveness of an absorbable implant for lateral cartilage support in subjects with nasal valve collapse (NVC) with 12 months follow-up. Thirty subjects with Nasal Obstruction Symptom Evaluation (NOSE) score ≥ 55 and isolated NVC were treated; 14 cases were performed in an operating suite under general anesthesia and 16 cases were performed in a clinic-based setting under local anesthesia. The implant, a polylactic acid copolymer, was placed with a delivery tool within the nasal wall to provide lateral cartilage support. Subjects were followed up through 12 months postprocedure. Fifty-six implants were placed in 30 subjects. The mean preoperative NOSE score was 76.7 ± 14.8 , with a range of 55 to 100. At 12 months, the mean score was 35.2 ± 29.2 , reflecting an average within-patient reduction of -40.9 ± 31.2 points. The majority (76%) of the subjects were responders defined as having at least one NOSE class improvement or a NOSE score reduction of at least 20%. There were no adverse changes in cosmetic appearance at 12 months postprocedure. Three implants in three subjects required retrieval within 30 days postprocedure and resulted in no clinical sequelae. The authors conclude that this study demonstrates safety and effectiveness of an absorbable implant for lateral cartilage support in subjects with NVC at 12 months postprocedure. Well-designed randomized clinical trials with larger patient populations and longer follow-up periods are needed to further assess absorbable nasal implants.

In a 2015 position statement, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) determined that the use of FDA-approved biomaterials can be utilized in sinonasal procedures to improve patient outcomes and reduce complications. These items, such as implants, stents, and packing materials, have functions

including, but not limited to, local drug delivery, stenting, and hemostasis. The AAO-HNS does not consider FDA-approved biomaterials for rhinologic application to be investigational, and recommends that the final decision regarding use of these biomaterials should be determined by the treating physician, factoring in best available scientific evidence, surgeon experience and the clinical situation, and individual patient preference. The references cited in the position statement do not specifically address non-steroid-releasing absorbable nasal implants, e.g., Latera.

ClinicalTrials.gov lists ongoing studies for the Latera.

Reference(s)

American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS). Position statement: the use of biomaterials in sinonasal procedures. September 2015. Available at: <https://www.entnet.org/content/position-statement-use-biomaterials-sinonasal-procedures>. Accessed April 2, 2019.

ClinicalTrials.gov website. Available at: <https://clinicaltrials.gov/>. Accessed April 2, 2019.

ECRI Institute. Custom Product Briefs-Guidance. Latera Absorbable Nasal Implant (Spirox, Inc.) for supporting nasal upper and lower lateral cartilage. February 2017.

Hayes Inc. Search & Summary. Latera Absorbable Nasal Implant (Spirox) for nasal vestibular lateral wall stenosis. Lansdale PA: Hayes, Inc.; March 16, 2018.

San Nicoló M, Stelter K, Sadick H, et al. Absorbable implant to treat nasal valve collapse. *Facial Plast Surg*. 2017 Apr;33(2):233-240.

Stryker website. Available at: <https://ent.stryker.com/medical-devices/nasal-implant/latera>. Accessed April 2, 2019.

Stolovitzky P, Sidle DM, Ow RA, et al. A prospective study for treatment of nasal valve collapse due to lateral wall insufficiency: Outcomes using a bioabsorbable implant. *Laryngoscope*. 2018 Nov;128(11):2483-2489.

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 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 prolonged air leaks (PAL) patients 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.

Prolonged air leak and presence of bronchopleural fistulae (BPF) are often encountered in clinical practice. 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 bronchopleural fistulae (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 in an attempt to establish its benefit in current clinical practice.

A 2017 Cochrane systematic review was performed to assess the effects of bronchoscopic lung volume reduction (BLVR) on the short- and long-term health outcomes in participants with moderate to severe chronic obstructive pulmonary disease (COPD) and determine the effectiveness and cost-effectiveness of each individual technique. Fourteen studies including 1979 participants were identified up to December 2016 which studied BVRs (AeriSeal, airway bypass stents, endobronchial coils, endobronchial valves, intrabronchial valves and vapor ablation). Most

studies compared a BLVR procedure to optimal medical care or to sham bronchoscopy. A randomized control trial (RCT) of 95 participants found that AeriSeal compared to control led to a significant median improvement in forced expiratory volume in one second (FEV₁) and higher QOL, as measured by the St Georges Respiratory Questionnaire (SGRQ). The quality of evidence was rated low to moderate. In one study (n=315), treatment with airway bypass stents compared to control did not lead to significant between-group changes in FEV₁ or SGRQ scores. There was no significant difference in mortality or AEs between the two groups. The quality of evidence was rated moderate to high. Three studies (n=461) showed that treatment with endobronchial coils compared to control led to a significant between-group mean difference in FEV₁ and SGRQ. There were no significant differences in mortality but AEs were significantly more common for participants treated with coils. The quality of evidence ranged from low to high. Five studies (n=703) found that endobronchial valves versus control led to significant improvements in FEV₁ and SGRQ scores. There were no significant differences in mortality between the two groups but AEs were more common in the endobronchial valve group. The quality of evidence ranged from low to high. In the comparison of partial bilateral placement of intrabronchial valves to control, one trial favored control in FEV₁ and one trial found no difference between the groups. There were no significant differences in SGRQ scores or mortality rates, but AEs were more frequent in participants treated with intrabronchial valves. The quality of evidence ranged between moderate to high. One study (n=69) found significant mean between-group differences in FEV₁ and SGRQ favoring vapor ablation over control. There was no significant between-group difference in mortality but vapor ablation led to significantly more AEs. The quality of evidence ranged from low to moderate. The review found that results for selected BLVR procedures can provide significant and clinically meaningful short-term (up to one year) improvements in health outcomes, but this was at the expense of increased AEs. The currently available evidence is not sufficient to assess the effect of BLVR procedures on mortality. These findings are limited by the lack of long-term follow-up data, limited availability of cost-effectiveness data, significant heterogeneity in results, and the open-label character of a number of the studies.

Cardillo et al. (2015) retrospectively reviewed the records of 3,832 patients who underwent pulmonary anatomic resections. The overall incidence of bronchopleural fistulas 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 bronchopleural fistulas. Very small, 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 observations.

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 bronchopleural fistulas 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 tracheo-bronchial stenting. The mortality was 40% in these patients reflecting the very high mortality with bronchopleural fistulas. Many patients required multiple bronchoscopic procedures and further drainage procedures. Bronchoscopic treatment has so far only been reported in small case series but may offer further treatment options in patients too unwell to undergo re-thoracotomy.

The diagnosis and management of bronchopleural fistulas remain a major therapeutic challenge and is associated with significant morbidity and mortality. While several case reports suggest the efficacy of balloon occlusion for bronchopleural fistulas in selected patients, there are no large-scale controlled trials evaluating the efficacy of this procedure (Sarkar, 2010).

Although rare, bronchopleural fistulas represent a challenging management problem and are associated with high morbidity and mortality. Treatment options include various surgical and medical procedures, including the use of bronchoscopy and different glues, coils and sealants. Therapeutic success has been variable, and the lack of consensus suggests that no optimal therapy is available. Further studies are required to establish the role of techniques and patient selection for endoscopic procedures, as well as which technique or combination will be most valuable (Lois 2005).

Although a minimally invasive technology to close bronchopleural fistulas is needed, further studies with larger study populations are necessary to determine patient selection criteria, safety and long-term efficacy of this technology.

American Association for Thoracic Surgery (AATS) consensus guidelines for the management of empyema associated with bronchopleural fistula (BPF) recommend:

- 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)

Reference(s)

Cardillo G, Carbone L, Carleo F, et al. The rationale for treatment of postresectional bronchopleural fistula: Analysis of 52 patients. *Ann Thorac Surg* 2015;100:251-7.

Lois M, Noppen M. Bronchopleural fistulas: an overview of the problem with special focus on endoscopic management. *Chest*. 2005 Dec;128(6):3955-65.

Mehta RM, Singla A, Bhat RS, et al. An innovative solution for prolonged air leaks: the customized endobronchial silicone blocker. *J Bronchology Interv Pulmonol*. 2018 Apr;25(2):111-117.

Sarkar P, Chandak T, Shah R, Talwar A. Diagnosis and management bronchopleural fistula. *Indian J Chest Dis Allied Sci*. 2010 Apr-Jun;52(2):97-104.

Shen R, Bribriescio A, Crabtree T, et al. The American Association for Thoracic Surgery consensus guidelines for the management of empyema. *J Thorac Cardiovasc Surg* 2017;153:e129-46.

Tsilimigras D, Antonopoulou A, Ntanasis-Stathopoulos I, et al. The role of BioGlue in thoracic surgery: a systematic review. *Journal of Thoracic Disease*, Vol 9, No 3 March 2017.

van Agteren JE, Hnin K, Grosser D, et al. Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2017 Feb 23;2:CD012158.

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

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 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. Potential advantages are fewer AEs, fewer lead complications and improved QOL.

The Micra™ Transcatheter Pacemaker System (Medtronic) received FDA premarket approval (P150033) on April 6, 2016. Additional information is available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P150033>. (Accessed May 22, 2019)

A Hayes report concluded that there is substantial uncertainty regarding the safety and efficacy of the Micra system, especially regarding the alleviation of symptoms associated with bradycardia. The body of evidence was of very low quality, limited by observational design, small number of studies, lack of contemporaneous comparisons with traditional transvenous pacemakers, lack of long-term safety data, limited follow-up, lack of direct patient-centered efficacy outcomes and manufacturer involvement. Well-designed and well-conducted randomized controlled trials with follow-up that is adequate to assess the incidence and safety of device retrieval are needed to compare the Micra with traditional devices (Hayes, 2017;updated 2018).

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).

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., 2018).

Micra Transcatheter Pacing Study

The Micra Transcatheter Pacing Study is a prospective, multicenter, single-arm study evaluating the safety, efficacy and long-term performance of the Micra leadless pacemaker in patients with indications for ventricular pacing. Funded by Medtronic. ClinicalTrials.gov #NCT02004873.

Using historical comparisons, Reynolds et al. (2016) performed an interim analysis of the primary end points when 300 patients reached 6 months of follow-up. The primary safety end point was freedom from system- or procedure-related major complications. The primary efficacy end point was the percentage of patients with low and stable pacing capture thresholds at 6 months. The safety and efficacy end points were evaluated against performance goals (based on historical data) of 83% and 80%, respectively. The authors also compared the rates of major complications with those in a control cohort of 2,667 patients with transvenous pacemakers from six previously published studies. The device was successfully implanted in 719 of 725 patients (99.2%). Ninety-six percent (696 of 725) of patients receiving the device achieved freedom from device- or procedure-related major complications through 6 months. The primary efficacy end point rate was 98.3% among 292 of 297 patients with paired 6-month data. Although there were 28 major complications in 25 patients, patients with transcatheter pacemakers had significantly fewer major complications than control patients. The authors concluded that the transcatheter pacemaker met the prespecified safety and efficacy goals. The device had a safety profile similar to that of a transvenous system while providing low and stable pacing thresholds.

Duray et al. (2017) reported 12-month safety data and 24-month electrical performance. The long-term safety objective was achieved with a freedom from major complication rate of 96.0% at 12 months. The risk of major complications for patients with Micra (n=726) was 48% lower than that for patients with transvenous systems through 12 months postimplant. Across subgroups of age, sex and comorbidities, Micra reduced the risk of major complications compared to transvenous systems. The authors reported that long-term performance of the Micra transcatheter pacemaker remains consistent with previously reported data. This study is limited by lack of comparison with a randomized control group and short-term follow-up. Further studies are needed to assess long-term efficacy, observed longevity and ease of removal.

At 24 months, Grubman et al. (2017) reported an overall system revision rate of 1.4% for patients with the Micra system compared to 5.3% in the traditional pacemaker group.

Ritter et al. (2015) published an interim report on 140 patients from 23 centers in 11 countries. Patients received the device to treat atrioventricular block (66%) or sinus node dysfunction (29%). The implant success rate was 100% (140/140). The primary endpoints were >85% freedom from unanticipated serious adverse device events (safety) and three-month mean pacing capture threshold (efficacy). The safety objective was assessed in all 140 implanted patients while the efficacy objective was assessed in the 60 subjects who had been followed through 3 months. During mean follow-up of 1.9 ± 1.8 months, the safety endpoint was met with no unanticipated serious adverse device events. Thirty AEs related to the system or procedure occurred, mostly due to transient dysrhythmias or femoral access complications. One pericardial effusion without tamponade occurred. In 60 patients followed to 3 months, the efficacy endpoint was met. The authors reported that early assessment shows the device can safely and effectively be applied. Study limitations include lack of randomization and control and small patient numbers. Long-term safety and benefit of the device will be further evaluated in the trial.

An observational, noncomparative registry was created to assess the safety and effectiveness of the Micra system in the post-approval setting. Early results suggest that the Micra transcatheter pacemaker has a high rate (99.6%) of implant success and a low rate (1.51%) of major complications through 30 days post implant. Longer follow-up is needed to confirm these results (Roberts et al., 2017).

LEADLESS II Trial

The LEADLESS II trial is a prospective, nonrandomized, multicenter study evaluating the Nanostim leadless pacemaker (St. Jude Medical) in patients requiring permanent single-chamber ventricular pacing. Funded by St. Jude Medical. ClinicalTrials.gov #NCT02030418. In October 2016, St. Jude Medical advised investigators in the LEADLESS II study to stop implanting Nanostim devices due to battery malfunctions. An estimated timeline for study resumption has not been announced.

Reddy et al. (2015) reported on the first 300 patients (primary cohort) who had reached the 6-month primary endpoint. Data from these patients was analyzed for the primary efficacy and safety endpoints at 6 months. The primary efficacy endpoint was acceptable pacing threshold and sensing amplitude. The primary safety endpoint was freedom from device-related serious AEs. The primary efficacy endpoint was met in 270 of the 300 patients (90%), and the primary safety endpoint was met in 280 of the 300 patients (93.3%). At 6 months, device-related serious AEs were observed in 6.7% of the patients. Events included device dislodgement with percutaneous retrieval (1.7%), cardiac perforation (1.3%), and pacing-threshold elevation requiring percutaneous retrieval and device replacement (1.3%). An additional 226 patients were enrolled as part of the ongoing trial. The total cohort of 526 patients was

assessed for device-related and non-device-related serious AEs. The device was successfully implanted in 504 of the 526 patients (95.8%). Data from these patients was analyzed together with data from the primary cohort that had extended follow-up beyond 6 months. In the total cohort, the mean sensing and pacing threshold values improved significantly over time. In the total cohort of 526 patients, the rate of device-related serious AEs was 6.5%, including cardiac perforation in 1.5% of the patients, device dislodgement in 1.1% and device retrieval due to elevated pacing thresholds in 0.8%. In the total cohort, there were 28 deaths (5.3%) during follow-up. The authors reported that the leadless pacemaker met prespecified pacing and sensing requirements in the large majority of patients. This study is limited by observational design and short-term follow-up. Further studies that directly compare leadless pacemakers with conventional devices are needed to determine the safety and efficacy of these devices.

In the LEADLESS trial, Reddy et al. (2014) conducted a prospective, non-randomized, single arm study evaluating the safety and clinical performance of the Nanostim leadless pacemaker. Thirty-three patients with a clinical indication for single-chamber (right ventricular) pacing (VVIR) were eligible for the device. The primary safety end point was freedom from complications at 90 days. Secondary performance end points included implant success rate, implant time and measures of device performance. The mean patient age was 77±8 years, and 67% of the patients were male (n=22/33). The most common indication for cardiac pacing was permanent atrial fibrillation with atrioventricular block (n=22, 67%). The implant success rate was 97% (n=32). Five patients (15%) required the use of >1 leadless cardiac pacemaker during the procedure. The overall complication-free rate was 94% (31/33). At 3 months follow-up, the investigators reported that pacing was comparable with traditional lead-based pacemakers in 32 of 33 patients. One patient developed right ventricular perforation and cardiac tamponade during the implant procedure, and eventually died as the result of a stroke. Study limitations include potential bias due to manufacturer sponsorship, small patient population and short-term follow-up. Additional research involving larger, well-designed prospective studies is needed to establish the role of leadless pacemakers in managing cardiac arrhythmias. Clinical trial #NCT01700244.

Knops et al. (2015) reported stable electrical performance without device-related AEs 1 year after implantation in an initial cohort of 31 patients from the LEADLESS trial. Comparative trials with longer follow-up are needed to assess the performance of leadless and conventional lead-based pacemakers and inform optimal case selection for each type of system.

Reddy et al. (2016) conducted a multicenter study on the feasibility and safety of acute and chronic retrieval of a leadless cardiac pacemaker. The study included patients enrolled in 3 multicenter trials, who received the Nanostim device, and who subsequently underwent a device removal attempt. The overall retrieval success rate was 94%. For patients whose leadless cardiac pacemaker had been implanted for <6 weeks (acute retrieval cohort), complete retrieval was achieved in 100% (n=5/5). For those implanted for ≥ 6 weeks (chronic retrieval cohort), retrieval was achieved in 91% (n=10/11) of patients.

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Code	Description
33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation

Implantable cardiac devices for percutaneous closure (occlusion) of the left atrial appendage (LAA) are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The Watchman™ LAA closure device (Boston Scientific) received FDA premarket approval (P130013) on March 13, 2015. Additional information is available at:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130013>. (Accessed May 24, 2019)

A Hayes report compared the safety and efficacy of percutaneous LAA closure devices with oral anticoagulation (OAC) medications, and with each other, to reduce stroke risk in patients with nonvalvular atrial fibrillation (AF). Studies indicate that percutaneous LAA closure may reduce the risk of stroke in some patients with AF and high risk of stroke with contraindications to OAC or unwillingness to adhere to long-term OAC therapy. However, device-mediated LAA closure is associated with a measurable risk of serious and potentially life-threatening complications such as major bleeding, pericardial effusion, stroke, device embolization and cardiac perforation or tamponade. The overall quality of evidence was moderate for the Watchman device. Randomized controlled trial (RCT) findings are offset by concerns regarding the lack of studies comparing the Watchman device relative to newer OAC medications. Also, there is uncertainty whether the benefit outweighs possible harms given the potential for device-related complications or mortality. Well-powered RCTs are needed to compare closure using the Watchman and other percutaneous LAA devices versus treatment with newer OACs and to test the use of newer OACs as an adjunct to LAA closure. Hayes concluded that there is insufficient data to evaluate the comparative effectiveness and safety of these devices (Hayes, 2018).

An ECRI report states that evidence from two RCTs suggests that the Watchman device may be not inferior to use of warfarin for preventing stroke among patients with nonvalvular AF. Larger RCTs and longer follow-up are needed to confirm these findings. Evidence from two small nonrandomized comparative studies is too weak to draw conclusions about how well the Watchman device compares with other minimally invasive LAA closure devices in stroke prevention among patients with nonvalvular AF. High-quality RCTs are required to address such comparison. Several clinical trials are in progress (ECRI, 2015; updated 2016).

A NICE guideline states that current evidence suggests that percutaneous occlusion of the LAA is efficacious in reducing the risk of thromboembolic complications associated with non-valvular AF. With regard to safety, there is a risk of life-threatening complications from the procedure, but the incidence of these is low. Therefore, this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit (NICE, 2010). In a separate report on the management of AF, NICE states that LAA occlusion should not be recommended as an alternative to anticoagulation unless anticoagulation is contraindicated or not well tolerated (NICE, 2014).

Reddy et al. (2017a) evaluated 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial. In patients with AF undergoing LAA closure using the Watchman device, protection against ischemic stroke and systemic embolism was similar to that achieved with warfarin, but LAA closure was associated with substantial reductions in hemorrhagic, disabling and fatal stroke. Further studies are needed to compare the benefit of LAA occlusion against oral anticoagulants other than warfarin in patients with AF, and to assess advantages for those with contraindications to anticoagulation.

The prospective, multicenter EWOLUTION registry (Boersma et al., 2016) reported 30-day periprocedural outcomes with the Watchman device. Implant data were available for 1021 patients at high risk of stroke and moderate-to-high risk of bleeding. The device was successfully implanted in 98.5% of patients with no flow or minimal residual flow achieved in 99.3% of implanted patients. Twenty-eight patients experienced 31 serious AEs (SAEs) within 1 day of the procedure. The most common SAE occurring within 30 days of the procedure was major bleeding requiring transfusion. Incidence of SAEs within 30 days was significantly lower for subjects deemed to be ineligible for OAC therapy compared with those eligible for OAC therapy (6.5 vs. 10.2%). The overall 30-day mortality rate was 0.7%. The authors reported that improvement in implantation techniques has led to a reduction of periprocedural complications previously limiting the net clinical benefit of the procedure. These results are limited by the observational study design and short-term follow-up.

Briceno et al. (2015) conducted a systematic review and meta-analysis evaluating the safety and efficacy of different approaches for preventing stroke in patients with nonvalvular AF. The groups were novel oral anticoagulants, the Watchman LAA occlusion device and warfarin. Efficacy outcomes were stroke or systemic embolism, and all-cause mortality. Safety outcome was major bleeding and procedure-related complications. Seven randomized controlled trials (n=73,978) were included in the analysis. There was a significant difference favoring novel oral anticoagulants for systemic embolism, all-cause mortality and safety outcomes compared with warfarin. No difference was seen between the Watchman device and warfarin for efficacy end points; however, the device had more complications.

