Omnibus Codes

Policy Number: 2022T0535LL
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Instructions for Use

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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.

Code	Description	Conclusion
0042T	Cerebral perfusion analysis using computed tomography with contrast administration, including post-processing of parametric maps with determination of cerebral blood flow, cerebral blood volume, and mean transit time	Proven in certain circumstances
0061U	Transcutaneous measurement of five biomarkers (tissue oxygenation [StO2], oxyhemoglobin [ctHbO2], deoxyhemoglobin [ctHbR], papillary and reticular dermal hemoglobin concentrations [ctHb1 and ctHb2]), using spatial frequency domain imaging (SFDI) and multi-spectral analysis	Unproven
0100T	Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy	Unproven
0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas	Unproven
0174T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure)	Unproven
0175T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation	Unproven
0207T	Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral	Unproven
0208T	Pure tone audiometry (threshold), automated; air only	Unproven

Code	Description	Conclusion
0209T	Pure tone audiometry (threshold), automated; air and bone	Unproven
0210T	Speech audiometry threshold, automated	Unproven
0211T	Speech audiometry threshold, automated; with speech recognition	Unproven
0212T	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated	Unproven
0247U	Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth	Unproven
0266T	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0267T	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0268T	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0269T	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0270T	Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0271T	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)	Unproven
0272T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day)	Unproven
0273T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming	Unproven
0330T	Tear film imaging, unilateral or bilateral, with interpretation and report	Unproven
0331T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment	Unproven
0332T	Myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment; with tomographic SPECT	Unproven
0335T	Insertion of sinus tarsi implant	Unproven
0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery (ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and	Unproven

Code	Description	Conclusion
	interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral	
0339T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery (ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral	Unproven
0351T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative	Unproven
0352T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred	Unproven
0353T	Optical coherence tomography of breast, surgical cavity; real-time intraoperative	Unproven
0354T	Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred	Unproven
0358T	Bioelectrical impedance analysis whole body composition assessment, with interpretation and report	Unproven
0394T	High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed	Unproven
0395T	High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed	Unproven
0397T	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)	Unproven
0398T	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed	Unproven
0408T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes	Unproven
0409T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only	Unproven
0410T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only	Unproven
0411T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only	Unproven
0412T	Removal of permanent cardiac contractility modulation system; pulse generator only	Unproven
0413T	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)	Unproven
0414T	Removal and replacement of permanent cardiac contractility modulation system pulse generator only	Unproven
0415T	Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)	Unproven

Code	Description	Conclusion
0416T	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator	Unproven
0417T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system	Unproven
0418T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system	Unproven
0440T	Ablation, percutaneous, cryoablation, includes imaging guidance; upper extremity distal/peripheral nerve	Unproven
0441T	Ablation, percutaneous, cryoablation, includes imaging guidance; lower extremity distal/peripheral nerve	Unproven
0442T	Ablation, percutaneous, cryoablation, includes imaging guidance; nerve plexus or other truncal nerve (e.g., brachial plexus, pudendal nerve)	Unproven
0444T	Initial placement of a drug-eluting ocular insert under one or more eyelids, including fitting, training, and insertion, unilateral or bilateral	Unproven
0445T	Subsequent placement of a drug-eluting ocular insert under one or more eyelids, including re-training, and removal of existing insert, unilateral or bilateral	Unproven
0469T	Retinal polarization scan, ocular screening with on-site automated results, bilateral	Unproven
0472T	Device evaluation, interrogation, and initial programming of intraocular retinal electrode array (e.g., retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed values with analysis, including visual training, with review and report by a qualified health care professional	Unproven
0473T	Device evaluation and interrogation of intraocular retinal electrode array (e.g., retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional	Unproven
0479T	Fractional ablative laser fenestration of burn and traumatic scars for functional improvement; first 100 cm2 or part thereof, or 1% of body surface area of infants and children	Unproven
0480T	Fractional ablative laser fenestration of burn and traumatic scars for functional improvement; each additional 100 cm2, or each additional 1% of body surface area of infants and children, or part thereof (List separately in addition to code for primary procedure)	Unproven
0485T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; unilateral	Unproven
0486T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; bilateral	Unproven
0487T	Biomechanical mapping, transvaginal, with report	Unproven
0491T	Ablative laser treatment, non-contact, full field and fractional ablation, open wound, per day, total treatment surface area; first 20 sq cm or less	Unproven
0492T	Ablative laser treatment, non-contact, full field and fractional ablation, open wound, per day, total treatment surface area; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)	Unproven

Code	Description	Conclusion
0493T	Contact near-infrared spectroscopy studies of lower extremity wounds (e.g., for oxyhemoglobin measurement)	Unproven
0506T	Macular pigment optical density measurement by heterochromatic flicker photometry, unilateral or bilateral, with interpretation and report	Unproven
0507T	Near-infrared dual imaging (i.e., simultaneous reflective and trans-illuminated light) of meibomian glands, unilateral or bilateral, with interpretation and report	Unproven
0508T	Pulse-echo ultrasound bone density measurement resulting in indicator of axial bone mineral density, tibia	Unproven
0509T	Electroretinography (ERG) with interpretation and report, pattern (PERG)	Unproven
0510T	Removal of sinus tarsi implant	Unproven
0511T	Removal and reinsertion of sinus tarsi implant	Unproven
0515T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; complete system (includes electrode and generator [transmitter and battery])	Unproven
0516T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only	Unproven
0517T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; pulse generator component(s) (battery and/or transmitter) only	Unproven
0518T	Removal of only pulse generator component(s) (battery and/or transmitter) of wireless cardiac stimulator for left ventricular pacing	Unproven
0519T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter)	Unproven
0520T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter), including placement of a new electrode	Unproven
0521T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording, and disconnection per patient encounter, wireless cardiac stimulator for left ventricular pacing	Unproven
0522T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, wireless cardiac stimulator for left ventricular pacing	Unproven
0525T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; complete system (electrode and implantable monitor)	Unproven
0526T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; electrode only	Unproven
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