PROTECT AF

The PROTECT AF trial included 707 patients with nonvalvular AF who had at least 1 risk factor for stroke. Patients were randomized to chronic warfarin treatment (n=244) or percutaneous placement of the LAA device (n=463). The clinical endpoint of the study was a composite measure of stroke, cardiovascular death and embolism. The safety assessment included serious AEs adverse events, including major bleeding, pericardial effusion and device embolization. After 1065 patient-years of follow-up, the efficacy event rate was 3.0 per 100 patient-years in the device group compared with 4.9 in the warfarin group - a relative reduction of 38%. However, serious safety events were more common in the device group (7.4 events per 100 patient-years) compared with the warfarin group (4.4). Most of these safety events were related to the procedural implant and pericardial effusion. Statistical analysis demonstrated that the LAA was 99.9% unlikely to be inferior to warfarin alone. At 2 years, both treatment groups had a similar intention-to-treat cumulative event rate. Since warfarin therapy is burdensome and carries risks of its own, closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with nonvalvular AF. However, these data likely do not justify routine LAA occlusion in all patients with nonvalvular AF, primarily because the trial did not demonstrate prevention of embolism and stroke in high-risk patients. In addition, the short duration of follow-up does not offer enough information regarding long-term safety and efficacy (Holmes et al., 2009).

In a 2.3 year follow-up to the PROTECT AF trial, Reddy et al. (2013b) reported primary efficacy event rates of 3.0 per 100 patient-years in the Watchman group and 4.3 in the warfarin group. These results met the criteria for noninferiority. There were more primary safety events in the Watchman group (5.5% per year) than in the control group (3.6% per year). After 3.8 years, Reddy et al. (2015) reported primary efficacy event rates of 2.3 per 100-patient-years in the Watchman group and 3.8 in the warfarin group. In this study, the Watchman device met criteria for both noninferiority and superiority, compared with warfarin, for preventing the combined outcome of stroke, systemic embolism and cardiovascular death, as well as superiority for cardiovascular and all-cause mortality. Patients in the device group had lower rates of both cardiovascular and all-cause mortality.

The PROTECT AF study reported that serious safety events were more common in the device group compared with the warfarin group. Using a cohort of patients in the PROTECT AF trial who underwent attempted LAA closure with the Watchman device (n=542) and those from a subsequent nonrandomized registry (Continued Access Registry) of patients undergoing Watchman implantation (n=460), Reddy et al. (2011) reported a significant improvement in the safety of the Watchman device with increased operator experience.

PREVAIL

The PREVAIL study (Holmes et al., 2014) is a multicenter, prospective randomized controlled trial to further assess the safety and efficacy of LAA occlusion using the Watchman device for stroke prevention compared with long-term warfarin therapy. Patients with nonvalvular AF who had a CHADS₂ (congestive heart failure, hypertension, age >75 years, diabetes mellitus and previous stroke/transient ischemic attack) score ≥ 2 or 1 and another risk factor were eligible. Patients were randomly assigned (in a 2:1 ratio) to undergo LAA occlusion and subsequent discontinuation of warfarin (n=269) or receive chronic warfarin therapy (n=138). There were three primary endpoints (two effectiveness and one safety): 1) the composite of ischemic stroke, hemorrhagic stroke, systemic embolism and cardiovascular or unexplained death; 2) the composite of ischemic stroke and systemic embolism, excluding events occurring in the first 7 days following randomization; and 3) the occurrence of all-cause mortality, ischemic stroke, systemic embolism or device or procedure-related events requiring open cardiac surgery or major endovascular intervention between the time of randomization and 7 days of the procedure or by hospital discharge, whichever is later. Due to the low overall trial event rates, there was limited power with the planned sample size to establish noninferiority for the primary efficacy endpoint. At 18 months, LAA occlusion was noninferior to warfarin for the second primary efficacy endpoint. Event rates were low and comparable in both arms. Early safety events occurred in 2.2% of the Watchman arm, significantly lower than in PROTECT AF, satisfying the safety performance goal. Using a broader, more inclusive definition of adverse effects, these still were lower in the PREVAIL trial than in PROTECT AF (4.2% versus 8.7%). Pericardial effusions requiring surgical repair decreased from 1.6% to 0.4%, and those requiring pericardiocentesis decreased from 2.9% to 1.5%. The authors concluded that these results provide additional data that LAA occlusion is a reasonable alternative to warfarin therapy for stroke prevention in patients with nonvalvular AF who do not have an absolute contraindication to short-term warfarin therapy.

In both the PROTECT AF and PREVAIL trials, patients were required to be candidates for long-term anticoagulation to facilitate randomization against a control group treated with warfarin. Neither study addressed the safety and efficacy of LAA occlusion in patients for whom anticoagulation is contraindicated. Additionally, neither study compared the safety and efficacy of the Watchman device with new oral anticoagulants.

Holmes et al. (2015) performed a meta-analysis on composite data from the PROTECT AF and PREVAIL trials and their respective registries comparing warfarin to the Watchman device for the prevention of stroke, systemic embolism and cardiovascular death in patients with nonvalvular AF. The analysis included 2,406 patients with 5,931 patient-years of follow-up. A total of 1,877 patients were treated with Watchman (1,145 registry patients) and 382 received warfarin. Patients receiving the Watchman device had significantly fewer hemorrhagic strokes, cardiovascular/unexplained death and nonprocedural bleeding compared with warfarin; however, there were more ischemic strokes in the device group. All-cause stroke or systemic embolism was similar between both strategies. The composite efficacy endpoint favored the Watchman patients, but did not reach statistical significance. The authors reported that further studies are needed to define risk thresholds for thromboembolism and bleeding at which patients with AF benefit from LAA occlusion therapy for stroke prevention and to compare the safety and efficacy of this strategy with target-specific oral anticoagulant agents.

ASAP

In the ASAP trial, Reddy et al. (2013a) conducted a multicenter, observational study to assess the safety and efficacy of the Watchman LAA closure device in nonvalvular AF patients (n=150) ineligible for warfarin therapy. The primary efficacy endpoint was the combined events of ischemic stroke, hemorrhagic stroke, systemic embolism and cardiovascular/unexplained death. History of hemorrhagic/bleeding tendencies (93%) was the most common reason for warfarin ineligibility. Serious procedure- or device-related safety events occurred in 13 patients (8.7%). All-cause stroke or systemic embolism occurred in 4 patients (2.3% per year): ischemic stroke in 3 patients (1.7% per year) and hemorrhagic stroke in 1 patient (0.6% per year). The authors concluded that the Watchman device is a reasonable alternative for patients at high risk for stroke but with contraindications to systemic oral anticoagulation. This study is limited by lack of randomization and control.

Reddy et al. (2017b) evaluated the acute procedural performance and complication rates for all Watchman implants performed in the United States since FDA approval. In 3,822 consecutive cases, implantation was successful in 3,653 patients (95.6%), with a median procedure time of 50 minutes. Implanting physicians (n=382) included 71% new, nonclinical trial implanters, who performed 50% of the procedures. Procedural complication rates included 39 pericardial tamponades (1.02%) (24 treated percutaneously, 12 surgically and 3 fatal); 3 procedure-related strokes (0.078%); 9 device embolizations (0.24%) (6 requiring surgical removal); and 3 procedure-related deaths (0.078%).

Joint guidelines from the American Heart Association (AHA), American College of Cardiology (ACC) and Heart Rhythm Society (HRS) address percutaneous occlusion of the LAA but do not provide specific recommendations regarding the use of these devices (January et al., 2014).

The ACC, HRS and Society for Cardiovascular Angiography and Interventions (SCAI) published a societal overview addressing issues critical to the appropriate integration of new technologies, such as the Watchman device, into the care of patients with AF. The authors urge that new technologies be disseminated thoughtfully, with emphasis on team-based care and the collection of the necessary data in longitudinal registries to determine ideal patient selection, effectiveness and safety (Masoudi et al., 2015). This same group also published an expert consensus document outlining institutional and operator recommendations for the establishment and maintenance of LAA occlusion programs (Kavinsky et al., 2016).

European Society of Cardiology (ESC) guidelines for the management of AF state that LAA occlusion may be considered in select patients, but the efficacy is less well established. Adequately powered controlled trials are urgently needed to inform the best use of LAA occlusion devices (Kirchhof et al., 2016).

American College of Chest Physicians (ACCP) clinical practice guidelines on antithrombotic therapy for the prevention of stroke in patients with AF make no formal recommendations regarding LAA closure devices and state that more definitive research is needed (You et al., 2012).

Additional Product Information

- Amplatzer® Cardiac Plug (St. Jude Medical) – not FDA approved at this time
- Amplatzer™ Amulet™ Left Atrial Appendage Occluder (St. Jude Medical) - not FDA approved at this time
- Watchman FLX – not FDA approved at this time

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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

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 emerging 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.

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. GVHD, 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 and cost-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 probe-based CLE (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.

Maes, et al. reviewed several screening and surveillance techniques for BE including chromoendoscopy, narrow band imaging, autofluorescence imaging and CLE, pointing out the areas that are well established as well as the new techniques that require more research. The major problem with all the studies that assessed the potential of advanced imaging techniques in BE is that they all were performed by expert endoscopists in tertiary referral centers with an enriched population with regard to the proportion of patients with dysplasia. The authors therefore concluded that, despite recent and promising developments in advanced imaging techniques, there currently is no evidence that they provide significant advantage in diagnosis or therapy decision making (2016).

In its guidelines on diagnosis and management of BE, the American College of Gastroenterology (ACG) states that routine use of advanced imaging techniques other than electronic chromoendoscopy is not recommended for endoscopic surveillance at this time. This recommendation is considered conditional, based on a very low level of evidence (Shaheen, et al., 2016).

In a review of endoscopic modalities for the diagnosis of BE, Sharma et al. cite the primary advantage of pCLE as being able to target abnormal tissue for biopsy therefore reducing the incidence of random sampling. However, the technical design of the instrument itself may hinder the targeted approach. The authors also stated that a high level of expertise with this technology is required of the physician in order to accurately interpret diagnostic findings (2016).

In a review of probe- and needle-based (n)CLE for pancreaticobiliary disease, Karia and Kahaleh concluded that CLE has been shown in multiple studies to be safe and effective at providing useful diagnostic information at the time of ERCP and endoscopic ultrasound (EUS). pCLE has been shown to have higher performance characteristics in the evaluation of indeterminate pancreaticobiliary strictures compared to endoscopic brush cytology and intraductal biopsy, possibly decreasing cost by reducing the need for repeat procedures. nCLE, though not as extensively studied as pCLE, has shown promise. Further studies are needed (2016).

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).

An interventional trial (NCT02057146) with 50 participants to assess the usefulness of probe based confocal laser endomicroscopy in the evaluation of suspected premalignant lesions in the biliary duct and pancreas was completed in December 2018. Results are pending. For more information, go to: www.clinicaltrials.gov (Accessed April 15, 2019).

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Code	Description
48160	Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells
48999	Unlisted procedure, pancreas
60659	Unlisted laparoscopy procedure, endocrine system
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
S2102	Islet cell tissue transplant from pancreas; allogeneic

Autologous pancreatic islet cell transplantation following total pancreatectomy for non-malignant conditions is proven and medically necessary per the UnitedHealth Group [Transplant Review Guidelines](#).

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 autotransplantation (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 preoperation 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 autotransplantation 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.

Results of a Hayes 2018 report of reviewed studies suggest that islet autotransplantation after total pancreatectomy (TP/IAT) may be associated with durable improvements in pain incidence and severity, reductions in use of narcotics for pain relief, and improvements in health-related quality of life, patient-reported health, and activities of daily living, while maintaining glycemic control and insulin independence in many cases. Despite the limitations of the available evidence, TP/IAT may be the only viable option for patients with CP with debilitating symptoms who have exhausted all available standard therapies.

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.

Wu et al. (2015) conducted a systematic review and meta-analysis of islet autotransplantation (IAT) after total pancreatectomy (TP) in chronic pancreatitis patients. Twelve studies reporting the outcomes of 677 patients were included in the review. The insulin independence rate at 1 year follow-up was 28.4% of 362 patients reported by five studies. The insulin independence rate at 2 year follow-up was 19.7% of 297 patients reported by three studies. The insulin independent rate for islet autotransplantation after total pancreatectomy at last follow-up was 3.72 per 100 person-years. The 30-day mortality was 2.1% and the mortality at last follow-up was 1.09 per 100 person-years. The authors concluded that islet autotransplantation is a safe modality for patients with chronic pancreatitis who need to undergo TP. A significant number of patients will achieve insulin independence for a long time after receiving enough IAT.

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.

Georgiev et al. (2015) assessed patient QOL and pain after pancreatectomy with autologous islet transplantation (TPAIT) for the treatment of chronic pancreatitis in 53 patients at the University of Arizona. The Rand SF-36 and McGill pain questionnaires and Visual Analogue Scale were used to assess patients preoperatively for QOL and pain resulting from life with chronic pancreatitis. After undergoing TPAIT, patients were followed with surveys administered at 1 month, 6 months, and 1 year to evaluate changes in their QOL and pain experienced. Significant improvement was reported in all components of every questionnaire within a year after surgery. Patient reported mean scores on QOL were found to fall within the range of the general population. The authors concluded that with TPAIT, patients reported a higher QOL when compared to preoperative values, as well as reduced levels of pain.

Bramis et al. (2012) performed a systematic review of the literature to evaluate the outcome of total pancreatectomy and islet autotransplantation for chronic pancreatitis. Five studies were included. TP/IAT was successful in reducing pain in patients with chronic pancreatitis. Comparing morphine requirements before and after the procedure, two studies recorded significant reductions. Concurrent IAT reduced the insulin requirement after TP. The impact on QOL was poorly reported.

The American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2019) states that islet autotransplantation 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 autotransplantation.

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Code	Description
53855	Insertion of a temporary prostatic urethral stent, including urethral measurement

The insertion of a temporary prostatic urethral stent is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Temporary urethral stents are either removable or absorbable. Temporary urethral stents include the Memokath™ and the Spanner® Temporary Prostatic Stent.

The Spanner® Temporary Prostatic Stent is intended for temporary use (up to 30 days) to maintain urine flow and allow voluntary urination in patients following minimally invasive treatment for benign prostatic hyperplasia (BPH) and after initial post-treatment catheterization. Alternative practices and procedures to The Spanner use include Foley catheterization, clean intermittent self-catheterization, suprapubic catheterization, and no catheterization.

The Spanner® Prostatic Stent is a temporary urethral endoprosthesis intended to relieve postoperative lower urinary tract symptoms (LUTS) in patients who undergo thermotherapy to treat an enlarged prostate. Spanner supports the urethra to prevent swollen tissue from blocking urinary flow and may be placed for up to a month before removal. Spanner is intended to also lower infection risks and preserve urinary control and sexual function when used instead of indwelling catheters or intermittent catheterization after transurethral microwave thermotherapy (TUMT) or similar procedures (ECRI, 2018).

The U.S. Food and Drug Administration (FDA) approved the Spanner® Temporary Prostatic Stent on December 14, 2006. Refer to the following website for additional information:

- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p060010
- www.accessdata.fda.gov/cdrh_docs/pdf6/p060010a.pdf

(Accessed April 2, 2019)

The Memokath has not yet received FDA approval.

Porpiglia et al. (2018) reported 3-year outcomes from a prospective study involving the temporary implantable nitinol device implantation for the treatment of BPH. Thirty-two patients with LUTS were enrolled. Follow-up assessments were made at 3 and 6 weeks, and 3, 6, 12, 24 and 36 months after the implantation. The change from baseline in IPSS, QOL score and Q_{max} was significant at every follow-up time point. After 36 months of follow-up, a 41% rise in Q_{max} was achieved (mean 10.1 mL/s), the median (IQR) IPSS was 12 (6-24) and the IPSS QoL was 2 (1-4). Four early complications (12.5%) were recorded, including one case of urinary retention (3.1%), one case of transient incontinence due to device displacement (3.1%), and two cases of infection (6.2%). No further complications were recorded during the 36-month follow-up. In the authors' opinion, the extended follow-up period supports the temporary stent to be safe, effective, and well-tolerated. Lack of randomization and small patient population are limitations to this study.

Kim et al. (2014) conducted a small controlled trial (n=27) to compare those patients who received treatment with a Memokath stent and a self-expandable covered metallic stent (UVENTA) for managing ureteral obstructions. Study results showed no significant differences between the two types of stents for benign and malignant ureteral obstructions. However, the clinical success rate was higher for the UVENTA stent (82.4%) compared with the Memokath stent (42.9%) (P=0.031). Patients who received the Memokath stent experienced tumor progression (n=2), stent migration (n=6), flank pain (n=1), and acute pyelonephritis (n=1).

Kimata et al. (2015) conducted a small prospective case series (n=37 elderly male patients) to evaluate the use of the Memokath in patients who required long-term urination management with Foley catheters. Patients were followed for a mean of approximately 33 months. A total of 21 patients (56.7%) were able to urinate without assistance after insertion of the Memokath stent. This study was hampered by several limitations, including lack of randomization and appropriate control group.

Following transurethral microwave thermotherapy, 186 patients were randomized to receive a Spanner (n=100) or the standard of care (n=86). The stent group reported significantly superior improvement in symptoms at the one week follow-up visit. Thereafter, there was no significant difference between the stent and control groups. The investigators concluded that the Spanner is a safe, effective and well tolerated temporary stent for severe prostatic obstruction resulting from therapy induced edema after transurethral microwave thermotherapy (Dineen et al., 2008). Shore et al. published the same study in 2007. The study results are limited in demonstrating meaningful improvement in clinical outcomes in the group that received the temporary prostatic stent compared to the patients in the control group.

Jordan et al. (2013) investigated the ability of the Memokath™ 044TW stent to maintain urethral patency after dilation or internal urethrotomy for recurrent urethral stricture. A total of 92 patients with recurrent bulbar urethral strictures were treated with dilation or internal urethrotomy and randomized to short-term urethral catheter diversion (n=29) or insertion of a Memokath 044TW stent (n=63). The primary end point was urethral patency, as assessed by passage of a calibrated endoscope. Secondary end points included urinary symptoms and uroflowmetry parameters. Stents were scheduled to remain in situ for 12 months. The rate of successful stent insertion was 93.6%. In stented patients, patency was maintained significantly longer than controls (median 292 vs 84 days). Patency was reflected in significantly improved uroflowmetry and symptom scores. The stent was removed in 100% of patients. The most frequently noted side effects in stented patients were bacteriuria, hematuria and penile pain, which were usually mild and transient. Stent dislocation and occlusion were observed in 8 and 3 patients, respectively. The authors concluded that patients with recurrent bulbar urethral strictures treated with dilation or urethrotomy and a Memokath 044TW stent maintained urethral patency significantly longer than those treated with dilation or urethrotomy alone. Given the lack of FDA approval for the Memokath stent, these data are insufficient to draw conclusions regarding the use of this device.

Goh et al. (2013) assessed the ease of insertion and removal of a temporary prostatic stent (the Spanner) following the use of a prostatic urethral measuring device (the Surveyor™) in patients with bladder outflow obstruction or urinary retention awaiting definitive surgery. 16 patients had the Spanner inserted following use of the Surveyor. All insertions were uncomplicated. No symptomatic infection was reported. The stents stayed in situ for a median of 10 days. 12 stents were removed prematurely due to severe symptoms or retention. A total of 12 stents had to be removed endoscopically. The authors concluded that the Spanner is easy to insert. Stent removal via the retrieval suture has been difficult necessitating the use of endoscopy in the majority of cases. Possible causes of stent failure include underestimation of the prostatic urethral length by the Surveyor leading to obstruction by apical prostatic tissue, excessive suture length between the stent and distal anchor permitting proximal migration or inadequate suture length leading to urinary incontinence. According to the authors, further design modifications are suggested.

Egilmez et al. (2006) evaluated the efficacy of intraurethral metal stents in preventing or eradicating urinary-tract infections (UTI) during the management of bladder outlet obstruction (BOO) by comparing the frequency and nature of the infections with indwelling-catheter-associated UTI. The SAS relative-risk test was used to compare the risks of UTI in 76 patients with temporary urethral stents, 60 patients with BOO who had never been catheterized nor stented, and 34 patients with a permanent indwelling urethral catheter (PIUC). Infection was assessed 1 month after placement of the devices. After insertion of the catheter, UTI developed in 79.4% of the patients who originally had sterile urine. However, after insertion of the stent, UTI developed in only 40.9% of the patients with sterile urine. In 21 (44.6%) of the catheterized patients who had infected urine, UTI was eradicated after stent insertion. The investigators concluded that urinary infection is a significant problem in patients with PIUC but is significantly less frequent and less severe in patients with urethral stents. These findings require confirmation in large controlled trials.

A series of 43 consecutive patients were stented with the Spanner temporary prostatic stent and reviewed retrospectively. Stents were removed and replaced every 3 months if tolerated. More than half of the patients (63%) had an unsatisfactory outcome, namely, immediate or delayed retention or elective removal because of unbearable symptoms. The remaining 37% of patients had a satisfactory outcome and either continued to have the stent in situ after a mean of five changes or are stent free after a successful voiding trial (Grimsley et al., 2007).

The American Urological Association's clinical guideline for the surgical management of LUTS attributed to BPH does not make a specific recommendation for or against temporary stents (Foster et al., 2018).

The National Institute for Health and Care Excellence (NICE) 2018 medical technology guidance on use of the Memokath-051 stent for ureteric obstruction concludes that the quality of reporting across all the studies was generally poor. None of the studies provided adequate details on patient characteristics, stent insertion procedures, follow-up, statistical analyses and uncertainty around the results. Migration rates and clinical success were the most commonly reported outcomes but definitions of clinical success varied, so statistical pooling could not be done.