Code	Description	Conclusion
0528T	Programming device evaluation (in person) of intracardiac ischemia monitoring system with iterative adjustment of programmed values, with analysis, review, and report	Unproven
0529T	Interrogation device evaluation (in person) of intracardiac ischemia monitoring system with analysis, review, and report	Unproven
0530T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; complete system (electrode and implantable monitor)	Unproven
0531T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; electrode only	Unproven
0532T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; implantable monitor only	Unproven
0547T	Bone-material quality testing by micro indentation(s) of the tibia(s), with results reported as a score	Unproven
0559T	Anatomic model 3D-printed from image data set(s); first individually prepared and processed component of an anatomic structure	Unproven
0560T	Anatomic model 3D-printed from image data set(s); each additional individually prepared and processed component of an anatomic structure (List separately in addition to code for primary procedure)	Unproven
0561T	Anatomic guide 3D-printed and designed from image data set(s); first anatomic guide	Unproven
0562T	Anatomic guide 3D-printed and designed from image data set(s); each additional anatomic guide (List separately in addition to code for primary procedure)	Unproven
0563T	Evacuation of meibomian glands, using heat delivered through wearable, open-eye eyelid treatment devices and manual gland expression, bilateral	Unproven
0567T	Permanent fallopian tube occlusion with degradable biopolymer implant, transcervical approach, including transvaginal ultrasound	Unproven
0581T	Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral	Unproven
0583T	Tympanostomy (requiring insertion of ventilating tube), using an automated tube delivery system, iontophoresis local anesthesia	Unproven
0584T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; percutaneous	Unproven
0585T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; laparoscopic	Unproven
0586T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; open	Unproven
0596T	Temporary female intraurethral valve-pump (i.e., voiding prosthesis); initial insertion, including urethral measurement	Unproven
0597T	Temporary female intraurethral valve-pump (i.e., voiding prosthesis); replacement	Unproven
0598T	Noncontact real-time fluorescence wound imaging, for bacterial presence, location, and load, per session; first anatomic site (e.g., lower extremity)	Unproven

Code	Description	Conclusion
0599T	Noncontact real-time fluorescence wound imaging, for bacterial presence, location, and load, per session; each additional anatomic site (e.g., upper extremity) (List separately in addition to code for primary procedure)	Unproven
0631T	Transcutaneous visible light hyperspectral imaging measurement of oxyhemoglobin, deoxyhemoglobin, and tissue oxygenation, with interpretation and report, per extremity	Unproven
0640T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); image acquisition, interpretation and report, each flap or wound	Unproven
0641T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); image acquisition only interpretation and report, each flap or wound	Unproven
0642T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); interpretation and report only, each flap or wound	Unproven
0647T	Insertion of gastrostomy tube, percutaneous, with magnetic gastropexy, under ultrasound guidance, image documentation and report	Unproven
0651T	Magnetically controlled capsule endoscopy, esophagus through stomach, including intraprocedural positioning of capsule, with interpretation and report	Unproven
0658T	Electrical impedance spectroscopy of 1 or more skin lesions for automated melanoma risk score	Unproven
0664T	Donor hysterectomy (including cold preservation); open, from cadaver donor	Unproven
0665T	Donor hysterectomy (including cold preservation); open, from living donor	Unproven
0666T	Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor	Unproven
0667T	Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor	Unproven
0668T	Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary	Unproven
0669T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each	Unproven
0670T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each	Unproven
0672T	Endovaginal cryogen-cooled, monopolar radiofrequency remodeling of the tissues surrounding the female bladder neck and proximal urethra for urinary incontinence	Unproven
0692T	Therapeutic ultrafiltration	Unproven
0693T	Comprehensive full body computer-based markerless 3D kinematic and kinetic motion analysis and report	Unproven
0694T	3-dimensional volumetric imaging and reconstruction of breast or axillary lymph node tissue, each excised specimen, 3-dimensional automatic specimen reorientation, interpretation and report, real-time intraoperative	Unproven
19105	Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma	Unproven

Code	Description	Conclusion
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
23929	Unlisted procedure, shoulder [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]	Unproven
29799	Unlisted procedure – Kinesio taping	Unproven
30117	Excision or destruction (e.g., laser) of intranasal lesion; internal approach [when used for nasal septal swell body reduction]	Unproven
30468	Repair of nasal valve collapse with subcutaneous/submucosal lateral wall implant(s)	Unproven
30999	Unlisted procedure, nose [when used for nasal septal swell body reduction]	Unproven for Coblation, Rhinophototherapy, and Nasal Implant
30999	Unlisted procedure, nose [when used to report rhinophototherapy, intranasal application of ultraviolet and visible light, bilateral]	Unproven
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
33267	Exclusion of left atrial appendage, open, any method (e.g., excision, isolation via stapling, oversewing, ligation, plication, clip)	Unproven
33268	Exclusion of left atrial appendage, open, performed at the time of other sternotomy or thoracotomy procedure(s), any method (e.g., excision, isolation via stapling, oversewing, ligation, plication, clip) (List separately in addition to code for primary procedure)	Unproven
33269	Exclusion of left atrial appendage, thoracoscopic, any method (e.g., excision, isolation via stapling, oversewing, ligation, plication, clip)	Unproven
33274	Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (e.g., fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (e.g., interrogation or programming), when performed	Unproven
33275	Transcatheter removal of permanent leadless pacemaker, right ventricular, including imaging guidance (e.g., fluoroscopy, venous ultrasound, ventriculography, femoral venography), when performed	Unproven
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	Proven in certain circumstances
33999	Unlisted procedure, cardiac surgery	Unproven for AtriClip
37799	Unlisted procedure, vascular surgery (when used to report aquapheresis (ultrafiltration))	Unproven
43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy	Unproven

Code	Description	Conclusion
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
53451	Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance	Unproven
53452	Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance	Unproven
53453	Periurethral transperineal adjustable balloon continence device; removal, each balloon	Unproven
53454	Periurethral transperineal adjustable balloon continence device; percutaneous adjustment of balloon(s) fluid volume	Unproven
53860	Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence	Unproven
53899	Unlisted procedure, urinary system [when used to report UroCuff test or Viveve system]	Unproven for the UroCuff test and Viveve system
55899	Unlisted procedure, male genital system [when used to report UroCuff]	Unproven
58999	Unlisted procedure, female genital system (nonobstetrical) [when used to report Viveve]	Unproven
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
64454	Injection(s), anesthetic agent(s) and/or steroid; genicular nerve branches, including imaging guidance, when performed	Unproven
64624	Destruction by neurolytic agent, genicular nerve branches including imaging guidance, when performed	Unproven
64999	Unlisted procedure, nervous system [when used to report cooled radiofrequency ablation]	Unproven for cooled radiofrequency ablation
68841	Insertion of drug-eluting implant, including punctal dilation when performed, into lacrimal canaliculus, each	Unproven
69705	Nasopharyngoscopy, surgical, with dilation of eustachian tube (i.e., balloon dilation); unilateral	Unproven
69706	Nasopharyngoscopy, surgical, with dilation of eustachian tube (i.e., balloon dilation); bilateral	Unproven
69799	Unlisted procedure, middle ear [when used to report balloon dilation]	Unproven
76120	Cineradiography/video radiography, except where specifically included	Unproven
76125	Cineradiography/video radiography 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

Code	Description	Conclusion
77469	Intraoperative radiation treatment management	Unproven
80145	Adalimumab	Unproven
80230	Infliximab	Unproven
80280	Vedolizumab	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
81599	Unlisted multianalyte assay with algorithmic analysis (when used to report PreTrm)	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
88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session	Unproven
90999	Unlisted dialysis procedure, inpatient or outpatient (when used to report aquapheresis (ultrafiltration))	Unproven
91113	Gastrointestinal tract imaging, intraluminal (e.g., capsule endoscopy), colon, with interpretation and report	Unproven
92274	Electroretinography (ERG), with interpretation and report; multifocal (mfERG)	Proven in certain circumstances
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
96999	Unlisted special dermatological service or procedure [when used to report multi-spectral digital skin lesion analysis]	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 for Kinesio taping and robotic lower body exoskeleton
99174	Instrument-based ocular screening (e.g., photo screening, automated-refraction), bilateral; with remote analysis and report	Proven in certain circumstances
99177	Instrument-based ocular screening (e.g., photo screening, 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
B4105	In-line cartridge containing digestive enzyme(s) for enteral feeding, each	Unproven

Code	Description	Conclusion
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
G0429	Dermal Filler injection(s) for the treatment of facial lipodystrophy syndrome (LDS) (e.g., as a result of highly active antiretroviral therapy)	Proven in certain circumstances
K1006	Suction pump, home model, portable or stationary, electric, any type, for use with external urine management system.	Unproven
K1007	Bilateral hip, knee, ankle, foot (HKAFO) device, powered, includes pelvic component, single or double upright(s), knee joints any type, with or without ankle joints any type, includes all components and accessories, motors, microprocessors, sensors	Unproven
K1018	External upper limb tremor stimulator of the peripheral nerves of the wrist	Unproven
K1019	Monthly supplies for use of device coded at K1018	Unproven
K1030	External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only	Unproven
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
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 cartilage support implant]	Unproven
L8701	Powered upper extremity range of motion assist device, elbow, wrist, hand with single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated	Unproven
L8702	Powered upper extremity range of motion assist device, elbow, wrist, hand, finger, single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated	Unproven
P2031	Hair analysis (excluding arsenic)	Unproven
Q2026	Injection Radiesse 0.1ml	Proven in certain circumstances
Q2028	Injection, sculptra, 0.5 mg	Proven in certain circumstances
S2102	Islet cell tissue transplant from pancreas; allogeneic	Unproven
S2117	Arthroereisis, subtalar	Unproven

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

Cerebral computed tomography perfusion (CTP) with contrast administration is proven and medically necessary for evaluation of acute cerebral ischemia (acute stroke).

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

Clinical Evidence

Current literature on CT perfusion imaging has focused on its feasibility and technical capabilities. Studies of early stroke interventions support the use of this approach for this indication. For other indications, prospective clinical studies are needed to determine the clinical value of CT perfusion imaging over standard non-contrast computed tomography. This includes standardization of result interpretation to determine the clinical utility of this imaging technology. Optimization of the technical acquisition of the images is of utmost importance. This imaging is sensitive to any patient motion, as well as the characteristics of the contrast bolus, particularly the duration. Additionally, the patient is exposed to relatively high doses of radiation, and there is a current lack of standardization between CTP vendor software and postprocessing techniques, and this may lead to variations in results (Vagal et al. 2019).

Cerebral perfusion analysis is performed to evaluate the blood supply to the brain utilizing computed tomography (CT). A contrast enhancement agent known as a tracer is administered. The blood transports the tracer to the brain, where the tracer perfuses, or fills, the tissue. This perfused tissue appears brighter in the CT image. The rate at which the tissue becomes brighter is proportional to the perfusion rate. A perfusion-weighted image is displayed by the software for the CT scanner, which measures the rate of change.

A 2020 ECRI Clinical Evidence Assessment compared CTP with contrast with non-contrast -enhanced computed tomography (NCCT) and other imaging modalities for evaluating acute ischemic stroke (AIS). It was concluded that the clinical utility has not been established due to too few date and the evidence is inconclusive.

Patchana et al. (2019) conducted a study to investigate if the data obtained from a computed tomography (CT) perfusion study on admission could correlate to outcomes for the patient, including the patient's length of stay in the hospital and their initial and final Glasgow Coma Scale (GCS), as well as the modified Rankin Scale (mRS) on discharge. The selection criteria included patients over age 18 with mild, moderate, or severe traumatic brain injury (TBI). CT perfusion studies were performed within 48 hours of admission, and GCS, length of stay, mRS, and discharge location were tracked, along with the patient's course of hospitalization. Preliminary data were obtained on six patients exhibiting TBI, ranging from mild to severe. The mean GCS of the patient cohort on admission was eight, with the most common mechanism of injury found to be falls (50%) and motor vehicle accidents (50%). Cerebral blood volume (CBV) seemed to increase with Rankin value (Pearson's correlations coefficient = 0.43 but was statistically insignificant (P = 0.21)). Cerebral blood flow (CBF) was found to be correlated with CBV, and both increased with Rankin score (Pearson's correlation coefficient = 0.56) but were statistically insignificant (P = 0.27). These results suggest that with a larger sample size, CBV and CBF may be correlated to patient outcome. The authors concluded that although more data is needed, preliminary results suggest that with larger patient populations, CT perfusion may provide information that can be correlated clinically to patient outcomes. This study shows that CBF and CBV may serve as useful indicators for prognostication of TBI patients.

Sun et al. (2019) performed a meta- analysis to investigate the role of computed tomography perfusion (CTP) in the identification of patients at risk for delayed cerebral ischemia (DCI) during the acute phase (<4 days) after aneurysmal subarachnoid hemorrhage (aSAH). The best CTP parameter, or the definition of abnormal CTP scan result were collected, and the data with the greatest overall predictive value for DCI was extracted to assess the strength of association between a positive CTP result and an impending DCI. Three articles involving 128 patients were included in the analysis. Among this population, DCI developed in 48 patients (37.5%). The pooled odds ratio was 32.15 (95% CI, 9.92-104.21), suggesting that the patients with

a positive CTP test in the acute phase after aSAH were approximately 32 times as likely to develop DCI compared with those without aSAH. The pooled sensitivity and specificity of CTP for detecting impending DCI after aSAH was 65% (95% CI: 0.49-0.78) and 91% (95% CI: 0.83-0.96). The authors concluded that CTP could detect abnormal brain perfusion before the occurrence of DCI. This may allow close monitoring and preemptive therapy for improvement in the prognosis in patients with aSAH.