ClinicalTrials.gov shows an ongoing trial on the use of the Spanner Temporary Prostatic Stent as an alternative to a urinary catheter to achieve bladder drainage in men (NCT02643849).

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Code	Description
53899	Unlisted procedure, urinary system (when used to report UroCuff)

Due to insufficient evidence of safety and/or efficacy, the UroCuff test for diagnosing male lower urinary tract disorders is unproven and not medically necessary.

Clinical Evidence

The UroCuff (SRS Medical, North Billerica, MA) is a diagnostic test for male lower urinary tract disorders (LUTS). Bladder pressure is measured noninvasively with a penile cuff (resembling a blood pressure cuff) instead of a catheter. Optionally, one or two surface EMG electrodes may be applied to the patient to monitor skeletal (sphincter or abdominal) muscle activity during testing. The UroCuff test is intended as an adjunct to a conventional flow study. While it is not a replacement for cystometry (which still remains the best gold standard), the UroCuff gives information on bladder contraction pressure and it can be used in some cases to confirm the likely diagnosis of obstruction, while avoiding the need for full cystometry.

The UroCuff is considered by the FDA to be a Class I device and is 510(k) exempt.

A systematic review by Malde and colleagues (2017) evaluated the performance of noninvasive tests in diagnosing bladder outlet obstruction (BOO) in men with LUTS. Of 2774 potentially relevant reports, 42 were eligible (n=4444 patients). The review revealed that according to the literature, a number of noninvasive tests have high sensitivity and specificity in diagnosing BOO in men. However, although the quality of evidence was typically moderate across the literature with a low overall risk of bias, the available evidence is limited by heterogeneity. While several tests have shown promising results regarding noninvasive assessment of BOO, invasive urodynamics remain the gold standard. The researchers concluded that noninvasive alternatives to standard urodynamic testing appear to be promising but were not equally accurate. Further research is needed before these tests are routinely used in place of urodynamics.

Matulewicz and Hairston compared the UroCuff test to invasive pressure flow studies (PFS) in 19 adult males with LUTS. Standard PFS were performed followed immediately by a penile cuff test (PCT) in the same test setting. Using PFS as the gold standard, the positive predictive value of the UroCuff PCT to diagnose BOO was found to be 92%. The sensitivity of the UroCuff test for detecting BOO was 75%. When compared to PFS, patients preferred the UroCuff 100% of the time. The researchers concluded that the UroCuff test was accurate in predicting BOO when compared to conventional invasive PFS in men with LUTS. It was well tolerated and preferred over standard PFS (2015).

Borrini et al. (2012) conducted a monocentric prospective study in 30 consecutive men presenting with LUTS to assess the diagnostic performances and the acceptability of the PCT in comparison with the PFS, the actual gold-standard, when diagnosing BOO. The "obstructed positive predictive value" of the PCT was 82% and the "non-obstructed-equivocal negative predictive value" was 88% compared with the PFS group at 39% and 22%, respectively.

The PFS group also had 39% with equivocal findings and 61% classified in both categories. The authors concluded that PCT was a reliable non-invasive tool for the diagnosis of BOO in male, in comparison with PFS. The predictive values of the PCT were relevant and it was very well tolerated.

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SRS Medical, North Billerica, MA. Website. Accessed May 20, 2019.

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

The transperineal placement of biodegradable material, peri-prostatic (via needle) is proven and medically necessary for use with radiotherapy for treating prostate cancer.

The transperineal placement of biodegradable material, peri-prostatic (via needle) is unproven and not medically necessary for all other indications due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The SpaceOAR™ System (Augmenix Inc., Waltham, MA) hydrogel spacer was cleared for marketing by the FDA through the 513(a) (1) (de novo) process on April 1, 2015. This FDA approval classifies the SpaceOAR System, and substantially equivalent devices of this generic type, into class II under the generic name, "Absorbable perirectal spacer" and product code OVB.

The SpaceOAR is used to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent to reduce the radiation dose delivered to the anterior rectum. The absorbable spacer maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time. For a complete list of indications and contraindications, refer to the Decision Summary at the following website:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN140030>. (Accessed April 2, 2019)

Paetkau et al. (2019) retrospectively evaluated 13 patients with SpaceOAR implant to determine future planning needs for patients with prostate cancer undergoing radiation therapy. Computerized tomography (CT) scans were taken pre- and post-implant. A prescription of 60 Gy in 20 fractions was planned on both scans. Six treatment plans were produced per anonymized dataset using either a structure of rectum plus the hydrogel, termed composite rectum wall (CRW), or rectal wall (RW) as an inverse optimization structure and intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) as a treatment technique. Dose-volume histogram metrics were compared between plans to determine which optimization structure and treatment technique offered the maximum rectal dose sparing. RW structures offered a statistically significant decrease in rectal dose over CRW structures, whereas the treatment technique (IMRT vs VMAT) did not significantly affect the rectal dose. There was improvement seen in bladder and penile bulb dose when VMAT was used as a treatment technique. The authors concluded that overall, treatment plans using the RW optimization structure offered the lowest rectal dose while VMAT treatment technique offered the lowest bladder and penile bulb dose.

Wu et al. (2018) evaluated 18 consecutive patients underwent transperineal ultrasound-guided placement of 10 cc of SpaceOAR hydrogel prior to HDR brachytherapy in the treatment of prostate cancer. Treatment plans were generated using an inverse planning simulated annealing algorithm. Rectal dosimetry for these 18 patients was compared with the 36 preceding patients treated with HDR brachytherapy without SpaceOAR. There was no difference in age, pretreatment prostate-specific antigen, Gleason score, clinical stage, prostate volume, or contoured rectal volume between those who received SpaceOAR and those who did not. Patients who received SpaceOAR hydrogel had significantly lower dose to the rectum as measured by percent of contoured organ at risk (median, V₈₀ < 0.005% vs. 0.010%, p = 0.003; V₇₅ < 0.005% vs. 0.14%, p < 0.0005; V₇₀ 0.09% vs. 0.88%, p < 0.0005; V₆₀ = 1.16% vs. 3.08%, p < 0.0005); similar results were seen for rectal volume in cubic centimeters. One patient who received SpaceOAR developed a perineal abscess 1 month after treatment. The authors concluded that transperineal insertion of SpaceOAR hydrogel at the time of HDR brachytherapy is feasible and decreases rectal radiation dose. Further investigation is needed with well-designed clinical trials and larger patient populations to further assess the clinical impact.

Chao et al. (2018) conducted a prospective analysis to report on the dosimetric benefits and late toxicity outcomes following injection of a hydrogel spacer between the prostate and rectum in 76 patients with T1-T3a prostate cancer treated with radiotherapy. There were no postoperative complications reported. Mean prostate size were 66.0cc (25.0cc - 187.0cc). Rectal dose volume parameters were observed with volume of rectum receiving 70Gy (rV70), 75Gy (rV75) and 78Gy (rV78) were 7.8%, 3.6% and 0.4%. 21% (16/76) developed acute grade 1 GI toxicities but all were resolved completely by 3 months post-treatment. 3% (2/76) developed late grade 1 GI toxicities. No patients experienced acute or late grade 2+ GI toxicities. The authors concluded that injection of hydrogel spacer resulted in a reduction of irradiated rectal dose volumes along with minimal GI toxicities, irrespective of prostate size. Additional studies with longer-term outcomes are needed to evaluate long-term toxicities.

Taggar et al. (2018) conducted a prospective study to evaluate placement of an absorbable rectal hydrogel spacer in 74 patients with prostate cancer undergoing low-dose-rate brachytherapy with palladium-103. Rectal dosimetry was compared with a consecutive cohort of 136 patients treated with seed implantation without a spacer. On average, 11.2-mm (SD 3.3) separation was achieved between the prostate and the rectum. The resultant mean rectal volume receiving 100% of prescribed dose (V100%), dose to 1 cc of rectum (D1cc), and dose to 2 cc of rectum (D2cc) were 0 (SD 0.05 cc), 25.3% (SD 12.7), and 20.5% (SD 9.9), respectively. All rectal dosimetric parameters improved significantly for the cohort with spacer placement as compared with the non-spacer cohort. Injection of rectal spacer is feasible in the post-LDR brachytherapy setting and reduces dose to the rectum with minimal toxicity. Prostate and urethral dosimetries do not appear to be affected by the placement of a spacer.

Pinkawa et al. (2017a) reported 5-year outcomes after prostate cancer radiation therapy with and without the use of a hydrogel spacer. Fifty-four patients were selected to receive a hydrogel spacer. Patients were surveyed before RT; at the last day of RT; and a median time of 2 months, 17 months, and 63 months after RT. For patients treated with a hydrogel spacer, mean bowel function and bother score changes of >5 points in comparison with baseline levels were found only at the end of RT (10-15 points; $P < .01$). No spacer patient reported moderate or big problems with his bowel habits overall. Mean bother score changes of 21 points at the end of RT, 8 points at 2 months, 7 points at 17 months, and 6 points at 63 months after RT were found for patients treated without a spacer. A bowel bother score change >10 points was found in 6% versus 32% ($P < .01$) at 17 months and in 5% versus 14% ($P = .2$) at 63 months with versus without a spacer. The authors conclude that hydrogel spacer application demonstrates excellent treatment tolerability, in particular regarding bowel problems. They encourage further studies with dose-escalated or re-irradiation concepts.

Pinkawa et al. (2017b) evaluated 167 consecutive patients who received prostate RT with 2-Gy fractions up to 76 Gy (without hydrogel, $n = 66$) or 76-80 Gy (with hydrogel, $n = 101$) were included. The numbers of interventions resulting from bowel problems during the first 2 years after RT were compared. Patients were surveyed prospectively before RT, at the last day of RT, and at a median of 2 and 17 months after RT using a validated questionnaire (Expanded Prostate Cancer Index Composite). Treatment for bowel symptoms (0 vs. 11%; $p < 0.01$) and endoscopic examinations (3 vs. 19%; $p < 0.01$) were performed less frequently with a spacer. Mean bowel function scores did not change for patients with a spacer in contrast to patients without a spacer (mean decrease of 5 points) >1 year after RT in comparison to baseline, with 0 vs. 12% reporting a new moderate/big problem with passing stools ($p < 0.01$). It was noted that statistically significant differences were found for the items "loose stools", "bloody stools", "painful bowel movements" and "frequency of bowel movements". The authors concluded that spacer injection is associated with a significant benefit for patients after prostate cancer RT.

Hamstra et al. (2017) reported the final outcomes from their single-blind phase III trial of image guided intensity modulated radiation therapy ($n=222$). The 3-year incidence of grade ≥ 1 (9.2% vs 2.0%; $P=.028$) and grade ≥ 2 (5.7% vs 0%; $P=.012$) rectal toxicity favored the spacer arm. Grade ≥ 1 urinary incontinence was also lower in the spacer arm (15% vs 4%; $P=.046$), with no difference in grade ≥ 2 urinary toxicity (7% vs 7%; $P=0.7$). From 6 months onward, bowel QOL consistently favored the spacer group ($P=.002$), with the difference at 3 years (5.8 points; $P < .05$) meeting the threshold for a MID. The control group the authors reported that the benefit of a hydrogel spacer in reducing the rectal dose, toxicity, and QOL declines after image guided intensity modulated radiation therapy for prostate cancer was maintained or increased with a longer follow-up period, providing stronger evidence for the benefit of hydrogel spacer use in prostate radiation therapy. Additional long-term outcomes are needed to determine the benefits of hydrogel spacers.

In a prospective, randomized patient-blinded clinical study, Karsh et al. (2017) compared image-guided intensity modulated prostate radiotherapy (79.2Gy in 44 fractions) in men with or without insertion of prostate-rectum hydrogel spacer (SpaceOar). The mean additional space created between the prostate and the rectum was just over 1cm, which allowed significant rectum and penile bulb radiation dose reduction resulting in less acute pain, lower rates of late rectal toxicity, and improved bowel and urinary QOL scores from 6 months through the 3-year follow-up period as compared to the control group. The authors concluded that spacer application significantly reduced rectal radiation

dose, resulting in long-term reductions in rectal toxicity, as well as improvements in bowel, urinary, and sexual QOL. Patient sample volumes were not reported.

Hedrick et al. (2017a) evaluated 10 patients (662 fields throughout treatment) treated daily with an endorectal balloon (ERB) and 16 patients (840 fields throughout treatment) treated with a hydrogel spacer (GEL) without an ERB. They concluded that prostate motion is clinically comparable between an ERB and a hydrogel spacer, and the time dependencies are similar.

Hedrick et al. (2017b) investigated the consistency of rectal sparing using multiple periodic quality assurance computerized tomography imaging scans (QACT) obtained during the course of proton therapy for patients with prostate cancer treated with a hydrogel spacer. Forty-one low- and intermediate-risk prostate cancer patients treated with image-guided proton therapy with rectal spacer hydrogel were analyzed. To assess the reproducibility of rectal sparing with the hydrogel spacer, three to four QACTs were performed for each patient on day 1 and during weeks 1, 3, and 5 of treatment. Each patient was set up in the treatment position and scanned. These QACTs were performed either immediately before or after the patient's treatment, so bladder filling was not necessarily at the ideal volume for treatment. The authors concluded that the use of hydrogel in conjunction with a diet program and use of stool softeners is effective in achieving consistent rectal sparing in patients undergoing proton therapy. However, they stated the limitations of this study to be that analysis only considered three to four time points in each patient's treatment, and a single QACT is not necessarily representative of the entire treatment. In addition, QACTs were obtained off-line and not temporally coincident with treatment delivery.

Jones et al. (2017) compared the rectal-sparing capabilities of rectal balloons (n=36) vs. absorbable injectable spacer gel in stereotactic body radiation therapy (SBRT) for prostate cancer. Treatment prescription dose was 45Gy in 5 fractions in 42 patients; for equal comparison, the remaining 30 patients were rescaled to 45Gy from 47.5Gy prescription (n=6) and 50Gy prescription (n=24). The injectable spacer gel outperformed the rectal balloon in the majority of the examined and relevant dosimetric rectal-sparing parameters. The rectal balloon did not outperform the injectable spacer gel in any measured rectal dose parameter.

Mariados et al. (2015) conducted a prospective multicenter randomized controlled pivotal trial to assess outcomes following absorbable spacer (SpaceOAR system) implantation. The study included 222 patients with clinical stage T1 or T2 prostate cancer who underwent computed tomography (CT) and magnetic resonance imaging (MRI) scans for treatment planning, followed with fiducial marker placement. Patients were randomized to receive spacer injection or no injection (control). Spacer safety and impact on rectal irradiation, toxicity, and QOL were assessed throughout 15 months. Spacer application had a 99% hydrogel placement success rate. The authors reported that there were no device-related AEs, rectal perforations, serious bleeding, or infections within either group. Overall acute rectal adverse event rates were similar between groups, with fewer spacer patients experiencing rectal pain (P=.02). There was no late rectal toxicity greater than grade 1 in the spacer group. At 15 months 11.6% and 21.4% of spacer and control patients, respectively, experienced 10-point declines in bowel QOL. MRI scans at 12 months verified spacer absorption. The authors concluded that spacer application was well tolerated. Increased perirectal space reduced rectal irradiation, reduced rectal toxicity severity, and decreased rates of patients experiencing declines in bowel QOL. The spacer appears to be an effective tool, potentially enabling advanced prostate radiation therapy protocols. However, the short follow-up period is a study limitation, as researchers have published the median time to late gastrointestinal grade >2 toxicity onset was 17 months (20). The study was also limited by the exclusion of patients with prostate volumes >80 mL, patients with extracapsular extension, and those with prior radiation or surgery. Patients with extracapsular extension have the theoretical risk of pushing posterior extracapsular disease farther from the prostate during radiation therapy, whereas patients with prior radiation or surgery may have perirectal scar formation, limiting space creation. The authors noted that the use of spacers in these populations should proceed cautiously in separate clinical trials.

Eckert et al. (2013) conducted a prospective study (n = 11) for evaluation of acute and chronic toxicity of IMRT to 78 Gy to the target volume by using the hydrogel spacer SpaceOAR™ for rectal separation. All patients had histologically confirmed, organ confined (T1-2 N0 M0) adenocarcinoma of the prostate (Gleason score 6-7, PSA levels below 20 ng/ml). After insertion of the hydrogel spacer, a subsequent MRI scan was performed to facilitate the radiation planning process by easy visualization of the hydrogel spacer. The authors concluded that the study was able to demonstrate the applicability of dose-escalated IMRT with limited radiation doses to the rectum. The decrease in rectal dose was associated with only mild rectal acute toxicity (no grade 2 or higher) which completely resolved after three months. This may result in a low rate of late toxicity. However, further evaluation is necessary including the definition of patients who might benefit from this approach, as well as a larger patient population.

Yeh et al. (2016) studied rectal toxicity rates in 326 patients administered a polyethylene glycol (PEG) hydrogel rectal spacer in conjunction with combination high-dose-rate brachytherapy at 16 Gy (average dose 15.5 Gy; standard deviation [SD] = 1.6 Gy) and external beam radiotherapy of 59.4 Gy (average dose 60.2 Gy; SD = 2.9 Gy). Clinical efficacy was determined by measuring acute and chronic rectal toxicity using the National Cancer Center Institute

Common Terminology Criteria for Adverse Events v4.0 grading scheme. Median followup was 16 months. The mean anterior-posterior separation achieved was 1.6 cm (SD = 0.4 cm). Rates of acute Grade 1 and 2 rectal toxicity were 37.4% and 2.8%, respectively. There were no acute Grade 3/4 toxicities. Rates of late Grade 1, 2, and 3 rectal toxicity were 12.7%, 1.4%, and 0.7%, respectively. There were no late Grade 4 toxicities. The authors concluded that acute and chronic rectal toxicities are low despite aggressive dose escalation. Longer term outcomes are needed to evaluate impact.

Tomita et al. (2013) conducted a retrospective study of 241 patients to examine risk factors for late rectal toxicity for localized prostate cancer patients treated with helical tomotherapy (HT). Follow-up was done at regular intervals using the Radiation Therapy Oncology Group grading scale. Tomita et al. summarized these as: Grade 1 toxicity represents minimal side effects not requiring medication for symptom control; Grade 2 toxicity indicates symptoms requiring medication; Grade 3 indicates complications requiring minor surgical intervention (i.e., laser coagulation); and Grade 4 requires hospitalization and major intervention. The time until the occurrence of late toxicity was represented as the period from the start date of helical tomotherapy. The result of this study indicates that the risk of late rectal toxicity correlates with increase in age and the rectal volume exposed to high doses in HT treatment for localized prostate cancer. Further follow-up and data accumulation may establish dose-volume modeling to predict rectal complications after HT.

Serrano et al. (2017) conducted a systematic review to evaluate current perspectives in reducing rectal injury in men receiving prostate cancer radiation therapy. In regard to tissue spacers, they note that with today's IMRT techniques, rectal toxicities are relatively low and, thus, adding tissue spacers to IMRT may have little additional reduction of rectal toxicity. However, these tissue spacers may be more beneficial in men receiving higher doses per fraction such as those on SBRT protocols. SBRT typically involves doses >5 Gy per fraction. The use of these spacers is promising as they show significant reduction in acute and late toxicities. However, longer follow-up is needed to further evaluate their role.

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for the treatment of prostate cancer (v1.2019) states "data suggests that rectal complications may be reduced using biomaterials placed to increase the distance between the rectum and the prostate that degrade after treatment is complete. Perirectal spacer materials may be employed when the other techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient related factors, such as medication usage and/or comorbid conditions. Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation."

A Hayes report (2018) summarized that whether the absorbable perirectal spacer can enable RT dose escalation to improve prostate cancer disease outcomes, the relationship of mild rectal toxicity with QOL, patient selection criteria, and cost-effectiveness are outstanding controversies with this technology.

In a custom product brief, ECRI (2018) concludes that SpaceOAR hydrogel is well tolerated and works as intended to reduce rectal irradiation long-term, but not acute, rectal toxicity, and it improves bowel quality of life (QOL), based on one randomized controlled trial and four prospective nonrandomized comparative studies.

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Code	Description
63268	Laminectomy for excision or evacuation of intraspinal lesion other than neoplasm, extradural; sacral
64999	Unlisted procedure, nervous system [when used to report surgical treatment of a Tarlov cyst not described by 63268]

Surgical treatment (that may include laminectomy and sacral reconstruction) of a Tarlov cyst from the sacrum is proven and medically necessary for patients who experience pain or neurologic symptoms attributed to the Tarlov cyst.

Clinical Evidence

Tarlov cysts are fluid-filled sacs that affect the nerve roots of the spine, especially near the base of the spine (sacral region). Many cases of Tarlov cysts are not associated with symptoms (asymptomatic). However, Tarlov cysts can grow in size eventually compressing or damaging adjacent nerve roots or nerves contained within the cyst (radiculopathy). The specific symptoms and their severity vary from one individual to another and with location along the spinal column. Tarlov cysts are difficult to diagnose because of the limited knowledge about the condition, and because many of the symptoms can mimic other disorders. They are usually diagnosed incidentally, and a specific treatment is not necessary.

Tarlov cysts should be operated on, only if they produce or have disabling neurologic symptoms clearly attributable to them. When these cysts compress nerve roots, they can cause lower back pain, sciatica (shock-like or burning pain in the lower back, buttocks, and down one leg to below the knee), urinary incontinence, headaches, sexual dysfunction, constipation, and some loss of feeling or control of movement in the leg and/or foot. Pressure on the nerves next to the cysts can also cause pain and deterioration of the surrounding bone. Individuals who are candidates for surgery should also have failed an appropriate course of non-operative treatments. (National Organization for Rare Disorders, 2015).