In a 2017 systematic review and meta-analysis, Mir et al. reported on the usefulness of computed tomography perfusion (CTP) in determining delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage (SAH). The systematic review identified 218 studies of which there were 6 cohort studies. These included a total of 345 patients, with 155 (45%) classified as having delayed cerebral ischemia and 190 as not having delayed cerebral ischemia (DCI). Admission disease severity was comparable across all groups. Four cohort studies reported CTP test characteristics amenable to the meta-analysis. The results showed the weighted averages and ranges of the pooled sensitivity and specificity of CTP in the determination of delayed cerebral ischemia were 0.84 (0.7– 0.95) and 0.77 (0.66–0.82), respectively. The pooled odds ratio of 23.14 (95% CI, 5.87–91.19) indicates that patients with aneurysmal SAH with positive CTP test results were approximately 23 times more likely to experience delayed cerebral ischemia compared with patients with negative CTP test results. Compared with other imaging measure to detect DCI, CTP demonstrated higher odds ratio in this meta- analysis. The authors concluded that their findings show a strong association between CTP perfusion deficits and the development of DCI, and this may be helpful in identifying patients with delayed cerebral ischemia before development of infarction and neurologic deficits. There are significant limitations to this systematic review and meta-analysis, and they include most of the studies contained signs of disease progression and test classification bias, no explanation for patient withdrawals from the study, nor did they report uninterpretable or intermediate test results. Other limitations in the literature include non-uniform definitions for DCI and an abnormal CTP test, interinstitutional differences in CTP protocol, and software programs used for post processing.

The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE 3) trial was designed to test the hypothesis that patients who were likely to have salvageable ischemic brain tissue as identified by perfusion imaging and who underwent endovascular therapy 6 to 16 hours after they were last known to have been well would have better functional outcomes than patients treated with standard medical therapy (Albers et al., 2018). This was a multicenter, randomized, open-label trial, with blinded outcome assessment, of thrombectomy in patients 6 to 16 hours after they were last known to be well and who had remaining ischemic brain tissue that was not yet infarcted. Patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion, an initial infarct size of less than 70 ml, and a ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of 1.8 or more were randomly assigned to endovascular therapy (thrombectomy) plus standard medical therapy (endovascular-therapy group) or standard medical therapy alone (medical-therapy group). The primary outcome was the ordinal score on the modified Rankin scale (range, 0 to 6, with higher scores indicating greater disability) at day 90. Endovascular therapy plus medical therapy, as compared with medical therapy alone, was associated with a favorable shift in the distribution of functional outcomes on the modified Rankin scale at 90 days (odds ratio, 2.77; P<0.001) and a higher percentage of patients who were functionally independent, defined as a score on the modified Rankin scale of 0 to 2 (45% vs. 17%, P<0.001). The 90-day mortality rate was 14% in the endovascular-therapy group and 26% in the medical-therapy group (P = 0.05), and there was no significant between-group difference in the frequency of symptomatic intracranial hemorrhage (7% and 4%, respectively; P = 0.75) or of serious adverse events (43% and 53%, respectively; P = 0.18). Estimates of the volume of the ischemic core and penumbral regions from CT perfusion or MRI diffusion and perfusion scans were calculated with the use of RAPID software (iSchemaView), an automated image postprocessing system.

Lansberg et al. (2017) conducted a multicenter cohort study of consecutive acute stroke patients (n=190) scheduled to undergo endovascular therapy within 90 minutes after a baseline CT perfusion (CTP) to examine the utility of CTP for selection of patients for endovascular therapy up to 18 hours after symptom onset. Patients were classified as “target mismatch” if they had a small ischemic core and a large penumbra on their baseline CT perfusion. Reperfusion was defined as >50% reduction in critical hypoperfusion between the baseline CT perfusion and the 36-hour follow-up magnetic resonance imaging (mean age = 66 years, median NIH Stroke Scale [NIHSS]516, median time from symptom onset to endovascular therapy = 55.2 hours). Rate of reperfusion was 89%. In patients with target mismatch (n=131), reperfusion was associated with higher odds of favorable clinical response, defined as an improvement of 8 points on the NIHSS (83% vs 44%; p50.002, adjusted odds ratio [OR]56.6, 95% confidence interval [CI]52.1–20.9). This association did not differ between patients treated within 6 hours (OR56.4, 95% CI51.5–27.8) and those treated > 6 hours after symptom onset (OR513.7, 95% CI51.4–140). The authors’ interpretation is that the robust association between endovascular reperfusion and good outcome among patients with the CT perfusion target mismatch profile treated up to 18 hours after symptom onset supports a randomized trial of endovascular therapy in this patient population. Study limitations include this being a cohort study without a control group, no definitive conclusion can be drawn

regarding the effect of endovascular treatment, and the very high re-perfusion rate, a tribute to the efficacy of stent-retrievers, was unexpected and limited the ability to compare outcomes between patients with and without re-perfusion.

In a systematic review, Shen et al. (2017) compared the diagnostic accuracy of CTP, NCCT and CTA in detecting acute ischemic stroke. These investigators searched 7 databases and screened the reference lists of the included studies. The risk of bias in the study quality was assessed using QUADASII. They produced paired forest plots in RevMan to show the variation of the sensitivity and specificity estimates together with their 95 % CI. They used a hierarchical summary ROC model to summarize the sensitivity and specificity of CTP in detecting ischemic stroke. These researchers identified 27 studies with a total of 2,168 patients. The pooled sensitivity of CTP for acute ischemic stroke was 82 % (95 % CI: 75 to 88 %), and the specificity was 96 % (95 % CI: 89 to 99 %); CTP was more sensitive than NCCT and had a similar accuracy with CTA. There were no statistically significant differences in the sensitivity and specificity between patients who underwent CTP within 6 hours of symptom onset and beyond 6 hours after symptom onset. No adverse events (AEs) were reported in the included studies. The authors concluded that CTP is more accurate than NCCT and has similar accuracy to CTA in detecting acute ischemic stroke. However, the evidence is not strong. These researchers also stated that there is potential benefit of using CTP to select stroke patients for treatment, but more high-quality evidence is needed to confirm this result. The authors noted that this study had several drawbacks. First, in the included studies, the characteristics of the patient varied, and patients in half of the studies may not be representative. Second, some of the included studies had very small sample size, and it might have influenced the estimation accuracy. Third, 13 studies did not report whether the investigators were blinded to the results of reference standard test and relevant clinical information, and it might have over-estimated the accuracy of CTP. Fourth, only 8 of 27 studies had low risk of bias. Finally, similar to other systematic reviews of the diagnostic test accuracy, the heterogeneities of the sensitivity and specificity in the included studies were high that may have impacted the reliability of the pooled results.

In a systematic review and meta-analysis, Cremers et al. (2014) concluded that CTP on admission cannot be used reliably to predict DCI. However, at the time of clinical deterioration, patients with DCI had a significantly decreased CBF and an increased MTT compared with patients without DCI using quantitative assessments. For diagnosing DCI, quantitative thresholds for CBF ranged from 25 to 36.3 mL/100 g per minute (with sensitivity ranging from 73% to 78% and specificity ranging from 63% to 76%) and for MTT from 5.0 to 6.5 seconds (with sensitivity ranging from 70% to 72% and specificity ranging from 70% to 81%). The authors addressed limitations, including that many different terms and definitions for DCI were used in the included studies. In their opinion, most definitions of these terms were comparable with the definition that was recently proposed by an international multidisciplinary research group. In addition, most studies used quantitative measurements whereas some studies also used semi-quantitative values. Other studies also determined perfusion by visual assessment. Lastly, the control patients differed between various studies.

The American College of Radiology (ACR) Appropriateness Criteria for Cerebrovascular Disease states that CTP can be used to evaluate cerebrovascular reserve; however, its role in the evaluation of acute stroke remains unproven because of sensitivity to motion, low signal-to noise ratio, and variation among software packages, and it requires the use of IV iodinated contrast, which may not be feasible in patients with renal dysfunction or contrast allergy. Noncontrast CT (NCCT) of the head is the first-line imaging test to evaluate for intracranial hemorrhage in patients presenting with acute stroke, whether AIS or hemorrhagic stroke.

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

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

Clinical Evidence

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

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

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

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

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

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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. On February 26, 2021, modifications to the external components were made and this device was rebranded The Argus 2s Retinal Prosthesis System. 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 7, 2021).

Schaffrath et al. (2019) conducted a post approval multi-center case series (with on/off tests) to assess the safety and visual outcomes of the Argus II Retinal Prosthesis System. The primary end point was the nature and rate of adverse events. Secondary end points included 3 visual function tests: square localization (SL), direction of motion, and grating visual acuity (GVA). Multicenter, post approval clinical trial was conducted at 9 sites in Germany and Italy. Data were collected from December 2, 2011, to September 30, 2017, and 47 patients were followed-up for 12 months or longer. The results showed during the first 12 months post-implantation, 23 patients (49%) experienced 51 nonserious adverse events and 12 (26%) experienced 13 serious adverse events (SAEs), 9 of which were judged to be related to the Argus II, and 4 of which were judged to be related to the procedure. The most common SAE was conjunctival erosion, reported in 4 patients. No significance testing was done for group analysis for the SL or direction-of-motion tests. When averaged across the group, patients' accuracy on the SL test, but not on the direction-of-motion test, appeared better when the Argus II was on than when it was switched off. For GVA, more patients at each point in time achieved the 2.9 GVA cutoff in the implanted eye when the Argus II was on compared with it switched off. The authors concluded safety and visual function outcomes in this clinical practice setting cohort of patients with Argus II implants were consistent with previously reported results. Longer follow-up of these patients and data from additional patients are required to better outline the risks and benefits of this approach to addressing blindness secondary to severe-to-profound outer retinal degeneration.

Dagnelie et al. (2017) conducted a multi-center case series (with on/off tests) study to test Argus II subjects on three real-world functional vision tasks. Testing was conducted in a hospital/research laboratory setting at the various participating centers. Twenty-eight Argus II subjects, all profoundly blind, were included in the study. Subjects were tested on the three real-world functional vision tasks: Sock Sorting, Sidewalk Tracking and Walking Direction Discrimination Task for the Sock Sorting task, percentage correct was computed based on how accurately subjects sorted the piles on a cloth-covered table and on a bare

table. In the Sidewalk Tracking task, an 'out of bounds' count was recorded, signifying how often the subject veered away from the test course. During the Walking Direction Discrimination task, subjects were tested on the number of times they correctly identified the direction of testers walking across their field of view. The mean percentage correct OFF versus ON for the Sock Sorting task was found to be significantly different for both testing conditions. On the Sidewalk Tracking task, subjects performed significantly better with the system ON than they did with the system OFF. Eighteen (18) of 27 subjects (67%) performed above chance with the system ON, and 6 (22%) did so with system OFF on the Walking Direction Discrimination task. The authors concluded that the Argus II subjects performed better on all three tasks with their systems ON than they did with their systems OFF. The study is however limited by the lack of comparison group with a different treatment mode or no treatment that could provide data on quality of life (QOL) and day-to-day function. These findings require confirmation in a larger study.

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 (2017) updated the 2016 Health Technology Assessment that examined the effects of the Argus II retinal prosthesis system in patients with advanced retinitis pigmentosa, and appraised the evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. The focus of the review included visual function, functional outcomes, QOL, and AEs in a total of 30 patients. One multicenter international study and one single-center study were included in the clinical review. In both studies, patients showed improved visual function with the Argus II system. At 5 years after implantation, 18/30 experienced no device or surgery related adverse effects, and 12/30 patients reported severe adverse events that were all treated with standard ophthalmic approaches. The authors concluded that based on evidence of moderate quality, patients with advanced retinitis pigmentosa who were implanted with the Argus II retinal prosthesis system showed significant improvement in visual function, real-life functional outcomes, and QOL that appeared sustained over time. Adverse events can be managed through standard ophthalmologic treatments.

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 is 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. This study is however limited by the lack of comparison group with a different treatment mode or no treatment that could provide data on quality of life (QOL) and real-life day-to-day function. These findings require confirmation in a larger study.

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

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

Clinical Evidence

Blood-based biomarker panels are tests to assess the expression of genes to theoretically calculate a risk of having CRC. BeScreened™-CRC is manufactured by Beacon Medical Inc. and partnered with Sonora Quest Laboratories is an ELISA-based multiplexed, CLIA laboratory developed colorectal cancer (CRC) screening test. It tests three plasma or serum cancer related proteins (carcinoembryonic antigen, extracellular matrix protein involved in early-stage tumor stroma changes, teratocarcinoma derived growth factor-1 (TGDF-1, Cripto-1) to determine an algorithmic analysis reported as a positive or negative result. https://www.beaconbiomedical.com/about-bescreened-crc. (Accessed May 22, 2021).