Caspar et al. (2003): There is agreement that symptomatic perineurial sacral cysts should be treated surgically. However, it is still debated whether the preference should be given to the curative option, consisting of excision of the cyst with duraplasty, or to drainage of the cyst to relieve symptoms. In this retrospective study the efficacy of microsurgical cyst resection with duraplasty is evaluated. In 15 patients presenting with pain and neurologic deficits, myelography and/or MRI detected sacral cysts. The clinical features suggested that the space-occupying lesions caused the disturbances. Microsurgical excision of the cyst along with duraplasty or plication of the cyst wall was performed in all the cases. Postoperative care included bed rest and CSF drainage for several days. In 13 out of 15 patients the preoperative radicular pain disappeared after surgery. The 2 patients with motor deficits and the 6 patients with bladder dysfunction recovered completely. In all except 1 of the 10 patients complaining of sensory disturbances a significant improvement was achieved. No complications were observed. Microsurgical excision of the cyst combined with duraplasty or plication of the cyst wall is an effective and safe treatment of symptomatic sacral cysts and, in the view of the authors, the method of choice. This was an uncontrolled retrospective study of extremely small sample size.

Guo et al. (2007) investigated the microsurgical results of symptomatic sacral perineural cysts of 11 patients and to discuss the treatment options of the past 10 years. Nine of the 11 patients (82%) experienced complete or substantial relief of their preoperative symptoms. One patient (Patient 4) experienced worsening of bladder dysfunction after surgery and recovered slowly to subnormal function during the subsequent 2 months. The symptoms of Patient 9 did not resolve, and magnetic resonance imaging showed that the cyst had reoccurred. The patient underwent reoperation 3 months later without any improvement. One patient (Patient 11) experience a cerebrospinal fluid leakage complication. This was an uncontrolled study of extremely small sample size.

Tanaka et al. (2006) investigated the surgical outcomes and indicators for surgical intervention. Twelve consecutive patients harboring symptomatic sacral perineural cysts were treated between 1995 and 2003. All patients were assessed for neurological deficits and pain by neurological examination. The researchers performed a release of the valve and imbrication of the sacral cysts with laminectomies in 8 cases or recapping laminectomies in 4 cases. After surgery, symptoms improved in 10 (83%) of 12 patients, with an average follow-up of 27 months. Ten patients had sacral perineural cysts with signs of positive filling defect. Two (17%) of 12 patients experienced no significant improvement. In one of these patients, the filling defect was negative. In conclusion, a positive filling defect may become an indicator of good treatment outcomes. This was an uncontrolled series of extremely small sample size.

The American Association of Neurological Surgeons (AANS) has no formal position statement regarding tarlov cysts.

Tarlov cysts are sacs filled with cerebrospinal fluid that most often affect nerve roots in the sacrum, the group of bones at the base of the spine. These cysts (also known as meningeal or perineural cysts) can compress nerve roots, causing lower back pain, sciatica (shock-like or burning pain in the lower back, buttocks, and down one leg to below the knee), urinary incontinence, headaches (due to changes in cerebrospinal fluid pressure), constipation, sexual dysfunction, and some loss of feeling or control of movement in the leg and/or foot. Pressure on the nerves next to the cysts can also cause pain and deterioration of surrounding bone.

Tarlov cysts may be drained and shunted to relieve pressure and pain, but relief is often only temporary and fluid build-up in the cysts will recur. Corticosteroid injections may also temporarily relieve pain. Other drugs may be prescribed to treat chronic pain and depression. Injecting the cysts with fibrin glue (a combination of naturally occurring substances based on the clotting factor in blood) may provide temporary relief of pain. Some scientists believe the herpes simplex virus, which thrives in an alkaline environment, can cause Tarlov cysts to become symptomatic. Making the body less alkaline, through diet or supplements, may lessen symptoms. Microsurgical removal of the cyst may be an option in selected individuals who do not respond to conservative treatments and who continue to experience pain or progressive neurological damage. (National Institute of Neurological Disorders and Stroke (NINDS), 2012).

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Code	Description
69799	Unlisted procedure, middle ear [when used to report balloon dilation]

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.

The Bielefeld balloon catheter, which is also referred to as the Bielefelder Ballonkatheter, Bielfeld, Bielefeld device, BET-Catheter, or, the TubaVent balloon catheter is intended to dilate the eustachian tube for treatment of chronic ETD in adults. Currently the evidence does not allow for any conclusive conclusions regarding efficacy, effectiveness, or safety of these devices (Hayes 2017; updated 2018).

The Acclarent Aera™ Eustachian balloon dilation system is intended for treatment of persistent Eustachian tube (ET) dysfunction. Evidence is inconclusive as to how well the Aera Eustachian balloon dilation system works. Overall, a very-low-quality body of evidence does not allow for definitive conclusions regarding the efficacy, effectiveness, or safety of eustachian tube balloon dilation with Acclarent systems; additional randomized controlled trials would be beneficial. (ECRI, 2018; Hayes, 2018).

In a prospective, multicenter, randomized, controlled trial, Anand et al. (2019) analyzed and investigated the durability of balloon dilation of the eustachian tube (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 (Eustachian Tube Dysfunction Questionnaire-7) 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.

Meyer et al. (2018) compared eustachian tube balloon dilation versus continued medical therapy for treating persistent Eustachian tube dysfunction (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 Eustachian Tube Dysfunction Questionnaire (ETDQ-7) scores 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. 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) assessed balloon dilation of the Eustachian tube with Eustachian tube balloon catheter in conjunction with medical management as treatment for Eustachian tube dilatatory 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 conclusions demonstrated superiority of balloon dilation of the Eustachian tube with balloon catheter plus medical management compared to medical management alone. However, a limitation of the study was the small sample size utilized.

Wang et al. (2018) performed a meta-analysis examining balloon dilatation and laser tuboplasty for the treatment of eustachian tube dysfunction (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 Eustachian tube dysfunction. The systematic literature search was conducted independently by two authors which resulted in 36 articles with 15 of them for inclusion in the study. 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 Eustachian tube dysfunction, however placebo controlled trials are still warranted.

Hwang et al. (2016) performed a systematic literature review on nine prospective studies, describing 713 and pooled data analysis and qualitative analysis was conducted. It was concluded that further investigations are warranted to establish a higher level of evidence of efficacy for dilation of the eustachian tube.

Randrup and Ovesen (2015) conducted a systematic review and meta-analysis of the evidence for balloon eustachian tuboplasty as a treatment modality for ETD. Twelve databases were searched and included a total of 443 patients. All

studies were of poor quality with a high risk of bias. No firm conclusions were made other than more RCTs or case controlled trials were needed.

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 inadequate in quantity and quality (NICE, 2011).

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 May 7, 2019)

The Acclarent Aera Eustachian Tube Balloon Dilation System (Acclarent Inc.) received U.S. FDA de novo clearance (DEN150056) on September 16, 2016, Product Code PNZ, eustachian tube balloon dilation device. Additional information is available at: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?id=den150056>. (Accessed May 7, 2019)

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Code	Description
76120	Cineradiography/videoradiography, except where specifically included
76125	Cineradiography/videoradiography to complement routine examination (List separately in addition to code for primary procedure)

The use of videofluoroscopy, cineradiography, Spinalyzer and similar technology and digital motion X-rays to diagnose spinal and skeletal dysfunction are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Dynamic spinal visualization may involve different imaging techniques, including videofluoroscopy of the spine (also known as cineradiography) and digital motion X-ray. Videofluoroscopy of the spine is a specialized X-ray (fluoroscopy) that visualizes and records actual spinal movement. These technologies allow internal body structures to be assessed simultaneously, such as the skeleton, intervertebral discs and ligaments, with corresponding external body movement. All of these methods use x-rays to create images either on film, on a video monitor, or on a computer screen. The Spinalyzer is used to visualize and measure the distortion of the spine and skeletal structure.

These imaging studies are used to assist with analysis of segment dysfunction. However, their inability to define structural changes such as impingement limits their utility. The lack of reference norms decreases the reliability of the test results.

The current literature evaluating the clinical utility of dynamic spinal visualization techniques, including but not limited to digital motion x-ray and cineradiography (videofluoroscopy), for the evaluation and assessment of the spine is limited to a few studies (Lee et al., 2002; Teyhen et al., 2007; O'Sullivan et al., 2012; Yaeger et al., 2014) involving

small numbers of participants. While these studies do indicate that there may be some benefit from the use of these technologies, further evidence from large controlled trials is needed to demonstrate that the results have significant impact on clinical care and are superior to currently available alternatives.

Dynamic spinal visualization is not addressed in the American College of Radiology (ACR) Appropriateness Criteria on chronic back pain suspected sacroiliitis-spondyloarthropathy (Bernard et al., 2017).

Reference(s)

Bernard SA, Kransdorf MJ, Beaman FD, et al. ACR Appropriateness Criteria[®] Chronic Back Pain Suspected Sacroiliitis-Spondyloarthropathy. J Am Coll Radiol. 2017 May;14(5S):S62-S70.

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O'Sullivan K, Verschueren S, Pans S, et al. Validation of a novel spinal posture monitor: comparison with digital videofluoroscopy. Eur Spine J. 2012 Dec;21(12):2633-9.

Teyhen DS, Flynn TW, Childs JD, et al. Fluoroscopic video to identify aberrant lumbar motion. Spine. 2007; 32(7):E220-229.

Yeager MS, Cook DJ, Cheng BC. Reliability of computer-assisted lumbar intervertebral measurements using a novel vertebral motion analysis system. Spine J. 2014 Feb 1;14(2):274-81.

Code	Description
19294	Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with partial mastectomy (List separately in addition to code for primary procedure)
77424	Intraoperative radiation treatment delivery, x-ray, single treatment session
77425	Intraoperative radiation treatment delivery, electrons, single treatment session
77469	Intraoperative radiation treatment management

Intraoperative radiation therapy, using low-energy x-rays or electrons, is unproven and not medically necessary for treating all indications due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Intraoperative radiation therapy (IORT) is a single dose of radiation using either low-energy x-rays or electrons and is most commonly delivered at the time of surgery (Correa et al., 2017).

TARGIT-A

The TARGIT-A trial, a randomized trial, was designed to test the hypothesis that a risk-adapted strategy using a single dose of targeted IORT using low energy x-rays (Intrabeam) in breast cancer patients suitable for breast conserving therapy is non-inferior to a conventional course of post-operative external beam radiotherapy (EBRT) delivered over several weeks. Patients were randomized to IORT (n=1113) or EBRT (n=1119). The primary endpoint was local recurrence in the conserved breast. The secondary endpoints included breast cancer and non-breast cancer mortality and local toxicity. Eligible patients were 45 years or older with invasive ductal carcinoma that was up to 3.5 cm in diameter and suitable for breast conserving surgery (Vaidya et al., 2010).

Vaidya et al. (2014) reported 5-year results for local recurrence and the first analysis of overall survival. Patients were randomized to IORT (n=1721) or EBRT (n=1730). The 5-year risk for local recurrence in the conserved breast was 3.3% for low energy x-ray IORT versus 1.3% for whole breast EBRT. The risk-adapted protocol recommended that if patients who had received IORT were found to have high risk factors postoperatively, they also received whole breast radiation. Supplemental EBRT after IORT was necessary in 15.2% of patients who received IORT (21.6% prepathology, 3.6% postpathology). A total of 3451 patients had a median follow-up of 2 years and 5 months, 2020 of 4 years and 1222 of 5 years. IORT concurrently with lumpectomy (prepathology, n=2298) had much the same results as EBRT: 2.1% versus 1.1%. With delayed IORT (postpathology, n=1153) the between-group difference was larger than 2.5% (TARGIT 5.4% vs EBRT 1.7%). Overall, breast cancer mortality was much the same between groups (2.6% for IORT vs 1.9% for EBRT).

ELIOT

Veronesi et al. (2013) conducted ELIOT, a single-institution trial, included patients with early breast cancer, aged 48 years or older, with a tumor size no larger than 2.5 cm. After undergoing standard breast-conserving surgery, patients were randomly assigned to receive a single dose of intraoperative radiotherapy of 21 Gy to the tumor bed during surgery (n=651) or conventional radiation therapy consisting of a 50-Gy postoperative external-beam dose to the whole breast with conventional fractionation plus a 10-Gy boost (n=654). The prespecified equivalence margin was local recurrence of 7.5% in the intraoperative radiotherapy group. The primary endpoint was occurrence of ipsilateral breast tumor recurrences (IBTR); overall survival was a secondary outcome. After a medium follow-up of

5.8 years, 35 patients in the intraoperative radiotherapy group and four patients in the external radiotherapy group had a recurrence. The 5-year recurrence risk was 4.4% in the IORT group and 0.4% in the EBRT group. 5-year overall survival was 96.8% in the IORT group and 96.9% in the EBRT. The authors noted that although the rate of recurrence in the IORT group was within the prespecified equivalence margin, the rate was significantly greater than with EBRT. Overall survival did not differ between groups. Improved selection of patients could reduce the rate of recurrence with IORT with electrons.

An updated ASTRO consensus statement on accelerated partial breast irradiation (APBI) states that, when compared with whole breast irradiation (WBI), IORT offers several benefits, including reduced treatment time and sparing of uninvolved tissue. However, the report recommends that patients interested in cancer control equivalent to that achieved with WBI post lumpectomy for breast conservation should be counseled that in two clinical trials the risk of recurrence was higher with IORT. Based on moderate quality evidence, the report also states that electron beam IORT should be restricted to women with invasive cancer who meet select criteria addressed in the full report. Low-energy x-ray IORT should only be used within the context of a prospective registry or clinical trial (Correa et al., 2017).

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer do not specifically address IORT using low-energy x-rays or electrons. The guidelines state that boost treatment in the setting of breast conservation can be delivered using enface electrons, photons or brachytherapy. When addressing APBI, the guidelines indicate that preliminary studies suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast radiation therapy. However, follow-up is limited and studies are ongoing. Patients are encouraged to participate in clinical trials (NCCN, 2019).

Reference(s)

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National Comprehensive Cancer Network (NCCN). *Clinical Practice Guidelines in Oncology. Breast cancer.* v1.2019.

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Vaidya JS, Wenz F, Bulsara M, et al; TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet.* 2014 Feb 15;383(9917):603-13. Erratum in: *Lancet.* 2014 Feb 15;383(9917):602.

Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol.* 2013 Dec;14(13):1269-77.

Code	Description
80299	Quantitation of therapeutic drug, not elsewhere specified [when used to report therapeutic drug monitoring for inflammatory bowel disease]
84999	Unlisted chemistry procedure [when used to report therapeutic drug monitoring for inflammatory bowel disease]

Laboratory measurement of antibodies and serum levels related to biologic agents (e.g., infliximab, adalimumab, vedolizumab, ustekinumab) for treating inflammatory bowel 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, 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).

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, TDM is being used to check the drug trough concentration and assess for the presence of anti-drug antibodies (Feuerstein et al., 2017).

Papamichael et al. (2019a) conducted a comprehensive literature review and provided expert opinion regarding the clinical utility of TDM for biologic therapies in IBD. For anti-tumor necrosis factor (anti-TNF) therapies, the authors found that proactive TDM to be appropriate after induction and at least once during maintenance therapy, but this was not the case for the other biologics. Reactive TDM (evaluation of drug concentrations and antidrug antibodies in

patients with primary nonresponse or secondary loss of response) was found to be appropriate for all agents both for primary non-response and secondary loss of response, according to panelist consensus. The panelists also agreed on several statements regarding TDM and appropriate drug and anti-drug antibody (ADA) concentration thresholds for biologics in specific clinical scenarios. The authors concluded that more data are needed especially on non-anti-TNF biologics to further define optimal drug concentration and ADA thresholds as these can vary depending on the therapeutic outcomes assessed.

According to Carman et al. (2018), the use of TDM in pediatric IBD is increasing in clinical practice, with similar efficacy to adults demonstrated in children with loss of response to anti-TNF therapy. The results of their systematic review demonstrated that additional prospective studies are needed in children to examine proactive monitoring and utility of TDM with newer biologics.

Adalimumab (ADA)

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 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 concentrations 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 stricturing 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.

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.

Infliximab (IFX)

In a systematic review on the efficacy of infliximab (IFX) in the treatment of IBD, Papamichael et al. (2019c) identified that although most of the data for proactive TDM is during the maintenance phase, it is most important during the induction phase when the disease is active and drug clearance is greatest. Their assessment is that reactive TDM is currently emerging as the new standard of care for optimizing anti-TNF therapy in IBD. The authors concluded that TDM can help physicians better understand and manage unwanted outcomes of IFX therapy, although several limitations still hinder widespread adoption of this clinical strategy in day to day clinical practice. These include cost, the long lag time from sampling to results, the interpretation of the results, and defining the optimal drug concentration thresholds to target as these can vary depending on the therapeutic goal of interest, the IBD phenotype, and the TDM assay used.

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 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. Increasing the IFX dose in patients who have HACAs is ineffective, whereas in patients with subtherapeutic IFX concentrations, this strategy may be a good alternative to changing to another anti-TNF agent. Further studies are needed to validate these findings.

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 $< 2 \mu\text{g/ml}$. 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 $> 2 \mu\text{g/ml}$ is associated with a greater probability of clinical remission and mucosal healing.

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 $> 5 \mu\text{g/mL}$ (hazard ratio, 0.03; 95% confidence interval, 0.01-0.1; $P < 0.0001$ versus trough $< 5 \mu\text{g/mL}$). 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.

Khanna et al. (2013) conducted a systematic review to evaluate the evidence supporting the use of TDM-based clinical algorithms for IFX and their role in clinical practice. Treatment algorithms for IBD have evolved from episodic monotherapy used in patients refractory to all other treatments, to long-term combination therapy initiated early in the disease course. Improved remission rates have been observed with this paradigm shift, nevertheless many patients ultimately lose response to therapy. Multiple TDM-based algorithms have been developed to identify patients that may benefit from measurement of IFX and ADA levels to guide adjustments to therapy. Although empiric dose optimization or switching agents constitute the current standard of care for secondary failure, these interventions have not been applied in an evidence-based manner.

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 $\geq 23.2 \text{ mcg/ml}$ 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 $25 \mu\text{g/mL}$ 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 $> 30.0 \mu\text{g/mL}$ at week 2, $> 24.0 \mu\text{g/mL}$ at week 6, and $> 14.0 \mu\text{g/mL}$ 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.

Ward et al. (2018) reviewed the available evidence on the pharmacokinetics and pharmacodynamics of VDZ in IBD and how drug levels, immunogenicity and other factors influence clinical outcomes. The results showed that VDZ clearance is increased with very high body weight and hypoalbuminemia, but is not influenced by the addition of an immunomodulator. Immunogenicity is uncommon. α 4 β 7 receptor saturation occurs at low serum VDZ drug levels, and measuring it alone is insufficient to predict clinical outcomes. Using quartile analysis of VDZ drug levels, there appears to be a modest exposure–response relationship during induction. Drug levels at week 6 of approximately >20 μ g/ml have been shown to be associated with improved clinical outcomes, including subsequent mucosal healing rates during maintenance and avoiding the need to dose escalate due to lack of response. The authors concluded that there are currently insufficient data to support the routine use of therapeutic drug monitoring during maintenance therapy. Further studies to elucidate the role of TDM of VDZ are needed.

Nanda et al. (2013) conducted a systematic review and meta-analysis of studies that reported clinical outcomes and IFX levels according to patients' 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.

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 reinitiation 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 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 \leq 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 μ g/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.

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.

Ustekinumab (UST)

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

In a 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 January 2019).

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.

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 multibiomarker 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.

Li et al. (2013) assessed how use of a multi-biomarker disease activity (MBDA) blood test for rheumatoid arthritis (RA) affects treatment decisions made by health care providers (HCPs) in clinical practice. At routine office visits, 101 patients with RA were assessed by their HCPs ($n = 6$), and they provided blood samples for MBDA testing. HCPs completed surveys before and after viewing the MBDA test result, recording dosage and frequency for all planned RA medications and physician global assessment of disease activity. Frequency and types of change in treatment plan that resulted from viewing the MBDA test result were determined. Prior to HCP review of the MBDA test, disease modifying anti-rheumatic drug (DMARD) use by the 101 patients included methotrexate in 62% of patients; hydroxychloroquine 29%; TNF inhibitor 42%; non-TNF inhibitor biologic agent 19%; and other drugs at lower frequencies. Review of MBDA test results changed HCP treatment decisions in 38 cases (38%), of which 18 involved starting, discontinuing or switching a biologic or non-biologic DMARD. Other changes involved drug dosage, frequency or route of administration. The total frequency of use of the major classes of drug therapy changed by less than 5%. Treatment plans changed 63% of the time when the MBDA test result was perceived as being not consistent or somewhat consistent with the HCP assessment of disease activity. The authors concluded that the addition of the MBDA test to clinical assessment led to meaningful changes in the treatment plans of 38% of RA patients being cared for by HCPs in office practice. Even though treatment was potentially improved, the overall quantity of drug use was minimally affected. This study was limited because it did not involve any follow-up to assess the influence of changes on health outcomes and it did not compare the Vectra test with other methods of disease activity assessment to determine whether they would have had similar influences on RA patient management.

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 MBDA 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.

Other clinical trials have also evaluated the Vectra DA test (Curtis et al., 2018; Markusse et al., 2014; Hirata et al., 2013). These trials had several limitations including retrospective analysis, lack of radiographic assessment, small number of patients with disease progression, no evaluation of the impact of this test on patient health outcomes, and insufficient follow-up. Well-designed studies are needed to demonstrate the efficacy of Vectra DA testing.

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. This conclusion was not changed in the January 2019 update of the Hayes report on this topic (Hayes, 2018. Updated January 2019).

For measurement of RA disease activity and detection of remission, the American College of Rheumatology (ACR) guidelines recommend use of the Clinical Disease Activity Index (CDAI), Disease Activity Score 28 (DAS28)-Erythrocyte Sedimentation Rate, Patient Activity Scale (PAS) or PASII, Routine Assessment of Patient Index Data 3, and Simplified Disease Activity Index instruments (SDAI). These guidelines state that other measures are available but are beyond the scope of current ACR guidelines (Singh et al., 2016).

For monitoring response to RA treatment, the European League Against Rheumatism (EULAR) recommends use of composite measures such as the CDAI, SDAI, and DAS28 that include joint counts. With regard to use of the Vectra MBDA test, the EULAR states that no strategy is available that compares the MBDA test with a clinical composite measure. In addition, 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).

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Code	Description
86849	Unlisted immunology procedure [when used to report antiprothrombin antibody testing for antiphospholipid syndrome]

Antiprothrombin antibody testing for antiphospholipid syndrome is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Antiprothrombin antibodies are members of the ill-defined, heterogeneous family of antiphospholipid antibodies, whose persistent presence in association with thromboembolic complications, recurrent miscarriage, or immune thrombocytopenia defines the antiphospholipid syndrome (APS).

Antiphospholipid syndrome (APS) is a rare autoimmune condition characterized by moderate-to-high levels of circulating anti-phospholipid antibodies.

ECRI (2017) conducted a review of the literature to assess antiprothrombin antibody testing for diagnosing primary APS. After reviewing the literature the authors concluded that the available evidence on aPT testing for diagnosing APS does not support its use as a substitute for the current 3 antibody criteria (anticardiolipin, anti-beta-2 glycoprotein I, and lupus anticoagulant).

ECRI (2017) also conducted a search of clinical guidelines associated with APS. The authors noted the following relevant guidelines:

- American College of Chest Physicians (2012) guideline on venous thromboembolism and pregnancy recommends screening for antiphospholipid antibodies in "women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation)." The guideline did not mention testing for anti-prothrombin(aPT).
- American College of Obstetricians and Gynecologists (2017) guideline on APS does not recommend testing for antibodies other than the lupus anticoagulant, anticardiolipin, and anti-β₂-glycoprotein I.
- British Society for Hematology (2012) guideline on APS does not mention testing for aPT.
- European League Against Rheumatism (2017) guideline on APS does not mention testing for (aPT).

Zigon et al (2013) stated that anti-prothrombin antibodies, measured with phosphatidylserine/prothrombin complex (aPS/PT) ELISA, have been reported to be associated with APS. They are currently being evaluated as a potential classification criterion for this autoimmune disease, characterized by thromboses and obstetric complications. Given the present lack of clinically useful tests for the accurate diagnosis of APS, these researchers evaluated in-house and commercial assays for determination of aPS/PT as a potential serological marker for APS. They screened 156 patients with systemic autoimmune diseases for antibodies against PS/PT, β₂-glycoprotein I, cardiolipin and for lupus anticoagulant activity. These investigators demonstrated a high degree of concordance between the concentrations of aPS/PT measured with the in-house and commercial assays. Both assays performed comparably relating to the clinical manifestations of APS, such as arterial and venous thromboses and obstetric complications. IgG aPS/PT represented the strongest independent risk factor for the presence of obstetric complications, among all tested aPL. Both IgG and IgM aPS/PT were associated with venous thrombosis, but not with arterial thrombosis. Most importantly, the association between the presence of IgG/IgM aPS/PT and lupus anticoagulant activity was highly significant. The authors concluded that aPS/PT antibodies detected with the in-house or commercial ELISA represent a promising serological marker for APS and its subsets.

Antiprothrombin antibody testing for the diagnosis of APS is a procedure and therefore not subject to FDA regulation. However, any medical devices, drugs, biologics, or tests used as part of this procedure may be subject to FDA regulation.

The antiprothrombin antibody test is a diagnostic test that falls under FDA regulation as either an "in-house" test with a hospital or proprietary laboratory, or as a marketed and distributed test kit or device. In-house testing falls under the rule of the Centers for Medicare & Medicaid Services (CMS) Clinical Laboratory Improvement Amendments (CLIA) of 1988. Premarket approval from the FDA is not required for this type of laboratory test. However, tests that are

marketed, distributed, and sold as kits or devices do fall under the FDA 510(k) and/or premarket approval (PMA) processes.

Reference(s)

Amengual O, Forastiero R, Sugiura-Ogasawara M, et al. Evaluation of phosphatidylserine-dependent antiprothrombin antibody testing for the diagnosis of antiphospholipid syndrome: Results of an international multicentre study. *Lupus*. 2017;26(3):266-276.

American College of Obstetricians and Gynecologists. Guideline for Antiphospholipid syndrome. *Obstet Gynecol*. 2017 ECRI Institute. Health Technology Information Service Hotline Response. Antiprothrombin Antibody Testing for Diagnosing Primary Antiphospholipid Syndrome. May 2017.

Hayes, Inc. Search and Summary. Antiprothrombin Antibody Testing for Diagnosis of Primary Antiphospholipid Syndrome Lansdale, PA: May 2015.

Zigon P, Cucnik S, Ambrozic A, et al. Detection of antiphosphatidylserine/prothrombin antibodies and their potential diagnostic value. *Clin Dev Immunol*. 2013;2013:724592.

Code	Description
93668	Peripheral arterial disease (PAD) rehabilitation, per session [when used to report Supervised Exercise Therapy (SET)]

Peripheral arterial disease rehabilitation / Supervised Exercise Therapy (SET), is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Peripheral arterial disease (PAD) is a common chronic cardiovascular condition that affects the lower extremities and can substantially limit daily activities and quality of life. Lifestyle interventions, including smoking cessation, diet modification, regular physical activity, and pharmacotherapy, are often prescribed to treat patients with PAD. (Hayes, Archived 2018).

Supervised exercise therapy (SET) involves the use of intermittent walking exercise, which alternates periods of walking to moderate-to-maximum claudication, with rest. SET has been recommended as the initial treatment for patients suffering from intermittent claudication, the most common symptom experienced by people with peripheral arterial disease (PAD). (Hayes, Archived 2018).

Both physical activity and medications are used to treat peripheral arterial disease. Vascular specialists agree that long daily walks are the best treatment for people with intermittent claudication, thereby increasing the distance of pain-free walking through the development of collateral circulation. Regular exercise improves symptoms of PAD by a number of methods, including helping the body use oxygen more efficiently and promoting improved circulation. Exercise for intermittent claudication takes into account the fact that walking causes pain. Patients whose legs hurt during physical activity often find it hard to follow a walking program. For this reason, the rehabilitation departments of some hospitals have created supervised exercise programs that offer support and encouragement. The usual duration of the program is 3 times a week for 12 weeks (36 visits). The goal of treatment is to improve endurance and decrease symptoms. (Hayes, Archived 2018).

Hayes (Archived 2018) conducted a literature search and review of supervised exercise therapy. They concluded that there is sufficient published evidence to evaluate this technology, but the study abstracts present conflicting findings regarding the effectiveness of SET for the treatment of PAD. 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.

Parmenter, et al (2015) completed a meta-analysis of randomized controlled trials (RCTs) of supervised exercise therapy that were completed between 1966 and August, 2014 of exercise training versus usual medical care in persons with peripheral artery disease (PAD). To qualify for the analysis, the RCTs had to include the Walking Impairment Questionnaire (WIQ) and Short-Form Health Survey component summary scores as outcomes to measure health-related QOL (HRQOL). Out of 16,669 studies, there were 15 RCTs that met these parameters. These 15 studies included 1257 participants, of which 543 participated in supervised exercise, 61 participating in resistance training and 316 participated in unsupervised exercise. Walking training to various levels of claudication pain improved perceived walking speed, distance and stairclimbing performance as measured by the WIQ, and self-reported physical function (SF-36) in people with PAD. Walking to claudication pain was the most common prescription studied and resulted in the most improvements in these outcomes. Exercise training improved the SF-PCS dimension, as well as perceived walking distance, speed and stair-climbing as measured by the WIQ, but not the SF-MCS score. Common limitations identified in the analysis were a lack of concealment of randomization, blinding of subjects, therapists and assessors, and measurement of key outcomes in greater than 85% of trial participants. Ten of the 15 studies reported a >15% drop-out rate. No studies blinded therapists administering exercise interventions or participants. Only four studies blinded assessors who measured at least one key outcome. Future studies should aim to blind assessors of such

subjective measures, and study alternative modes and prescriptions of exercise alternative to walking. There was also no comparison of results to participants who were treated with home exercise programs.

In a Cochrane review, Fokkenrood et al (2013) provided an accurate overview of studies evaluating the effects of supervised exercise programs (SETs) versus non-supervised exercise therapy on maximal walking time or distance on a treadmill for people with intermittent claudication. Two review authors independently selected trials and extracted data. A total of 14 studies involving a total of 1,002 male and female participants with PAD were included in this review. Follow-up ranged from 6 weeks to 12 months. In general, supervised exercise regimens consisted of 3 exercise sessions per week. All trials used a treadmill walking test as one of the outcome measures. The overall quality of the included trials was moderate to good, although some trials were small with respect to the number of participants, ranging from 20 to 304. Supervised exercise therapy showed statistically significant improvement in maximal treadmill walking distance compared with non-supervised exercise therapy regimens, with an overall effect size of 0.69 (95 % CI: 0.51 to 0.86) and 0.48 (95 % CI: 0.32 to 0.64) at 3 and 6 months, respectively. This translated to an increase in walking distance of approximately 180 meters that favored the supervised group. Supervised exercise therapy was still beneficial for maximal and pain-free walking distances at 12 months, but it did not have a significant effect on QL parameters. The authors concluded that SET has statistically significant benefit on treadmill walking distance (maximal and pain-free) compared with non-supervised regimens. Moreover, they stated that the clinical relevance of this has not been demonstrated definitively; additional studies are needed that focus on QL or other disease-specific functional outcomes, such as walking behavior, patient satisfaction, costs, and long-term follow-up.

Research has shown that taking part in exercise and physical activity can lead to improvements in symptoms in the short term for people with intermittent claudication. However, the benefits of exercise are quickly lost if it is not frequent and regular. Supervised exercise programs have been shown to produce superior results when compared with advice to exercise (unsupervised) in the short term, but they are more expensive, and there is a lack of robust evidence on long-term effectiveness. A community-based randomised controlled trial is required to compare the long-term clinical and cost effectiveness of a supervised exercise programs and unsupervised exercise. The trial should enroll people with peripheral arterial disease-related claudication, but exclude those with previous endovascular or surgical interventions. The primary outcome measure should be maximal walking distance, with secondary outcome measures including quality of life, function, levels of uptake of exercise programs and long-term engagement in physical activity. (NICE, 2014).

Niccoli et al. (2010) conducted a randomized controlled trial of 169 patients receiving supervised exercise therapy (SET) for intermittent claudication. The SET program consisted of at least two training sessions per week each lasting over 30 minutes, during the first 3 months of a 1-year program. No differences were found between program involving only walking and a combination of exercises, nor between individual and group training.

A Cochrane systematic evidence review (Bendermacher et al, 2006) found that supervised exercise therapy has not been proven to be better than non-supervised exercise therapy in managing patients with intermittent claudication. Randomized and controlled clinical trials comparing supervised exercise programs with non-supervised exercise programs for people with intermittent claudication were selected. Two authors independently selected trials and extracted data. One author assessed trial quality and this was confirmed by a second author. For all continuous outcomes the authors extracted the number of participants, the mean differences, and the standard deviation. If data were available, the standardized mean difference was calculated using a fixed-effect model. These researchers identified 27 trials, of which 19 had to be excluded because the control group received no exercise therapy at all. The remaining 8 trials involved a total of 319 male and female participants with intermittent claudication. The follow-up ranged from 12 weeks to 12 months. In general, the supervised exercise regimens consisted of 3 exercise sessions per week. All trials used a treadmill walking test as one of the outcome measures. The overall quality of the included trials was good, though the trials were all small with respect to the number of participants, ranging from 20 to 59. Supervised exercise therapy showed statistically significant and clinically relevant differences in improvement of maximal treadmill walking distance compared with non-supervised exercise therapy regimens in the short-term, with an overall effect size of 0.58 at 3 months. This translated to a difference of approximately 150 meters increase in walking distance in favor of the supervised group. However, there is a high possibility of a training effect as the supervised exercise therapy groups were trained primarily on treadmills (and the home based were not) and the outcome measures were treadmill based. The authors concluded that supervised exercise therapy is suggested to have clinically relevant benefits compared with non-supervised regimens in the short-term, which is the main prescribed exercise therapy for people with intermittent claudication. However, the clinical relevance has not been demonstrated definitively and will require additional studies with a focus on durability of outcomes and improvements in QOL (Bendermacher et al, 2006).

Reference(s)

Bendermacher BL, Willigendael EM, et al. Supervised exercise therapy for intermittent claudication in a community-based setting is as effective as clinic-based. *J Vasc Surg.* 2007;45(6):1192-1196.

Fokkenrood HJ, Bendermacher BL, Lauret GJ, et al. Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication. Cochrane Database Syst Rev. 2013.

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National Institute for Health and Care Excellence (NICE). Lower limb peripheral arterial disease. update November 2014.

Nicolaï SP, Hendriks EJ, Prins MH, et al. Optimizing supervised exercise therapy for patients with intermittent claudication. J Vasc Surg. November, 2010.

Parmenter BJ, Dieberg G, Phipps G, et al. Exercise training for health-related quality of life in peripheral artery disease: a systematic review and meta-analysis. Vasc Med. 2015;20:30–40.

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

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

Clinical Evidence

A Hayes report on bioelectrical impedance (bioimpedance) analysis (BIA) for assessment of lymphedema states that there is insufficient evidence to draw definitive conclusions regarding the diagnostic value of BIA in assessing lymphedema (2019).

Qin et al. (2018) conducted a single center retrospective study testing sensitivity, specificity, and diagnostic accuracy of bioimpedance spectroscopy (BIS) in diagnosing lymphedema. In this study of 58 patients, the authors concluded that BIS carries an excessively high rate of false-negative results to be dependably used as a diagnostic modality for lymphedema.

A 2018 multicenter, prospective, open-label study known as COMPASS examined the clinical usefulness of BIS-guided fluid management for preserving residual renal function (RRF) and cardiac function in non-anuric peritoneal dialysis (PD) patients over a one-year period. Subjects totaling 137 were randomly assigned to the BIS group (n=67) or the control group (n=70). The authors concluded that routine BIS-guided fluid management in non-anuric PD patients did not provide additional benefit in any of the outcome measures. Further research is warranted (Oh et al.)

Whitworth and Cooper evaluated a single-institution prospective surveillance program using newer techniques including BIS to facilitate early detection and treatment of breast cancer-related lymphedema (BCRL). The study group was comprised of 596 participants (79.6% considered to be high risk), with a mean follow-up period of 17 months. 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. The authors stated that a randomized trial evaluating BIS is underway although results are not yet published (2017).

Bundred et al. (2015) conducted a comparative study of bioimpedance with perometry for early detection and intervention of lymphedema after axillary node clearance. The primary outcome measure was the incidence of lymphedema at 2 and 5 years following node clearance. Study results indicate that arm volume measurements remains the gold standard and it is not clear if bioimpedance is clinically effective and useful to detect lymphedema.

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

Barrio et al (2015) 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.

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 (2019).

There are multiple trials in progress studying the use of BIS in early assessment of BCRL. For more information, go to <https://clinicaltrials.gov/>. (Accessed April 16, 2019)

Reference(s)

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- Bundred NJ, Stockton C, Keeley V, et al. Comparison of multi-frequency bioimpedance with perometry for the early detection and intervention of lymphedema after axillary node clearance for breast cancer. *Breast Cancer Res Treat*. 2015; 151(1):121-9.
- Erdogan I, Selamoglu D, Alco G, et al. Bioelectrical impedance for detecting and monitoring lymphedema in patients with breast cancer. Preliminary results of the Florence nightingale breast study group. *Lymphat Res Biol*. 2015; 13(1):40-5.
- Hayes, Inc. Medical Technology Directory. Bioelectrical Impedance (Bioimpedance) Analysis for Assessment of Lymphedema. Lansdale, PA: Hayes, Inc.; March 2015; Updated March 2019.
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Breast Cancer. v1.2019.
- Oh KH, Baek SH, Joo KW, et al. Control of fluid balance guided by body composition monitoring in patients on peritoneal dialysis (COMPASS) study. Does Routine Bioimpedance-Guided Fluid Management Provide Additional Benefit to Non-Anuric Peritoneal Dialysis Patients? Results from COMPASS Clinical Trial. *Perit Dial Int*. 2018 Mar-Apr;38(2):131-138.
- Qin ES, Bowen MJ, Chen WF. Diagnostic accuracy of bioimpedance spectroscopy in patients with lymphedema: A retrospective cohort analysis. *J Plast Reconstr Aesthet Surg*. 2018 Jul;71(7):1041-1050.
- Whitworth PW, Cooper A. Reducing chronic breast cancer-related lymphedema utilizing a program of prospective surveillance with bioimpedance spectroscopy. *Breast J*. 2018 Jan;24(1):62-65.

Code	Description
94011	Measurement of spirometric forced expiratory flows in an infant or child through 2 years of age
94012	Measurement of spirometric forced expiratory flows, before and after bronchodilator, in an infant or child through 2 years of age
94013	Measurement of lung volumes (i.e., functional residual capacity [FRC], forced vital capacity [FVC], and expiratory reserve volume [ERV]) in an infant or child through 2 years of age

Spirometry and other pulmonary function tests are unproven and not medically necessary in children under the age of three due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

In a 2019 review, Gallucci et al. analyzed the tools utilized in and compared different guidelines related to asthma monitoring. While spirometry is cited as main test for detecting and measuring airway obstruction in all patients over 5 years of age, the outcome of spirometry is often dependent on the operator and it should optimally be performed by expert personnel. During childhood, impulse oscillometry (IOS) and the technique of forced oscillations (FOT) may be used to assess lung function as an alternative to spirometry, since measurements are made from tidal breathing and younger children are better able to comply. Finally, the authors stated that IOS has proved to be more useful than spirometry in early detection of asthmatic children from normal cohorts.

In a clinical guideline on the diagnostic evaluation of infants with recurrent or persistent wheezing, the American Thoracic Society (ATS) reported being unable to find any large clinical studies that used consistent case definitions and outcomes. Most of the studies cited were case series, providing the lowest quality of evidence on the GRADE scale. The guideline development committee did not reach consensus on a clinical recommendation for or against infant PFTs, due to the paucity of evidence. They urged that, given the frequency with which infantile wheezing occurs, there is an urgent need for more rigorous research to be conducted in this field (Ren et al., 2016).

Total specific airway resistance (sRtot) has been introduced as an alternative technique to assess lung function with a particular application to younger children with asthma. A prospective, non-interventional study by Jerzyńska et al. was conducted to evaluate the utility of sRtot versus spirometry for assessment of lung function in well-controlled asthmatic children versus non-asthmatics. Subjects (N=885) ages 4-18 underwent body plethysmography and spirometry (when capable) with reversibility tests. Of 788 subjects who could perform both tests, 578 were diagnosed with asthma. Subjects with asthma were treated for a minimum of 6 months and then their diagnosis was confirmed or refuted. Asthma was confirmed in 471 patients: 142 patients were ages 4-6, and 329 were 7-18 years old. Change in response to bronchodilator in children with asthma was significant for sRtot but not for forced expiration volume in 1 second (FEV1); sRtot was more sensitive and specific in identifying children with reversible obstruction than spirometry. There was a significant association between sRtot and asthma diagnosis in patients 4 -6 years old to differentiate subjects with asthma from those without asthma. A ratio of FEV1 to forced vital capacity below 80% was not significantly associated with asthma. The authors concluded that these findings support the recommendation of performing sRtot rather than spirometry in young children as a fairly sensitive marker of asthma (2015).

The ATS, in a 2013 clinical guideline on the classification, evaluation, and management of childhood interstitial lung disease in infancy, suggests infant PFT be utilized to better characterize physiologic alterations (weak recommendation). However, no controlled clinical trials were identified on this topic and therefore, observational

evidence and clinical experience informed judgments were made regarding PFT. Strong recommendations for initial diagnostic testing include echocardiography and thin-section CT using the lowest radiation dose that provides adequate diagnostic information (Kurland et al).

In a 2013 workshop report on the diagnosis and management of chronic pulmonary conditions in children under 6 years of age, the ATS stated that no evidence yet exists for any lung function monitoring measures as to whether incorporating them in to clinical care improves patient outcomes; such studies are urgently needed. Despite the lack of empirical evidence, clinical experience suggests that lung function monitoring might be helpful in some clinical settings such as infants and young children with cystic fibrosis, bronchopulmonary dysplasia, or recurrent wheeze (Rosenfeld et al).