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

Bhardwaj et, al. (2020) used a two-stage design to measure 275 protein markers by proximity extension assay (PEA), first in plasma samples of a discovery set consisting of 98 newly diagnosed CRC cases and 100 age- and gender-matched controls free of neoplasm at screening colonoscopy. An algorithm predicting the presence of early- or late-stage CRC was derived by least absolute shrinkage and selection operator regression with .632+ bootstrap method, and the algorithms were then validated using PEA again in an independent validation set consisting of participants of screening colonoscopy with and without CRC (n = 56 and 102, respectively). Three different signatures for all-, early-, and late-stage CRC consisting of 9, 12, and

11 protein markers were obtained in the discovery set with areas under the curves (AUCs) after .632 + bootstrap adjustment of 0.92, 0.91, and 0.96, respectively. External validation among participants of screening colonoscopy yielded AUCs of 0.76 [95% confidence interval (95% CI), 0.67-0.84], 0.75 (95% CI, 0.62-0.87), and 0.80 (95% CI, 0.68-0.89) for all-, early-, and late-stage CRC, respectively. The authors concluded that although the identified protein markers are not competitive with the best available stool tests, the combination of identified protein markers with other informative blood-based markers could contribute to the development of a promising blood-based test for CRC screening. Additionally, this study is based on more biomarkers and a different algorithm from BeScreened -CRC.

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

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

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

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

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

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

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

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

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

Clinical Evidence

Eyelid Thermal Pulsation

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

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

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

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

In a prospective randomized, multi-center clinical trial, Blackie et al. (2018) evaluated the effect of a single vectored thermal pulsation (VTP) treatment in contact lens wearers with 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, especially in the context of an open-label trial. Furthermore, this study was funded by the manufacturer of Lipiflow (TearScience, Inc) and lack comparison to established treatments.

In a prospective, randomized, parallel-group, single-masked study, Hagen et al. (2018) compared the efficacy of a single bilateral 12-minute vectored thermal pulsation (VTP) procedure versus daily oral doxycycline for 3 months for moderate-to-severe 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 and that a single 12-minute VTP treatment was at least as effective as a dose of doxycycline for 3 months, in improving MG function and all measured signs of MGD. According to the authors, given the minimal risk profile of the single VTP procedure over long-term doxycycline use, a single VTP presents a favorable alternative to long-term antibiotic use. According to the authors, this is a small study that can serve as a pilot study for additional investigations. It was disclosed that 2 of the authors are either a consultant or employee of TearScience, Inc.. Furthermore, the study may have been too small to detect clinically significant differences between groups.

Blackie et al. (2016) evaluated the sustained effect (up to 1 year) of a single, 12-minute vectored thermal pulsation (VTP) treatment in improving 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±23.2The authors concluded that a single VTP treatment can deliver a sustained mean improvement in meibomian gland function and mean reduction in dry eye symptoms, over 12 months. A single VTP treatment provides significantly greater mean improvement in meibomian gland function and dry eye symptoms as compared to a conventional, twice-daily, 3-month regimen. According to the authors, a significant limitation of this study is that the investigators were not masked, which could have introduced a bias in the findings. This study was funded by the manufacturer of Lipiflow (TearScience, Inc) and the lead authors are affiliated with TearScience, Inc.

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

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

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

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

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

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

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

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

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

Reference(s)

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

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

Clinical Evidence

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

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

administer the test, yet calibration with the app is required; special headphones are required; the sample was not completely a random selection and only participants with normal hearing were included; and the authors were involved in the development of the app, which could have introduced a bias in the interpretation of the findings. Future studies are needed to explore the validity of this app.

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

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

Saliba et al. (2017) in a prospective study compared the accuracy of 2 previously validated mobile-based hearing tests in determining pure tone thresholds and screening for hearing loss to determine the accuracy of mobile audiometry in noisy environments through noise reduction strategies. A total of 33 adults with or without hearing loss were tested (mean age of 49.7 years; women, 42.4 %). Air conduction thresholds measured as pure tone average and at individual frequencies were assessed by conventional audiogram and by 2 audiometric applications (consumer and professional) on a tablet device. Mobile audiometry was performed in a quiet sound booth and in a noisy sound booth (50 dB of background noise) through active and passive noise reduction strategies. On average, 91.1 % (95 % CI: 89.1 % to 93.2 %) and 95.8 % (95 % CI: 93.5 % to 97.1 %) of the threshold values obtained in a quiet sound booth with the consumer and professional applications, respectively, were within 10 dB of the corresponding audiogram thresholds, as compared with 86.5 % (95 % CI: 82.6 % to 88.5 %) and 91.3 % (95 % CI: 88.5 % to 92.8 %) in a noisy sound booth through noise cancellation. When screening for at least moderate hearing loss (pure tone average greater than 40 dB HL), the consumer application showed a sensitivity and specificity of 87.5 % and 95.9 %, respectively, and the professional application, 100 % and 95.9 %. Overall, patients preferred mobile audiometry over conventional audiograms. The authors concluded that mobile audiometry could correctly estimate pure tone thresholds and screen for moderate hearing loss. Adding noise reduction strategies in mobile audiometry could provide a portable effective solution for hearing assessments outside clinical settings where noise is a factor. Study limitations include the following: small sample size, the number of adults with audiometric hearing loss was limited which per the author could have affected sensitivity and specificity, each ear was counted separately which could have inflated sample size, also the earbuds used in mobile testing is different than commercial testing. Additional studies with larger samples are needed to validate the efficacy of mobile-based hearing.

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

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

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Mahomed F, Swanepoel DW, Eikelboom RH, et al. Validity of automated threshold audiometry: A systematic review and meta-analysis. Ear Hear. 2013;34(6):745-752.