In a 2009 guideline, published jointly with the European Respiratory Society, the ATS addresses lung function tests in children 6 years of age and older. While they acknowledge that the use of such tests in children younger than 6 years of age was beyond the scope of their guideline, they state that with appropriate training, preschool children may be able to perform spirometry. Forced oscillation procedures and interrupter resistance (Rint) to measure airway resistance can be applied in children as young as 3 years of age (Reddel et al).

The 2018 Global Initiative for Asthma (GINA) guidelines specific to children 5 years and younger state that due to the inability of this age group to perform reproducible expiratory maneuvers, lung function testing, bronchial provocation testing, and other physiological tests do not have a major rule in the diagnosis of asthma. However, by 4-5 years of age, children are often capable of performing reproducible spirometry if coached by an experienced technician.

A 2017 NICE guideline addressing diagnosis, monitoring and management of chronic asthma states to perform a spirometry at each visit or at least after 3 or 6 months from the beginning of therapy and then every 1–2 years.

The National Heart, Lung, and Blood Institute (NHLBI) National Asthma Education and Prevention Program (NAEPP) Expert Panel recommends that spirometry measurements before and after the patient inhales a short-acting bronchodilator should be undertaken for patients in whom the diagnosis of asthma is being considered, including children 5 years of age or older. For children 0-4 years of age, the panel recommends that the evaluation include the history, symptoms, physical examination and assessment of QOL, as diagnosis can be difficult in this age group. A therapeutic trial with medications will also aid in the diagnosis (2007).

Reference(s)

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Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention (2018 update). Website. https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1.3.pdf. Accessed April 26, 2019.

Jerzyńska J, Janas A, Galica K, et al. Total specific airway resistance vs spirometry in asthma evaluation in children in a large real-life population. *Ann Allergy Asthma Immunol*. 2015 Oct;115(4):272-6.

Kurland G, Deterding RR, Hagood JS, et al. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Respir Crit Care Med* Vol 188. 2013 Aug 1;188(3):376-94.

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Ren CL, Esther CR, Debley JS, et al. Official American Thoracic Society clinical practice guidelines: diagnostic evaluation of infants with recurrent or persistent wheezing. *Am J Respir Crit Care Med*. 2016 Aug 1; 194(3):356-730.

Rosenfeld M, Allen J, Arets BH, et al. An official American Thoracic Society workshop report: optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheezing in children less than 6 years of age. *Ann Am Thorac Soc*. 2013 Apr;10(2):S1-S11.

Code	Description
96902	Microscopic examination of hairs plucked or clipped by the examiner (excluding hair collected by the patient) to determine telogen and anagen counts, or structural hair shaft abnormality

Microscopic examination of hair to determine telogen and anagen counts or structural hair shaft abnormality is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The microscopic examination of hair is called a trichogram (also referred to as a hair mount, pluck test and Unit Area Trichogram). It is semi-invasive test that can be used to identify hair growth rate and anagen (hair growth) and/telogen (hair resting phase) ratio. It involves taking epilated hairs from different parts of the scalp and examining the roots under a microscope and assessing the percentage of hairs in each growth cycle (Mubki et al., 2014). A trichogram may be used to provide hair growth cycle information for alopecia, and male and female pattern baldness.

In a 2011 quantitative analysis regarding the clinical validity of hair analysis, Kosanovic et al. concluded that although researchers have found many correlations of essential elements to diseases, metabolic disorders, environmental exposures, and nutritional status, opponents of the concept of hair analysis object that hair samples are unreliable due to the influence of external factors such as patient variables and the lack of laboratory standardization regarding pre analytical and analytical procedures. When using hair to quantify exposure to environmental contaminants, caution is needed in the interpretation of exposure data.

Microscopic analysis of hair for hair loss issues is not supported by clinical evidence. The trichogram has been evaluated in terms of reproducibility and clinical relevance and been used in very few clinical trials. Hairs in early anagen, and vellus hairs are easily missed in a standard pluck because of their small size, and plucking is also known to change the course of the hair cycle. Because of the relative values of anagen/telogen generated and the lack of exhaustive sampling, this technique is generally a poor indicator of disease activity and/or disease severity (Duhurat et al., 2009).

Reference(s)

Dhurat R, Saraogi P. Hair evaluation methods: merits and demerits. Int J Trichology. 2009 Jul;1(2):108-19. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938572/>. Accessed July 9, 2019.

Kosanovic M, Jokanovic M. Quantitative analysis of toxic and essential elements in human hair. Clinical validity of results. Environ Monit Assess. 2011 Mar;174(1-4):635-43. <https://www.researchgate.net/publication/44619200>. Accessed July 8, 2019.

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Code	Description
29799	Unlisted procedure, casting or strapping [when used to report Kinesio Taping]
97139	Unlisted therapeutic procedure (specify) [when used to report Kinesio Taping]
97799	Unlisted physical medicine/rehabilitation service or procedure [when used to report Kinesio taping]
A9999	Miscellaneous DME supply or accessory, not otherwise specified [when used to report Kinesio Taping]

The use of Kinesio taping is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Kinesio taping (KT) involves the application of elastic therapeutic tape for a number of conditions including pain, swelling and edema, scar healing, proprioceptive facilitation, and relaxation of muscles. An important feature of KT is its elasticity of about 120-140% of its initial length. It subsequently provides a constant pulling (shear) force to the skin over which it is applied unlike traditional white athletic tape. The fabric of this specialized tape is air permeable and water resistant and can be worn for repetitive days. KT is being used immediately following injury and during the rehabilitation process.

In this systematic review, Li et al. (2019) explored the effects of KT on pain and disability in individuals with chronic low back pain (CLBP). A total of 10 articles were included in this meta-analysis. 627 participants were involved, with 317 in the KT group and 310 in the control group. The authors explored the effects of KT on pain and disability. While it was identified that KT was not superior to the placebo taping in pain reduction (either alone or in conjunction with the physical therapy (PT)) the KT significantly improved disability when compared to the placebo taping. It was concluded by the authors since KT is convenient for application, it could be used for individuals with CLBP in some cases, especially when the patients could not get other PT.

Mak et al. (2019) studied the effects of facilitatory KT on muscle activity and performance between regular KT-users and non-users. Sixty participants, including 27 regular KT-users and 33 non-users, performed maximal grip assessment with and without facilitatory KT, which was applied to their wrist extensor muscles of the dominant forearm. Wrist extensors electromyographic activity, maximal grip strength, and perceived performance comparisons were conducted. The group of KT-users showed an increase in grip strength with application of facilitatory KT, when compared to tapeless condition. The group of non-users demonstrated similar grip strength with and without KT application. No significant differences were found in the muscle activity or perceived performance in either group. The authors concluded facilitatory KT promotes maximal grip strength only among regular KT users, but its effect is trivial.

Interestingly, such effect is not related to any electrophysiological change in the KT applying muscle, which may indicate an indirect working mechanism leading to the increased grip strength.

A systematic review was performed by Nelson (2016) to summarize the results of randomized controlled trials (RCTs) investigating the effects of KT on CLBP. A search was performed on the electronic databases PubMed, MEDLINE, SPORT Discus and Science Direct, up to June 17, 2015 with five studies, involving 306 subjects, meeting the inclusion criteria of the study. Moderate evidence suggests KT, as a sole treatment or in conjunction with another treatment, is no more effective than conventional physical therapy and exercise with respect to improving pain and disability outcomes. The author concluded that KT is not a substitute for traditional PT or exercise and may be most beneficial as an adjunctive therapy for individuals with CLBP. More high quality studies are needed to strengthen the evidence of the effectiveness of KT on CLBP and should include large enough sample sizes to enable subgroup comparisons.

Araujo et al. (2018) investigated the effectiveness of KT in patients with CLBP as it is a common intervention. This was a randomized controlled trial with 6 month follow up. 148 participants were randomly assigned to the experimental group (KT with skin convolutions) or control group (KT without convolutions-Sham Taping). Participants from both groups had the tape reapplied twice a week for four weeks. The outcomes measured were pain intensity, disability and global impression of recovery after 6 months. One participant was lost from the experimental group and two from the control group. After 6 months there were no statistically significant differences between the 2 groups. One item to point out was the vast age range in the participant selection from 18 to 80 years in age.

To determine the effects of KT on pain, function, gait and neuromuscular control concerning patients with knee osteoarthritis (OA) Rahlf et al. (2018) conducted a randomized sham-controlled trial with 141 patients with clinical and radiographic diagnosis of knee OA. The participants had KT, sham tape or no tape for 3 consecutive days. Self-reported pain, stiffness and function were measured by the Western Ontario and McMaster Universities Arthritis Index (WOMAC). Further tests included the Balance Error Scoring System (BESS-Test), 10-m Walk Test (10MWT), the maximum voluntary isometric contraction force (MVIC) of the quadriceps femoris and knee active range of motion (active ROM). Significant effects were found for WOMAC pain (tape vs. sham $p=0.053$; tape vs. control $p=0.047$), stiffness (tape vs. sham $p=0.012$; tape vs. control $p\leq 0.001$) and physical function (tape vs. sham $p=0.034$; tape vs. control $p=0.004$). No interactions were found for balance, muscle strength, walking speed or active ROM. The authors concluded wearing KT for three consecutive days had beneficial effects regarding self-reported clinical outcomes of pain, joint stiffness and function. This emphasizes that KT might be an adequate conservative treatment for the symptoms of knee OA.

A meta-analysis of studies investigating the efficacy of KT application was performed by Csapo and Alegre (2015). A total of 19 studies comprising data of 530 subjects and 48 pairwise comparisons of muscle strength were included. The methodological quality of these studies ranged from moderate to good. The analysis showed the application of KT to facilitate muscular contraction has no or only negligible effects on muscle strength and the effects of KT are not muscle-group dependent. Current evidence suggests that knee extensor and flexor as well as ankle plantar flexor and grip strength cannot be improved by KT application in young (~25 years) and healthy subjects of both sexes. The authors concluded that while the application of KT may have some therapeutic benefits, the usage of these tapes does not promote strength gains in healthy adults. Conclusions about the strength-enhancing effects of KT application on other muscle groups and in other cohorts, such as healthy elderly subjects, require further investigation.

To investigate the effects of KT for stroke patients with hemiplegic shoulder pain (HSP), Huang et al. (2017) conducted a double-blind, placebo-controlled clinical trial. Twenty-one stroke patients with HSP were randomly assigned to 2 groups: a therapeutic KT group and a control group. A 3-week intervention involving a conventional rehabilitation protocol and therapeutic KT was conducted. In the therapeutic group, KT was applied using the insertion origin muscle and space-correction technique. In the control group, the participants were given similar taping patterns, but without tension, which did not cover the joints. Numerical rating scale scores, Shoulder Pain and Disability Index, ultrasound findings and pain-free passive range of motion (ROM) of the affected shoulder, were evaluated before and after the intervention. The therapeutic KT group showed more improvement in the numerical rating scale, degrees of pain-free ROM in shoulder flexion, external rotation, internal rotation, and Shoulder Pain and Disability Index than the sham KT group. The authors concluded that KT is generally a safe therapy for treating HSP stroke patients. The sample size was limited and only the short-term results of KT were investigated. Studies with larger sample sizes and longer follow-up periods are recommended.

In a randomized, placebo-controlled, blind, clinical trial, Dos Santos Gloria et al. (2017) compared the effect of KT and placebo taping on muscle torque, muscle activity and jumping performance for soccer players. Thirty athletes were randomly allocated into two groups - group A contained the participants using the KT and group B using the placebo. The participants were instructed to perform the Hop test's and were submitted to an isokinetic evaluation of the knee extensors as well as an electromyographic evaluation of the rectus femoris muscle of the dominant lower limb. Next, KT was performed for the activation of the rectus femoris muscle in Group A and placebo taping was performed in Group B. The participants were reevaluated 30 minutes after taping and 24 hours after the first

evaluation using the same tests. Intra-group and inter-group comparisons were made considering the three evaluation times. No statistically significant differences were found between group A or B at any evaluation time regarding any of the tests. The authors concluded the KT was no more effective than the placebo on peak muscle torque, muscle activity or jumping performance among the soccer players.

Lee et al. (2016) conducted a randomized control study to examine the effects of KT therapy on degenerative knee arthritis patients' pain, function, and joint range of motion. The 30 patients with degenerative knee arthritis were divided into two groups: the conservative treatment group (CTG, n=15) who received conservative PT and the KT group (KTG, n=15) who received KT therapy. All patients received treatment three times per week for four weeks. The KT group had elastic tapes applied to the hamstring muscles, anterior tibialis, quadriceps femoris, and gastrocnemius. The ROM was measured using joint goniometers, pain was measured using visual analog scales (VAS), and functional evaluation was conducted using the Korean Western Ontario and McMaster Universities Osteoarthritis Index (K-WOMAC). Comparison of the CTG and KTG revealed that the VAS and KWOMAC scores were significantly decreased and the ROM was significantly increased in the KTG. The authors concluded that KT therapy is considered to be an effective nonsurgical intervention method for pain relief, daily living activities, and ROM of degenerative knee arthritis patients. The findings of this study need to be validated by well-designed studies.

Wageck et al. (2016) conducted a randomized clinical trial in which participants were allocated to either the experimental group, which received three simultaneous KT applications, or the control group, which received a single sham KT application. Seventy-six older people with knee osteoarthritis (OA) were participants. The experimental group received three simultaneous KT techniques to treat pain, strength and swelling. The control group received sham taping. All participants kept the taping on for 4 days. The outcomes measured were: concentric muscle strength of knee extensors and flexors, pressure pain threshold, lower-limb swelling, physical function and knee-related health status. At Day 4, there were no significant between-group differences for knee extensor muscle strength, knee flexor muscle strength, the pressure pain threshold at any measured point, volumetry and perimetry at any measured point. The lack of significant between-group difference was also seen at the follow-up assessment on Day 19. The authors concluded that the present study showed that a 4-day application of KT techniques had no significant effect on pain, muscle strength, swelling, knee-related health status, or physical function in older people with knee OA.

Nunes et al. (2015) conducted a randomized controlled trial (n=36) to assess the effects of KT in individuals with ankle sprain. The active treatment group consisted of KT and the control group received an inert KT. Treatment was administered over a period of 3 days. Study results showed that KT was not effective at reducing ankle swelling after an ankle sprain.

In a small randomized controlled trial, Cho et al. (2015) evaluated KT in older adults with knee OA (n=46). Patients were randomized to a group receiving KT with tension or without tension (placebo). Pain intensity was measured using a visual analog scale (VAS). The active treatment group experienced reduced pain during walking and significantly improvement in active ROM. The active treatment group experienced significant improvements in pain compared with controls. The study was limited by its small sample size, which limits the generalizability of the results to a wider population. The study also lacked blinding and had limited follow-up to assess the durability of functional improvements observed in the short term.

Martinez-Gramage et al. (2014) conducted a randomized controlled trial to evaluate the effect of KT on gastrocnemius surface electromyography activity and the ankle ROM during walking in healthy individuals (n=36). Results showed that KT significantly reduced the duration of gastrocnemius activity over a period of 72 hours compared with controls; however, this reduction was not accompanied by a similar reduction in the amplitude of surface electromyography activity.

In a nonrandomized controlled trial, Kaya et al. (2011) compared the efficacy of the KT versus standard PT modalities in 55 patients with shoulder impingement syndrome. The first consecutive 25 patients were enrolled in the PT group and the second consecutive 30 patients were enrolled in the KT group. Baseline characteristics were similar for the two groups. Patients were treated with KT three times with intervals of 3 days, or with a daily program of local PT modalities for 2 weeks. Both groups followed a home exercise program. Response to treatment was evaluated with the Disability of Arm, Shoulder, and Hand (DASH) scale. The DASH Outcome Measure is a 30-item, self-report questionnaire designed to measure physical function and symptoms in patients with musculoskeletal disorders of the upper limb. A decrease in the score indicates improvement. Night pain, daily pain, and pain with motion were assessed with a 100-mm VAS. Outcome measures were assessed at baseline and at the first and second weeks of treatment although the DASH score was evaluated only before and after treatment. KT was more efficacious for relieving symptoms of shoulder impingement than the standard PT modalities during the first week but not completely efficacious during the second week since the VAS scores were similar between the two groups at that follow-up. Limitations of the study included a lack of randomization and inadequate follow-up.

In a 2-part study, Paoloni et al. (2011) evaluated the immediate- and short-term efficacy of KT for treating chronic low back pain in 39 patients. The first part of the study used an intrasubject pretest/posttest procedure in which mean VAS scores for pain and FR values were obtained by sEMG as a measure of lumbar muscle function at baseline and after tape application. In the second part of the study, the patients were randomized into 3 groups: KT Plus Exercise, KT Alone, and Exercise Alone. Outcomes, which were assessed at 1 month after therapy by an investigator who was blinded to treatment assignment, included pain assessed by VAS, disability assessed by sEMG, and disability assessed by the Roland Morris Disability Questionnaire (RMDQ). In the first part of the study, after application of KT, the mean VAS decreased in the entire group from 7.4 at baseline to 5.7. The VAS response rate was 33.3% (13 of 39 patients), and normalized FR was observed in 17 (43.6%) patients. In the second part of the study, a significant reduction in mean VAS scores was observed in each of the 3 groups compared with baseline: KT Plus Exercise (7.6 to 3.7), KT Alone (7.1 to 3.1) and Exercise Alone (7.6 to 3.5). The mean RMDQ score decreased in each group compared with baseline but the difference was significant only for the Exercise Alone group. While the KT appeared to be safe and possibly efficacious in the short term, there is insufficient evidence to determine its true effects on patient outcomes. The study is limited by its small sample size and short follow-up time.

A randomized controlled trial by González-Iglesias et al. (2009) examined the short-term effects of KT applied to the cervical spine in patients with acute whiplash-associated disorder (WAD). Forty-one patients were randomly assigned to 1 of 2 groups: the experimental group received KT to the cervical spine (applied with tension) and the placebo group received a sham KT application (applied without tension). Both neck pain (11-point numerical pain rating scale) and cervical ROM data were collected at baseline, immediately after the KT application, and at a 24-hour follow-up by an assessor blinded to the treatment allocation of the patients. Patients receiving KT experienced a greater decrease in pain immediately post-application and at the 24-hour follow-up. However, patients in the experimental group obtained a greater improvement in range of motion than those in the control group. Improvements in pain and cervical range of motion were small, therefore, future studies are needed with longer follow-up times to evaluate whether KT enhances outcomes.

In a prospective, randomized, double-blinded, clinical study using a repeated-measures design, Thelen et al (2008) determined the short-term clinical efficacy of KT when applied to college students with shoulder pain, as compared to a sham tape application. A total of 42 subjects with clinically diagnosed rotator cuff tendonitis and/or impingement were randomly assigned to 1 of 2 groups: therapeutic KT group or sham KT group. Subjects wore the tape for 2 consecutive 3-day intervals. Self-reported pain and disability and pain-free active ROM were measured at multiple intervals to evaluate for differences between groups. While the therapeutic KT group showed improvement in pain-free shoulder abduction ($p = 0.005$) after tape application, no other differences between groups regarding ROM, pain, or disability scores at any time interval were found.

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Code	Description
97799	Unlisted physical medicine/rehabilitation service or procedure [when used to report physical medicine/rehabilitation services and/or procedures performed utilizing the robotic lower body exoskeleton device]
E1399	Durable medical equipment, miscellaneous [when used to report robotic lower body exoskeleton device]
L2999	Lower extremity orthoses, not otherwise specified [when used to report robotic lower body exoskeleton device]

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.

Hayes et al. (2018) conducted a systematic search of the literature investigating overground 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 overground 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 overground 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.

ECRI (2017) conducted an evidence review of medical literature to evaluate powered wearable exoskeletons in the rehabilitation and community settings. Evidence for powered wearable exoskeleton use by patients with SCI is limited to 10 short-term noncomparative studies: 7 assess the ReWalk, 1 assesses the Ekso GT, and 2 assess the Indego. These studies include outcomes data on only 129 patients with SCI who underwent exoskeleton training in rehabilitation centers. The authors of this review concluded with low confidence that after ReWalk training, some patients with SCI who were unable to walk can walk unassisted for a short distance at a slow rate of speed in a rehabilitation setting, and that a few of those who learned to walk also learned to ascend and descend stairs with assistance in that setting. The authors also concluded with low confidence that with minimal assistance some patients with SCI who were unable to walk or had difficulty walking can walk for a short distance at a slow rate of speed and walk on outdoor surfaces, ramps, and grass wearing an Indego exoskeleton in a rehabilitation setting. The authors commented that no studies assessed short- or long-term safety and efficacy of these devices in the home/community setting; therefore, determining the optimal training required for personal use and whether using this technology in the home/community setting offers a benefit in terms of independence and QOL compared with other assistive devices used to enable standing or mobility is not possible at this time.

Cheung et al. (2017) completed a literature survey 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; $P \leq .00001$; $I^2 = 0\%$). 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.

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.

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
99174	Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with remote analysis and report
99177	Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with on-site analysis

Diagnosis Code	Description
F70	Mild intellectual disabilities
F71	Moderate intellectual disabilities
F72	Severe intellectual disabilities
F73	Profound intellectual disabilities
F78	Other intellectual disabilities
F79	Unspecified intellectual disabilities
F80.0	Phonological disorder
F80.1	Expressive language disorder
F80.2	Mixed receptive-expressive language disorder
F80.4	Speech and language development delay due to hearing loss
F80.81	Childhood onset fluency disorder
F80.82	Social pragmatic communication disorder
F80.89	Other developmental disorders of speech and language
F80.9	Developmental disorder of speech and language, unspecified
F81.0	Specific reading disorder
F81.2	Mathematics disorder

Diagnosis Code	Description
F81.81	Disorder of written expression
F81.89	Other developmental disorders of scholastic skills
F81.9	Developmental disorder of scholastic skills, unspecified
F82	Specific developmental disorder of motor function
F84.2	Rett's syndrome
F84.0	Autistic disorder
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
F84.9	Pervasive developmental disorder, unspecified
F88	Other disorders of psychological development
F89	Unspecified disorder of psychological development
F90.0	Attention-deficit hyperactivity disorder, predominantly inattentive type
F90.1	Attention-deficit hyperactivity disorder, predominantly hyperactive type
F90.2	Attention-deficit hyperactivity disorder, combined type
F90.8	Attention-deficit hyperactivity disorder, other type
F90.9	Attention-deficit hyperactivity disorder, unspecified type
G80.0	Spastic quadriplegic cerebral palsy
G80.1	Spastic diplegic cerebral palsy
G80.2	Spastic hemiplegic cerebral palsy
G80.3	Athetoid cerebral palsy
G80.4	Ataxic cerebral palsy
G80.8	Other cerebral palsy
G80.9	Cerebral palsy, unspecified
H93.25	Central auditory processing disorder
Q05.0	Cervical spina bifida with hydrocephalus
Q05.1	Thoracic spina bifida with hydrocephalus
Q05.2	Lumbar spina bifida with hydrocephalus
Q05.3	Sacral spina bifida with hydrocephalus
Q05.4	Unspecified spina bifida with hydrocephalus
Q05.5	Cervical spina bifida without hydrocephalus
Q05.6	Thoracic spina bifida without hydrocephalus
Q05.7	Lumbar spina bifida without hydrocephalus
Q05.8	Sacral spina bifida without hydrocephalus
Q05.9	Spina bifida, unspecified
Q07.00	Arnold-Chiari syndrome without spina bifida or hydrocephalus
Q07.01	Arnold-Chiari syndrome with spina bifida
Q07.02	Arnold-Chiari syndrome with hydrocephalus
Q07.03	Arnold-Chiari syndrome with spina bifida and hydrocephalus
Q90.0	Trisomy 21, nonmosaicism (meiotic nondisjunction)
Q90.1	Trisomy 21, mosaicism (mitotic nondisjunction)
Q90.2	Trisomy 21, translocation
Q90.9	Down syndrome, unspecified
Q91.0	Trisomy 18, nonmosaicism (meiotic nondisjunction)
Q91.1	Trisomy 18, mosaicism (mitotic nondisjunction)
Q91.2	Trisomy 18, translocation

Diagnosis Code	Description
Q91.3	Trisomy 18, unspecified
Q91.4	Trisomy 13, nonmosaicism (meiotic nondisjunction)
Q91.5	Trisomy 13, mosaicism (mitotic nondisjunction)
Q91.6	Trisomy 13, translocation
Q91.7	Trisomy 13, unspecified
Q92.0	Whole chromosome trisomy, nonmosaicism (meiotic nondisjunction)
Q92.1	Whole chromosome trisomy, mosaicism (mitotic nondisjunction)
Q92.2	Partial trisomy
Q92.5	Duplications with other complex rearrangements
Q92.7	Triploidy and polyploidy
Q92.8	Other specified trisomies and partial trisomies of autosomes
Q92.9	Trisomy and partial trisomy of autosomes, unspecified
Q93.0	Whole chromosome monosomy, nonmosaicism (meiotic nondisjunction)
Q93.1	Whole chromosome monosomy, mosaicism (mitotic nondisjunction)
Q93.2	Chromosome replaced with ring, dicentric or isochromosome
Q93.3	Deletion of short arm of chromosome 4
Q93.4	Deletion of short arm of chromosome 5
Q93.51	Angelman syndrome
Q93.59	Other deletions of part of a chromosome
Q93.7	Deletions with other complex rearrangements
Q93.81	Velo-cardio-facial syndrome
Q93.82	Williams Syndrome
Q93.88	Other microdeletions
Q93.89	Other deletions from the autosomes
Q93.9	Deletion from autosomes, unspecified
Q95.2	Balanced autosomal rearrangement in abnormal individual
Q95.3	Balanced sex/autosomal rearrangement in abnormal individual
Q95.5	Individual with autosomal fragile site
Q95.8	Other balanced rearrangements and structural markers
Q95.9	Balanced rearrangement and structural marker, unspecified
Q96.0	Karyotype 45, X
Q96.1	Karyotype 46, X iso (Xq)
Q96.2	Karyotype 46, X with abnormal sex chromosome, except iso (Xq)
Q96.3	Mosaicism, 45, X/46, XX or XY
Q96.4	Mosaicism, 45, X/other cell line(s) with abnormal sex chromosome
Q96.8	Other variants of Turner's syndrome
Q96.9	Turner's syndrome, unspecified
Q98.0	Klinefelter syndrome karyotype 47, XXY
Q98.1	Klinefelter syndrome, male with more than two X chromosomes
Q98.3	Other male with 46, XX karyotype
Q98.4	Klinefelter syndrome, unspecified
Q99.2	Fragile X chromosome
R41.840	Attention and concentration deficit

Instrument-based ocular photoscreening is proven and medically necessary for one of the following:

- As a mass screening instrument for children 13 years of age (ends on 4th birthday); or
- In individuals 4 years of age and older who are developmentally delayed and are unable or unwilling to cooperate with routine visual acuity screening

Instrument-based ocular photoscreening is unproven and not medically necessary for all other individuals including children less than 1 year of age due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Ocular photoscreening has been investigated as an alternative screening method to detect risk factors for amblyopia, which include strabismus, high refractive errors, anisometropia, and media opacities.

The U.S. Preventive Services Task Force (USPSTF, 2017) concludes with moderate certainty that vision screening to detect amblyopia or its risk factors in children aged 3 to 5 years has a moderate net benefit. They also conclude that the benefits of vision screening to detect amblyopia or its risk factors in children younger than 3 years are uncertain, and that the balance of benefits and harms cannot be determined for this age group.

In a retrospective study, Longmuir et al. (2013) reported their experience with vision screening in children and compared the results of photoscreening in children younger than 3 years with those of children of preschool age and older. During the 11 years of the study, 210,695 pediatric photoscreens were performed at 13,750 sites. In the <3-year age group, the unreadable rate was 13.0%, the referral rate was 3.3%, and the overall positive-predictive value was 86.6%. In the 3- to 6-year-old children, the unreadable rate was 4.1%, the referral rate was 4.7%, and the overall positive-predictive value was 89.4%. The authors concluded that no statistically significant difference was found in screening children from 1 to 3 years old compared with screening children >3 years old. According to the authors, these results confirm that early screening, before amblyopia is more pronounced, can reliably detect amblyogenic risk factors in children younger than 3 years of age, and they recommend initiation of photoscreening in children aged 1 year and older.

In a cross-sectional study, Longmuir et al. (2010) reported on a cohort of preschool children screened by a photoscreening program (using MTI PhotoScreener) over a 9-year period from a single, statewide vision screening effort. Children who failed the photoscreening were referred to local eye care professionals who performed a comprehensive eye evaluation. Over the 9 years of the continuously operating program, 147,809 children underwent photoscreens to detect amblyopic risk factors at 9746 sites. Because of abnormal photoscreen results, 6247 children (4.2%) were referred. The overall positive predictive value (PPV) of the MTI PhotoScreener was 94.2%.

The National Center for Children's Vision and Health (NCCVH) Recommended Practices for vision screening for children ages 36 to <72 Months have provided the following recommendations:

- All children aged 36 months to younger than 72 months should be screened annually (best practice) or at least once (acceptable minimum standard) during the interval between their third and sixth birthdays. Exceptions to this include children with the following: readily observable ocular abnormalities, neurodevelopmental disorders, systemic conditions that have associated ocular abnormalities, first-degree relatives with strabismus or amblyopia, a history of prematurity (<32 completed weeks), and parents who believe their child has a vision problem. These children should be referred directly to an ophthalmologist or optometrist for a comprehensive eye examination. Children who have received an eye examination from an eye care professional within the prior 12 months do not need to be screened. A vision screening program based on best practice standards should be the goal.
- Children who are unable or refuse to complete testing are considered untestable. These children are more likely to have vision problems than testable children, and thus should be rescreened either the same day or soon afterward, but in no case later than 6 months. Children with cognitive, physical, or behavioral issues likely to preclude rescreening and those unable to be rescreened in a timely manner because of administrative or other issues should be referred directly for a comprehensive eye examination.
- Currently, there are 2 best practice vision screening methods for children aged 36 to younger than 72 months: (1) monocular vision acuity testing and (2) instrument-based testing using autorefraction.
 - For visual acuity testing, appropriately scaled (logMAR) single crowded HOTV letters or LEA Symbols surrounded by crowding bars at a 5-ft (1.5-m) test distance with the child matching or reading the optotypes aloud should be used. A passing score is the correct identification of three of three or three of four optotypes with each eye at the 20/50 level for children aged 36 through 47 months and at the 20/40 level for children aged 48 to younger than 72 months. Acceptable practices are to use the HOTV or LEA Symbols calibrated for a 10-ft (3-m) test distance or to use a single line of these optotypes surrounded by a rectangular crowding bar on all four sides. Other optotypes like Allen pictures and the Tumbling E should not be used.
 - The other best practice vision screening method is instrument-based screening using either the Retinomax autorefractor or the SureSight Vision Screener set in child mode and programmed with the VIP Study pass/fail criteria software for 90% specificity (version 2.24 or 2.25) in minus cylinder form. Using the Plusoptix photoscreener is considered acceptable practice, as is adding the PASS stereoacuity test as a supplement to one of the best practice screening methods.
- Vision screening requires training and certification of screening personnel, acquiring sufficient and appropriate space, obtaining and maintaining equipment and supplies, as well as recording and reporting the screening results to the family, primary care provider/medical home, and when indicated the school or appropriate state agency.

- A best practice for children who fail vision screening includes documentation of the referral to and subsequent comprehensive eye examination by an optometrist or ophthalmologist (Cotter et al., 2015).

The American Academy of Ophthalmology (AAO) Preferred Practice Patterns for Pediatric Eye Evaluations (2017) state that vision screening should be performed at an early age and at regular intervals throughout childhood. The elements of vision screening vary depending on the age and level of cooperation of the child. Subjective visual acuity testing is preferred to instrument-based screening in children who are able to participate reliably. Instrument-based screening is useful for some young children and those with developmental delays. Instrument-based screening techniques, such as photoscreening and autorefractometry, are useful for assessing amblyopia and reduced-vision risk factors for children ages 1 to 5 years, as this is a critical time for visual development. Instrument-based screening can occur for children at age 6 years and older when children cannot participate in optotype-based screening.

The American Academy of Ophthalmology, the American Association for Pediatric Ophthalmology and Strabismus, and the American Association of Certified Orthoptists coauthored a policy statement regarding the use of instrument-based screening devices. These devices are available commercially and have had extensive validation, both in field studies as well as in the pediatrician's offices. Screening instruments detect amblyopia, high refractive error, and strabismus, which are the most common conditions producing visual impairment in children. If available, they can be used at any age but have better success after 18 months of age. Instrument-based screening can be repeated at each annual preventive medicine encounter through 5 years of age or until visual acuity can be assessed reliably using optotypes. Using these techniques in children younger than 6 years can enhance detection of conditions that may lead to amblyopia and/or strabismus compared with traditional methods of assessment (Donahue and Baker, 2016a, 2016b).

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Code	Description
B4104	Additive for enteral formula (e.g., fiber)
B4105	In-line cartridge containing digestive enzyme(s) for enteral feeding, each
B9998	NOC for enteral supplies

Digestive enzyme cartridges (e.g., Relizorb™) for use with enteral tube feeding are unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

RELIZORB™ (immobilized lipase) is a single-use, point-of-care digestive enzyme cartridge that connects in-line with existing enteral pump sets. The device is designed to break down fats present in enteral formulas from triglycerides into fatty acids and monoglycerides to allow for their absorption and utilization by the body. This breakdown of fats is intended to mimic the function of the enzyme lipase in patients who do not excrete sufficient levels of pancreatic lipase (Alcresta Therapeutics).

On July 12, 2017, Relizorb was cleared by the FDA for marketing through the 510(k) process, which was an update to the 2015 de novo approval (DEN150001). The device is indicated for use in pediatric (aged 5 years and above) and adult patients to hydrolyze fats with enteral feeding only. Further information can be found at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/K163057.pdf. (Accessed April 19, 2019)

In 2018, Stevens et al. reported the results of the manufacturer sponsored ASSURE study, which evaluated safety, tolerability, and improvement of fatty acid (FA) status in red blood cell (RBC) membranes, a marker of long-term FA absorption, with an in-line digestive cartridge (RELIZORB) that hydrolyzes fat in enteral formula in patients with Cystic Fibrosis (CF). Thirty six patients with a mean age of 13.8 and use of overnight EN for a mean of 6.2 years mean participated in a multicenter, 90-day open-label study during which RELIZORB was used with overnight EN. The primary endpoint was change over time in RBC uptake of docosahexaenoic acid (DHA) + eicosapentaenoic acid (EPA). Gastrointestinal symptoms were collected to evaluate safety and tolerability. Several clinical and anthropometric parameters were also assessed throughout the study. The results showed fat absorption significantly improved as shown by increased RBC levels of DHA+EPA, improved omega-6/omega-3 ratio, and increased plasma levels of DHA+EPA. RELIZORB use was not associated with any unanticipated adverse events. The authors concluded that RELIZORB use was found to be safe, well tolerated, and resulted in increased levels of FAs in RBCs and plasma. This is the first prospective study to show EN can improve FA abnormalities in CF. Improvement in omega-3 levels has been shown to help pulmonary and inflammatory status as well as anthropometric parameters in CF, therefore RELIZORB may have important long-term therapeutic benefits in patients with CF. The findings of this study need to be confirmed with independently conducted randomized controlled trials.

Freedman et al. (2017) evaluated the safety, tolerability and fat absorption of the Relizorb in-line digestive cartridge in 33 patients with cystic fibrosis and exocrine pancreatic insufficiency (EPI) receiving enteral nutrition. The study was comprised of 3 periods: a 7-day run-in period, a randomized, double-blind, placebo-controlled, crossover period and a 7-day open-label safety period. During the initial 7 day run-in period, patients were treated with Peptamen 1.5 supplemented with pancreatic enzyme replacement therapy (PERT) and documented their gastrointestinal (GI) symptoms. During the double-blind crossover period, patients received Impact Peptide 1.5 hydrolyzed by Relizorb or placebo. Patients treated with enteral nutrition hydrolyzed by Relizorb achieved a 2.8-fold increase in fatty acid concentrations compared with placebo. In the final open label treatment period, patients received PERT-supplemented Impact Peptide 1.5 hydrolyzed by Relizorb for 7 days and recorded their GI symptoms. During this treatment period, 42.4% of patients discontinued PERT and continued administration of enteral nutrition with Relizorb. All patients reported a lower incidence and severity of GI symptoms with Relizorb during this period as compared with enteral nutrition supplemented with PERT during the initial 7 day run-in phase. There were no adverse experiences associated with cartridge use, and a decrease in the frequency and severity of most symptoms of malabsorption was observed with cartridge use. Study limitations include small sample size and short-term follow-up. Further studies are needed to assess the long-term safety and efficacy of the Relizorb digestive enzyme cartridge.

In a 2016 evidence based guideline, the Cystic Fibrosis Foundation (CFF) lists this delivery system as an option for pancreatic enzyme replacement therapy following g-tube placement. However CFF states that an evaluation of its benefits and limits should be considered before use (Schwarzenberg et al, 2016).

Reference(s)

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Code	Description
L5781	Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system
L5782	Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system, heavy duty

The use of vacuum pumps for residual limb volume management and moisture evacuation systems among amputees is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Amputation of the lower limbs leads to impaired balance and ambulation. Proper fit of the prosthesis is a determining factor for successful ambulation and overall functioning. Lower limb prostheses are used to replace the functionality of the lower limb extremities in amputees. In addition, vacuum pump residual limb volume management and moisture evaluation systems have been developed for use with lower limb prostheses to improve overall ambulation and functioning of the lower extremities.

Clinical Evidence

Gholizadeh et al. (2016) conducted a review of current evidence on elevated vacuum suspension systems used in patients with lower leg prosthetics. Articles published from 2001 to March 2016 totaled 26. The number of participants averaged 7 for transtibial and 6 for transfemoral amputees. Most studies evaluated the short-term effects of vacuum systems by measuring stump volume changes, gait parameters, pistoning, interface pressures, satisfaction, balance, and wound healing. Professionals (n=155) replied to the questionnaire and supported results from the literature. Elevated vacuum systems may have some advantages over the other suspension systems, but may not be appropriate for all people with limb loss. The authors concluded that elevated vacuum suspension could improve comfort and QOL for people with limb loss. However, future investigations with larger sample sizes are needed to provide strong statistical conclusions and to evaluate long-term effects of these systems.

Hoskins et al. (2014) performed a case study to measure residual limb wound size over time in persons with transtibial amputation while using prostheses with vacuum-assisted suspension. Six subjects with residual limb wounds were fit with vacuum-assisted suspension sockets. Wound surface area was calculated using ImageJ software at the time of fit and each subsequent visit until closure. Results suggest that well-fitting sockets with vacuum-assisted suspension in compliant individuals did not preclude wound healing. Further research is required to substantiate these case-based observations.

In a prospective before-and-after study, Samitier et al. (2014) evaluated vacuum-assisted socket systems (VASS) in amputees. Patients (n=16) were initially assessed using their prosthesis with the regular socket and then subsequently evaluated again 4 weeks after being fitted with the VASS. Study investigators evaluated functional outcomes, such as Medicare Functional Classification Level, Berg Balance Scale, Four Square Step Test, Timed Up and Go Test, the 6-Min Walk Test, the Locomotor Capabilities Index, Satisfaction with Prosthesis (SAT-PRO questionnaire), and Houghton Scale. Use of the VASS resulted in statistically significant improvements in balance, gait, and transfers. Despite these positive outcomes, additional well-designed studies with larger patient populations and appropriate comparators are necessary to establish the efficacy of the VASS in lower-limb amputees.

Trabeallesi et al. (2012) conducted a randomized controlled study to evaluate the effects of a VASS in 20 dysvascular trans-tibial amputees with wounds or ulcers on the stump. Prosthesis use was the primary outcome measure. Secondary outcome measures were mobility with the prosthesis, pain associated with its use, and wound or ulcer healing. The study also included a control group of patients who were trained to use a standard suction socket system prosthesis after ulcer and wound healing. At 12 weeks following rehabilitation, all VASS users were able to walk independently with their prosthesis (median Locomotor Capability Index (LCI) value = 42); while only 5 control patients were able to walk independently. At the 2-month follow-up, the participants used their VASS prostheses for 62 hours a week, which was significantly longer than the control group using the standard prosthesis for 5 hours per week. However, after 6 months of follow-up, any significant differences observed between the VASS and control groups were no longer apparent. In addition, pain and wound healing did not significantly differ between the two groups. The authors concluded that these findings showed that the VASS prosthesis allowed early fitting with prompt ambulation recovery without inhibiting wound healing or increasing pain.

Klute et al. (2011) conducted a 3-week randomized crossover study to investigate the effect of a VASS as compared with a pin locking suspension system on lower extremity amputees (NCT00117793). Twenty unilateral, transtibial amputees were enrolled. Primary outcome measures included activity level, residual limb volume before and after a 30-minute treadmill walk, residual limb pistoning, and Prosthesis Evaluation Questionnaire. Five subjects completed the protocol. Activity levels were significantly lower and residual limb pistoning was significantly less while wearing the VASS versus the pin suspension. Maintenance of residual limb volume was nearly equal for both systems during and after treadmill walking. Questionnaire results suggest a preference for the PIN over the VASS. Participants indicated that their residual limb was healthier, they had a higher level of mobility, and they found their prosthesis less frustrating while wearing the PIN. Limitations of the study include the fact that the prestudy prosthetic prescription of all participants who completed the protocol was a PIN suspension, so a 3-week period to acclimate to the VASS may not have been long enough for some individuals. Retaining subjects was also a challenge. The authors concluded that in this small study, a skilled prosthetist could equally control for daily limb volume fluctuations using conventional, nonvacuum systems, and that participants favored the pin system. Further research is required.

Sanders and Fatone conducted a systematic review of peer reviewed literature to assess what is known about measurement and management of residual limb volume changes in persons with lower-limb amputation. The literature search identified 162 publications, with 52 selected for review based on inclusion criteria. Relating to volume management, while a variety of techniques including VASS have been proposed to control or accommodate residual limb volume, investigation of and evidence regarding their effectiveness is limited. Limitations to the published studies included a lack of testing on less healthy individuals with comorbidities that could influence residual limb volume, the absence of clinical practices for how to select and fit individuals appropriately with these systems, and the lack of

studies on pediatric amputees. The authors concluded that while insights can be drawn from the available research, further studies are required (2011).

An interventional trial (NCT01559909) with 10 participants to assess if the socket height alters the motion of the leg and changes the way one walks when using VASS compared to conventional socket suspension technology was completed in December 2013, but results have not been published. For more information, go to: www.clinicaltrials.gov. (Accessed April 15, 2019).

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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](#).

Clinical Evidence

On February 18, 2013, Oxford Performance Materials (OPM) received 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 PEEK polymer. See the following for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf12/k121818.pdf. (Accessed May 9, 2019)

On January 19, 2017, the Food and Drug Administration (FDA) granted 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. See the following for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf16/k161090.pdf. (Accessed May 9, 2019)

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 cm². 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. This study was limited by a small study population.