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Code	Description
0247U	Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth
81599	Unlisted multianalyte assay with algorithmic analysis (when used to report PreTrm)

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

Clinical Evidence

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

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

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

Saade et al. (2016) conducted the prospective Proteomic Assessment of Preterm Risk study to discover, verify and validate biomarkers for preterm birth. A total of 5,500 pregnant women between 17-28 weeks gestation were followed from 2011-2014

at 11 clinical sites in the United States. Of those, 5,235 remained in the study until their delivery and 4,825 were analyzed (410 were excluded due to being on progesterone therapy for preventing preterm birth). Of those 4,825 women, 4,292 carried their babies to term while 248 experienced spontaneous preterm birth (285 had medically indicated preterm births and were excluded.) Of these 248 sPTB subjects, 31 were excluded for pre analytic reasons, leaving 217, 86 of which were used in discovery, 50 in verification, and 81 in validation. The discovery and verification process identified 2 serum proteins, insulin-like growth factor binding protein 4 (IBP4) and sex hormone-binding globulin (SHBG), as predictors of spontaneous preterm delivery. The study found that the test was able to predict whether a woman would deliver before 37 weeks with 75 percent sensitivity and 74 percent specificity, and an area under the receiver operating curve of .75. It was able to predict delivery before 35 weeks with 100 percent sensitivity and 83 percent specificity and an AUC of .93. These biomarkers may predict risk for preterm sPTB. However, the study had several limitations including small sample size and had insufficient number of women with prior preterm delivery, and less than one-third of participants had transvaginal ultrasound cervical length performed. Further studies are needed to determine the clinical application of this test and how it relates to the current techniques used to identify high risk for preterm labor.

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Hayes Inc. Precision Medicine Research Brief. PreTRM (Sera Prognostics) Lansdale, PA: Hayes, Inc.; July 2019.

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Saade GR, Boggess KA, Sullivan SA, et al. Development and validation of a spontaneous preterm delivery predictor in asymptomatic women. Am J Obstet Gynecol. 2016;214(5): 633.e1-633.e24.

Sera Prognostics website. Available at: https://www.pretrm.com/about-pretrm/. Accessed May 14, 2021.

Code	Description
0266T	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
0267T	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)
0268T	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
0269T	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
0270T	Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)
0271T	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
0272T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day)
0273T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (e.g., battery status, lead impedance, pulse amplitude, pulse width, therapy frequency, pathway mode, burst mode, therapy start/stop times each day); with programming

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

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

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

(Accessed April 29, 2021)

The Barostim neo™ received FDA premarket approval on August 16, 2019 (product code DSR) for treatment of heart failure. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P180050. (Accessed April 29, 2021)

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

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

Recruiting has been completed for the 300-patient Calm-2 trial (NCT03179800), a prospective, multi-center randomized, sham-controlled, double-blinded study using the MobiusHD device in patients with drug-resistant hypertension. This study has a primary completion date of May 2021 with a final completion date of May 2026. For more information, go to www.clinicaltrials.gov. (Accessed April 29, 2021)

de Leeuw et al. (2017) assessed the long-term safety and efficacy of BAT by analyzing data from patients included in 1 of 3 trials that focused on treatment-resistant hypertension (US Rheos® Feasibility Trial, the DEBuT-HT Trial and the Rheos® Pivotal Trial). Collectively, 383 patients were available for analysis: 143 patients completed 5 years of follow-up and 48 patients completed 6 years of follow-up. In the entire cohort, systolic blood pressure fell from 179±24 mm Hg to 144±28 mm Hg, diastolic pressure dropped from 103±16 mm Hg to 85±18 mm Hg and heart rate fell from 74±15 beats per minute to 71±13 beats per minute. The effect of BAT was greater than average in patients with signs of heart failure and less than average in patients with isolated systolic hypertension. In 27% of patients, it was possible to reduce the number of medications from a median of 6 to a median of 3. After a follow-up of 6 years, the authors concluded that BAT maintains its efficacy for persistent

reduction of blood pressure in patients with resistant hypertension without major safety issues. Limitations of this study include use of the first-generation Rheos® system, lack of randomization in 2 of 3 studies and lack of a control group during long-term follow-up.

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

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

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

After completion of the randomized Rheos® Pivotal Trial, Bakris et al. (2012) conducted an open-label, nonrandomized follow-up study to assess the long-term safety and efficacy of BAT. Clinically significant responder status was assessed according to FDA-mandated criteria. Of 322 patients implanted, 76% (n=245) qualified as clinically significant responders. An additional 10% were indeterminate. Among long-term responders receiving BAT, the mean blood pressure drop was 35/16 mm Hg. Medication use was reduced by the end of the randomized phase and remained lower through the follow-up period. Among responders, 55% achieved targeted blood pressure reduction goals sustained through 22 to 53 months of follow-up.

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

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

Heart Failure

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

Zile et al (2020) evaluated the safety and effectiveness of BAT in patients with heart failure with reduced ejection fraction (HFrEF) in the Baroreflex Activation Therapy for Heart Failure (BeAT-HF) clinical trial. This prospective, multi-center RCT involved 408 participants with HFrEF randomized into two study arms, one receiving BAT with optimal medical management or one receiving optimal medical management alone. There was a total of four patient cohorts. Effectiveness endpoints were the change from baseline to 6 months in 6-min hall walk distance (6MHW), Minnesota Living with HF Questionnaire quality-of-life

(QOL) score, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. The safety endpoint included the major adverse neurological or cardiovascular system or procedure-related event rate (MANCE). The fourth cohort, Cohort D, which included the intended use population that reflected the Food and Drug Administration (FDA)-approved instructions for use (enrollment criteria plus NT-proBNP of less than 1,600 pg/ml), consisted of 245 participants followed-up for 6 months (120 in the BAT group and 125 in the control group). The authors concluded that BAT was safe and significantly improved QOL, exercise capacity, and NT-proBNP. They noted that the study has several limitations including not examining morbidity and mortality or change in cardiovascular structure or function endpoints, the lack of blinding in this trial, and that there might be subject to placebo effects. The researchers indicated that further studies are needed to examine the impact of BAT on the frequency of hospitalization and mortality and identify patients with HFrEF most likely to gain lasting benefit from this type of intervention.

In 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.

Lee et al. (2020) evaluated the clinical accuracy and utility of the Antares topographer in the diagnosis of dry eye disease (DED). Thirty-three consecutive patients underwent analyses of their non-invasive first tear-film break-up time (NIF-BUT), tear meniscus height (TMH) and meibography with the Antares topographer. The meibography with the LipiView scan was conducted. Slit-lamp examinations were done for assessments of meibomian glands (MG) and fluorescein tear-film break-up time (FBUT). Schirmer 1 test was done. The Ocular Surface Disease Index (OSDI) scores were graded. Thirty-three eyes of 33 patients (mean age 61.5 ± 10.6 years, range 37.5-76.4 years, 27.3% males) completed the study. According to the Antares measurements, the NIF-BUT of the patient population was 5.0 ± 3.4 seconds on average (1.1-15.0 seconds), and the TMH was 0.2 ± 0.1 mm at center (0.1-0.5 mm). The average OSDI score was 22.4 ± 16.6 points (0.0-79.5 points). When correlations were calculated, significant correlations were found between the NIF-BUT from the Antares topographer and FBUT (r = 0.538, P = .001), and between MG dropout from the Antares topographer and that from the LipiView interferometer (r = 0.446, P=.009). Antares NIF

BUT and FBUT were in agreement with one another (95% limits of agreement (LOA) -5.04 ± 6.37, P=.198) as were the infrared images from the Antares topographer and those from the LipiView interferometer (95% LOA -0.25 ± 0.35, P=.073). The authors concluded that the Antares topographer is useful in the diagnosis of DED. Among its outputs, the NIF-BUT and MG dropout most closely correlated with currently accepted modes of diagnosis. The authors indicated that concurrent clinical examinations are recommended for clinical follow-up. While this study reports correlations, it doesn't test diagnostic performance or clinical utility of tear film imaging.