In a systematic review, Diment et al. (2018) evaluated the clinical efficacy and effectiveness of using 3D printing to develop medical devices. A double-blinded review method was used to select all abstracts up to January 2017 that reported on clinical trials of a three-dimensional (3D)-printed medical device. The studies were ranked according to their level of evidence, divided into medical fields based on the International Classification of Diseases chapter divisions and categorized into whether they were used for preoperative planning, aiding surgery or therapy. The Downs and Black Quality Index critical appraisal tool was used to assess the quality of reporting, external validity, risk of bias, risk of confounding and power of each study. Of the 3084 abstracts screened, 350 studies met the inclusion criteria. 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. According to the authors, the efficacy and effectiveness of 3D-printed devices remain undetermined for the majority of medical fields. The authors stated that all fields require more rigorous and long-term assessments into the efficacy, effectiveness and safety of 3D-printed devices before they are introduced into standard clinical practice.

In a systematic literature review, Tack et al. (2016) summarized the literature on surgical 3D-printing applications used on patients. Three major literature databases were screened for case series (more than three cases described in the same study) and trials of surgical applications of 3D printing in humans. A total of 227 surgical papers were analyzed and summarized using an evidence table. The papers described the use of 3D printing for surgical guides, anatomical models, and custom implants. 3D printing is used in multiple surgical domains, such as orthopedics, maxillofacial surgery, cranial surgery, and spinal surgery. In general, the advantages of 3D-printed parts are said to include reduced surgical time, improved medical outcome, and decreased radiation exposure. According to the authors, the subjective character and lack of evidence supporting the majority of these advantages does not allow for conclusive statements.

Choi and Kim (2015) conducted a systematic review of the literature 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. According to the authors, 3D printing technology is innovative since there is insufficient scientific data to support the use of this application.

Park et al. (2016) evaluated the efficacy of custom-made three-dimensional (3D)-printed titanium implants for reconstructing skull defects. From 2013 to 2015, 21 patients (8-62 years old, mean = 28.6-year old) 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 and short follow-up time.

Francaviglia et al. (2017) conducted a study to present their preliminary experience with a custom-made cranioplasty, using electron beam melting (EBM) technology, in a series of ten patients. EBM is a new sintering method for shaping titanium powder directly in three-dimensional (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 a small study population.

Reference(s)

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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 (no implants) then activating small motors to move the arm and hand as the user intends (no electrical stimulation).

The MyoPro® is designed to enable individuals to support and assist movement of a weak or deformed hand and arm. Patients can self-initiate and control movement of a partially paretic upper limb using their own myoelectric signals. Similar to how a myoelectrically controlled prosthetic operates; the MyoPro orthosis utilizes surface EMG sensing technology to enable volitional motion of the impaired limb. When the user tries to move their extremity, sensors in the orthosis detect, process, and amplify the weak myoelectric signal, which activates motors to move the extremity in the desired direction. The user is in complete control of their own extremity; the orthosis assists with movement only once a signal is detected (Hayes, 2018).

A 2019 Hayes report report concluded that there is insufficient published evidence to assess the safety and/or impact of robotic rehabilitation of upper extremities on health outcomes or management of patients with degenerative neurological conditions.

McCabe et al. (2019) performed a retrospective study is to demonstrate feasibility of the implementation of an upper limb myoelectric orthosis for the treatment of persistent moderate upper limb impairment following stroke (>6 months). Nine patients (>6 months post stroke) participated in treatment at an outpatient Occupational Therapy department utilizing the MyoPro myoelectric orthotic device. Group therapy was provided at a frequency of 1-2 sessions per week (60-90 minutes per session). Patients were instructed to perform training with the device at home on non-therapy days and to continue with use of the device after completion of the group training period. Outcome measures included Fugl-Meyer Upper Limb Assessment (FM) and modified Ashworth Scale (MAS). Patients demonstrated improvement of 9.0±4.8 points on a measure of motor control impairment (FM) during participation in group training. The training was administered in a group setting using a 1:4 ratio (therapist to patients). Muscle tone improved for muscles. The authors concluded that myoelectric orthosis use is feasible in a group clinic setting and in home-use structure for chronic stroke survivors. Clinically important motor control gains were observed on FM in 7 of 9 patients who participated in training. Limitations include non-randomization and small sample size.

A 2018 ECRI Custom Product Brief identified one case series (n = 18) examining the device MyoPro. The report concluded that the evidence is insufficient to determine how well the MyoPro 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, and study use of the device in different patient populations.

A 2018 Hayes report concluded that there is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management associated with the use of the MyoPro Orthosis for upper extremity paralysis/paresis after stroke.

Peters et al. (2017) performed an observational cohort study (n=18) to determine the immediate effect of a portable, myoelectric elbow-wrist-hand orthosis on paretic upper extremity (UE) impairment in chronic, stable, moderately impaired stroke survivors. Each subject performed a series of tests including the Fugl-Meyer Assessment and the Box and Blocks test. The subjects completed the tests in the same order with and without wearing a MyoPro Motion-G myoelectric elbow-wrist-hand orthosis. The subjects exhibited reduced UE impairment while wearing the myoelectric elbow-wrist-hand orthosis and increased quality in performing all functional tasks while wearing the myoelectric

elbow-wrist-hand orthosis, with 3 subtasks showing significant increases (feeding [grasp], feeding [elbow] and drinking [grasp]). The authors concluded that statistically significant results were demonstrated for many activities including elbow extension, grasping items, finger extension, and manual dexterity. This is an uncontrolled study with a small sample size.

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 repetitive task-specific practice in a person with chronic, moderate upper extremity impairment. A total of 16 people were 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 a repetitive task-specific practice 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 repetitive task-specific practice 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

Reference(s)

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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

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, we 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 specialised 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.

Hair analysis has been proposed as an aid in the diagnosis of several conditions including mineral or protein deficiency, allergies, hair loss, autism, schizophrenia, and mood disorders. Hair has also been used as a specimen source for drug testing. The clinical utility of hair loss for these conditions and for drug testing in pain management or substance abuse treatment has not been established. Interpretation of hair analysis may be unreliable and there are no referenced norms to support or establish that hair can be a consistent biological marker or that completion of such tests will change medical management (Tamburo et al., 2015; Younge et al., 2015).

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: macroelements, 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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Code	Description
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

It is estimated that approximately 50% of human immunodeficiency virus (HIV) patients who are treated with highly active antiretroviral therapy (HAART) develop significant loss of fatty tissue (lipoatrophy) in the face. 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).

The U.S. Food and Drug Administration (FDA) 510(k) documents refer to Prolaryn products 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.).

According to the 510(k) documentation, Radiesse Laryngeal Implant is indicated for: vocal fold medialization and vocal fold insufficiency that may be improved by injection of a soft tissue bulking agent. Radiesse Laryngeal Implant injection augments the size of the displaced or deformed vocal fold so that it may meet the opposing fold at the midline for improved phonation. Vocal fold insufficiency associated with serious aspiration difficulties may be an urgent indication.

The Radiesse Laryngeal Implant (BioForm Medical Inc.) received FDA 510(k) clearance (K070090) as substantially equivalent to legally marketed predicate devices on March 1, 2007, for vocal fold medialization and treatment of vocal fold insufficiency that can be improved by injection of a soft-tissue bulking agent. The Radiesse Laryngeal Implant is intended to augment the size of the displaced or deformed vocal fold so that it may meet the opposing vocal fold at the midline for improved phonation.

The FDA categorizes Radiesse and Sculptra as medical devices (injectable implants, vocal cord medialization) with product code MIX.

On December 22, 2006, the FDA approved Radiesse, an injectable (under the skin) implant to restore or correct signs of facial lipodystrophy, or fat loss, in people with human immunodeficiency virus (HIV). For additional information, refer to the following website: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?id=k070090>. (Accessed April 2, 2019)

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 2, 2019)

Vallejo et al. (2018) conducted a clinical trial including 147 patients with HIV-induced lipodystrophy 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. Number of sessions, total volume injected, and overall costs of treatment were also analyzed. Objective improvement in facial lipodystrophy, 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 lipodystrophy 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.

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 $P < 0.033$).

In a multicenter 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.

Carroll and Rosen (2011) evaluated the long-term effectiveness of CaHA as a vocal fold injectable by assessing data from a cohort of patients who underwent injection for glottal insufficiency. The change in Voice Handicap Index (VHI)-10 scores between preinjection scores and best postinjection scores as well as between the preinjection 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.

The safety and effectiveness of Radiesse for the treatment of facial lipoatrophy was evaluated in a prospective, open-label, multi-center study of 100 patients with HIV and facial lipoatrophy. Patients received an initial treatment (initial injection and an additional injection at 1 month as needed). Six months later, all patients were assessed for the need for a touch up injection. Effectiveness was assessed at 3, 6 and 12 months from initial treatment by means of a Global Aesthetic Improvement Scale (GAIS) rating, cheek skin thickness measurements, and patient satisfaction assessment. Safety was assessed by the recording of AEs through 12 months. Mean cheek thickness doubled in 6 months and was maintained over 12 months (Silvers et al. 2006).

The use of Sculptra or poly-L-lactic acid to treat facial lipoatrophy resulted in significant and prolonged improvement in HIV-infected patients in several clinical trials (Levy et al., 2008; Nelson and Stewart, 2012; Shuck, 2013; Bassichis, 2012; Duracinsky, 2014; Jagdeo, et al., 2015).

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. They recommend use of the Facial Appearance Inventory (FAI) and FACE-Q in future studies for HA filler treatment of HIV FLA.

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Date	Action/Description
10/01/2019	<p>Coverage Rationale</p> <ul style="list-style-type: none"> • Simplified content • Added coverage guidelines for: <ul style="list-style-type: none"> Bone microindentation testing (BMT) (CPT code 0547T) <ul style="list-style-type: none"> ○ Added language to indicate bone microindentation testing (BMT) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy Transperineal periurethral balloon continence devices (e.g., ProAct™) (CPT codes 0548T, 0549T, 0550T, and 0551T) <ul style="list-style-type: none"> ○ Added language to indicate 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 Three dimensional (3D) printed anatomic models (CPT codes 0559T, 0560T, 0561T, and 0562T) <ul style="list-style-type: none"> ○ Added language to indicate the use of three dimensional (3D) printed anatomic models is unproven and not medically necessary for all indications, including but not limited to medical education and surgical planning, due to insufficient evidence of safety and/or efficacy Coblation nasal septal swell body reduction (CPT code 30999) <ul style="list-style-type: none"> ○ Added language to indicate coblation nasal septal swell body reduction for the treatment of nasal obstruction is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy UroCuff test (CPT code 53899) <ul style="list-style-type: none"> ○ Added language to indicate the UroCuff test for diagnosing male lower urinary tract disorders is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy • Revised coverage guidelines for: <ul style="list-style-type: none"> Implantable neurostimulation devices for the treatment of central sleep apnea (CPT codes 0424T, 0425T, 0426T, 0427T, 0428T, 0429T, 0430T, 0431T, 0432T, 0433T, 0434T, 0435T, and 0436T) <ul style="list-style-type: none"> ○ Updated list of applicable CPT codes; revised description for 0430T Multifocal electroretinogram (mfERG) and pattern electroretinogram (PERG) or pattern electroretinogram optimized for glaucoma screening (PERGLA) (CPT codes 0509T and 92274) <ul style="list-style-type: none"> ○ Updated list of applicable CPT codes: <ul style="list-style-type: none"> ▪ Added 92274 ▪ Removed 92499 Intracardiac ischemia monitoring systems (e.g., AngelMed Guardian System) (CPT codes 0525T, 0526T, 0527T, 0528T, and 0529T) <ul style="list-style-type: none"> ○ Updated list of applicable CPT codes; removed 0530T, 0531T, and 0532T Refined autologous adipose cell transfer (CPT code 27599) <ul style="list-style-type: none"> ○ Replaced language indicating "refined autologous adipose cell transfer is unproven and not medically necessary for the treatment of meniscal tears" with "refined autologous adipose cell transfer is unproven and not medically necessary to treat conditions of the knee" ○ Updated list of applicable CPT codes; revised description for 27599 Kinesio taping (CPT codes 29799, 97139, 97799 and HCPCS code A9999) <ul style="list-style-type: none"> ○ Updated list of applicable HCPCS codes; added A9999 Absorbable nasal implants (CPT code 30999 and HCPCS code L8699) <ul style="list-style-type: none"> ○ Changed brand name for the Latera Absorbable Nasal Implant from "Spirox®" to "Stryker" Surgical treatment of a Tarlov cyst from the sacrum (CPT codes 63268 and 64999) <ul style="list-style-type: none"> ○ Updated list of applicable CPT codes: <ul style="list-style-type: none"> ▪ Added 63268 ▪ Added notation for 64999 to indicate this unlisted code is used to report surgical treatment of a Tarlov cyst not described by 63268

Date	Action/Description
	<p>Antiprothrombin antibody testing for antiphospholipid syndrome (CPT code 86849)</p> <ul style="list-style-type: none"> ○ Updated list of applicable CPT codes; added notation for 86849 to indicate this unlisted code is used to report antiprothrombin antibody testing for antiphospholipid syndrome <p>Instrument-based ocular photoscreening (CPT codes 99174 and 99177)</p> <ul style="list-style-type: none"> ○ Updated list of applicable ICD-10 diagnosis codes: <ul style="list-style-type: none"> ▪ Added F80.0, F80.1, F80.2, F80.81, F80.82, F80.89, F80.9, F81.0, F81.2, F81.81, F81.89, F81.9, F84.2, F88, F89, Q93.51 Q93.59, and Q93.82 ▪ Removed E78.71, E78.72, F07.9, F09, F45.8, G12.0, G20, G21.4, G23.0, G23.1, G23.2, G23.8, G23.9, G37.0, G37.5, G40.001, G40.009, G40.011, G40.019, G40.101, G40.109, G40.111, G40.119, G40.201, G40.209, G40.211, G40.219, G40.301, G40.309, G40.311, G40.319, G40.401, G40.409, G40.411, G40.419, G40.501, G40.509, G40.801, G40.802, G40.803, G40.804, G40.811, G40.812, G40.813, G40.814, G40.821, G40.822, G40.823, G40.824, G40.89, G40.901, G40.909, G40.911, G40.919, G40.A01, G40.A09, G40.A11, G40.A19, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, G52.7, G60.8, G71.2, G72.3, G83.81, G83.82, G83.83, G83.84, G83.89, G83.9, G90.09, G90.3, G93.1, G97.31, G97.32, I67.2, I67.81, I67.82, I67.89, I68.0, I68.8, I69.00, I69.010, I69.011, I69.012, I69.013, I69.014, I69.015, I69.018, I69.019, I69.020, I69.021, I69.023, I69.031, I69.032, I69.033, I69.034, I69.039, I69.041, I69.042, I69.043, I69.044, I69.049, I69.051, I69.052, I69.053, I69.054, I69.059, I69.061, I69.062, I69.063, I69.064, I69.065, I69.069, I69.090, I69.091, I69.092, I69.093, I69.098, I69.10, I69.110, I69.111, I69.112, I69.113, I69.114, I69.115, I69.118, I69.119, I69.120, I69.121, I69.123, I69.131, I69.132, I69.133, I69.134, I69.139, I69.141, I69.142, I69.143, I69.144, I69.149, I69.151, I69.152, I69.153, I69.154, I69.159, I69.161, I69.162, I69.163, I69.164, I69.165, I69.169, I69.190, I69.191, I69.192, I69.193, I69.198, I69.20, I69.210, I69.211, I69.212, I69.213, I69.214, I69.215, I69.218, I69.219, I69.220, I69.221, I69.223, I69.231, I69.232, I69.233, I69.234, I69.239, I69.241, I69.242, I69.243, I69.244, I69.249, I69.251, I69.252, I69.253, I69.254, I69.259, I69.261, I69.262, I69.263, I69.264, I69.265, I69.269, I69.290, I69.291, I69.292, I69.293, I69.298, I69.30, I69.310, I69.311, I69.312, I69.313, I69.314, I69.315, I69.318, I69.319, I69.320, I69.321, I69.323, I69.331, I69.332, I69.333, I69.334, I69.339, I69.341, I69.342, I69.343, I69.344, I69.349, I69.351, I69.352, I69.353, I69.354, I69.359, I69.361, I69.362, I69.363, I69.364, I69.365, I69.369, I69.390, I69.391, I69.392, I69.393, I69.398, I69.80, I69.810, I69.811, I69.812, I69.813, I69.814, I69.815, I69.818, I69.819, I69.820, I69.821, I69.823, I69.831, I69.832, I69.833, I69.834, I69.839, I69.841, I69.842, I69.843, I69.844, I69.849, I69.851, I69.852, I69.853, I69.854, I69.859, I69.861, I69.862, I69.863, I69.864, I69.865, I69.869, I69.890, I69.891, I69.892, I69.893, I69.898, I69.90, I69.910, I69.911, I69.912, I69.913, I69.914, I69.915, I69.918, I69.919, I69.920, I69.921, I69.923, I69.931, I69.932, I69.933, I69.934, I69.939, I69.941, I69.942, I69.943, I69.944, I69.949, I69.951, I69.952, I69.953, I69.954, I69.959, I69.961, I69.962, I69.963, I69.964, I69.965, I69.969, I69.990, I69.991, I69.992, I69.993, I97.810, I97.811, I97.820, I97.821, Q14.2, Q87.81, Q93.5, R29.5, R62.0, S12.000A, S12.000B, S12.001A, S12.001B, S12.100A, S12.100B, S12.101A, S12.101B, S12.200A, S12.200B, S12.201A, S12.201B, S12.300A, S12.300B, S12.301A, S12.301B, S12.400A, S12.400B, S12.401A, S12.401B, S12.500A, S12.500B, S12.501A, S12.501B, S12.600A, S12.601A, S12.601B, S12.9XXA, S14.101A, S14.102A, S14.103A, S14.104A, S14.105A, S14.106A, S14.107A, S14.109A, S14.111A, S14.112A, S14.113A, S14.114A, S14.115A, S14.116A, S14.117A, S14.119A, S14.121A, S14.122A, S14.123A, S14.124A, S14.125A, S14.126A, S14.127A, S14.129A, S14.131A, S14.132A, S14.133A, S14.134A, S14.135A, S14.136A, S14.137A, S14.139A, S14.151A, S14.152A, S14.153A, S14.154A, S14.155A, S14.156A, S14.157A, S22.009A, S22.009B, S22.019A, S22.019B, S22.029A, S22.029B, S22.039A, S22.039B, S22.049A, S22.049B, S22.059A,

Date	Action/Description
	<p>S22.059B, S22.069A, S22.069B, S22.079A, S22.079B, S22.089A, S22.089B, S24.101A, S24.102A, S24.103A, S24.104A, S24.109A, S24.109D, S24.109S, S24.111A, S24.112A, S24.113A, S24.114A, S24.119A, S24.131A, S24.132A, S24.133A, S24.134A, S24.139A, S24.151A, S24.152A, S24.153A, S24.154A, S24.159A, S32.009A, S32.009B, S32.019A, S32.019B, S32.029A, S32.029B, S32.039A, S32.039B, S32.049A, S32.049B, S32.059A, S32.059B, S32.10XA, S32.10XB, S32.2XXA, S32.2XXB, S34.101A, S34.102A, S34.103A, S34.104A, S34.105A, S34.109A, S34.111A, S34.112A, S34.113A, S34.114A, S34.115A, S34.119A, S34.121A, S34.122A, S34.123A, S34.124A, S34.125A, S34.129A, S34.131A, S34.132A, S34.139A, S34.3XXA, T20.00XS, T20.011S, T20.012S, T20.019S, T20.02XS, T20.03XS, T20.04XS, T20.05XS, T20.06XS, T20.07XS, T20.09XS, T20.10XS, T20.111S, T20.112S, T20.119S, T20.12XS, T20.13XS, T20.14XS, T20.15XS, T20.16XS, T20.17XS, T20.19XS, T20.20XS, T20.211S, T20.212S, T20.219S, T20.22XS, T20.23XS, T20.24XS, T20.25XS, T20.26XS, T20.27XS, T20.29XS, T20.30XS, T20.311S, T20.312S, T20.319S, T20.32XS, T20.33XS, T20.34XS, T20.35XS, T20.36XS, T20.37XS, T20.39XS, T20.40XS, T20.411S, T20.412S, T20.419S, T20.42XS, and T20.43XS</p> <ul style="list-style-type: none"> • Removed coverage guidelines for: <ul style="list-style-type: none"> ○ Computer-assisted musculoskeletal surgical navigational for orthopedic procedures (CAOS) and the use of intra-operative kinetic balance sensor for implant stability during knee replacement arthroplasty (CPT codes 0054T, 0055T, 0396T, and 20985); refer to the policy titled Computer-Assisted Surgical Navigation for Musculoskeletal Procedures for applicable coverage guidelines ○ Optical coherence tomography (OCT) (CPT codes 0470T and 0471T) (no longer requires clinical review) ○ The use of implantable bronchial valves as an alternative to lung volume reduction surgery (LVRS) in patients with emphysema (CPT codes 31647, 31648, 31649, and 31651) (no longer requires clinical review) ○ Ultrasound elastography (CPT codes 76981, 76982, and 76983) (no longer requires clinical review) <p>Supporting Information</p> <ul style="list-style-type: none"> • Updated <i>Clinical Evidence</i> and <i>References</i> sections to reflect the most current information • Archived previous policy version 2019T0535ZZ

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.