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

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

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. Available at: https://www.aao.org/guidelines-browse. Accessed May 16, 2021.

Dry Eye WorkShop (DEWS). Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007c;5(2):108-152.

Ji YW, Lee J, Lee H, et al. Automated measurement of tear film dynamics and lipid layer thickness for assessment of Non-Sjögren Dry Eye Syndrome with meibomian gland dysfunction. Cornea. 2017 Feb;36(2):176-182.

Lee JS, Jun I, Kim EK, et al. Clinical accuracy of an advanced corneal topographer with tear-film analysis in functional and structural evaluation of dry eye disease. Semin Ophthalmol. 2020 Feb 17;35(2):134-140.

Lee SM, Lee JE, Kim SI, et al. Effect of topical glaucoma medication on tear lipid layer thickness in patients with unilateral glaucoma. Indian J Ophthalmol. 2019 Aug;67(8):1297-1302.

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

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

Clinical Evidence

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

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

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

Jacobson et al. (2010) conducted a large prospective study evaluating global I-MIBG uptake and clinical outcomes. The study was known as the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure study (ADMIRE-HF). In this study, planar I-MIBG and SPECT perfusion imaging were performed in 961 patients with NYHA class II or III heart failure (HF) and LVEF ≤35 %. The majority of patients (66 %) had ischemic cardiomyopathy. Over a median follow-up of 17 months, the primary composite endpoint (heart failure progression, arrhythmic events and cardiac death) occurred more frequently among those with a global reduction in sympathetic innervation (prospectively defined as a late HMR <1.6). Although the frequency of arrhythmic events was significantly higher among those with a HMR <1.6, the vast majority were non-sustained VT. SCD, resuscitated sudden

cardiac arrest, and appropriate ICD discharges (shock or anti-tachycardia pacing) were a small portion of the total composite endpoints (21 %). Quantification of regional defects was attempted in a subgroup of patients but did not provide any additional value to global indices of I-MIBG uptake in predicting prognosis.

Reference(s)

Agostini D, Ananthasubramaniam K, Chandna H, et al., ADMIRE-HF investigators. Prognostic usefulness of planar ^{123}I-MIBG scintigraphic images of myocardial sympathetic innervation in congestive heart failure: Follow-up data from ADMIRE-HF. J Nucl Cardiol. 2019 Aug 29. Epub ahead of print.

Jacobson AF, Senior R, Cerqueira MD, et al., Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol. 2010 May 18; 55(20):2212-21.

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

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

Clinical Evidence

Flexible flatfoot (Flexible Pes Planovalgus, Pes Planus) is 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.

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

Baryeh et al. (2021) conducted a systematic review to examine the outcomes of adult flatfoot deformity (AFFD) when treated surgically with subtalar arthroereisis. Nine studies met the inclusion criteria and were reviewed for both clinical and radiological outcomes as well as reported complications. A total of 167 patients underwent 190 procedures. Six of the 9 studies used the American Orthopedic Foot and Ankle Society (AOFAS) score, 3 used the visual analog scale (VAS), 1 used the SF-36, and 1 used the Visual analogue scale foot and ankle (VAS-FA). Radiological measurements included Meary's angle, TN, Kite angle, and T1MT. The results showed five papers used the AOFAS hindfoot score with one using the foot and ankle outcome score (FAOS) , one used the VAS-FA score and three used the VAS for reporting outcomes. In general, this systematic review

suggests treatment with subtalar arthroereisis, either alone or as an adjunct, results in improvement of clinical and radiological outcome; however; it is unclear if the improvement would have occurred regardless. Only one paper used subtalar arthroereisis as the sole intervention and among the remaining papers, there was heterogeneity among additional procedures used. Sinus tarsi pain is the most common complication and in this review resulted in removal of 29% of implants. This review is limited by all studies being case series conducted at single centers, as well as only 2 being prospectively designed. Additionally, the heterogeneity of the procedures used also adds to the difficulty in identifying whether the improvements in clinical and radiological parameters were due to the use of subtalar arthroereisis or as a result of the additional procedures. Additional high quality are needed to establish the best use of subtalar arthroereisis in the management of AAFD.

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

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

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

Despite the good clinical results of subtalar arthroereisis for the management of flexible flatfoot in children, it is mostly performed using a metallic screw which typically requires 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).

Numerous implant systems have received FDA approval through the 510(k) process. See the following website for more information (use product code HWC): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed May 7, 2021).

American College of Foot and Ankle Surgeons (ACFAS)

A panel convened to develop a consensus statement (using The RAND/UCLA Appropriateness Method (RAM)) on the appropriate clinical management of adult acquired flatfoot deformity (AAFD). Invitations were extended to members with clinical expertise in treating adult acquired flatfoot. Questions were developed that would address basic topics to cover in the consensus statements, and members performed comprehensive review of the published literature, and over the course of 11 months, developed a set of consensus statements. The recommendations were graded in accordance with the quality of the evidence on which the panel based their decisions, as described by the Oxford Centre for Evidence- Based Medicine grading system. The panel concluded that the use of a subtalar implant alone for Stage IIb AAFD has limited evidence demonstrating its use in the absence of advanced disease of surrounding tissues. There is a high rate of explanation in adults with flexible IIa deformity. (Piraino 2020).

Reference(s)

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Indino C, Villafañe JH, D'Ambrosi R, et al. Effectiveness of subtalar arthroereisis with endorthesis for pediatric flexible flat foot: a retrospective cross-sectional study with final follow up at skeletal maturity. Foot Ankle Surg. 2018 Dec 21. pii: S1268-7731(18)30505-8.

Piraino JA, Theodoulou MH, Ortiz J, et al. American College of Foot and Ankle Surgeons Clinical Consensus Statement: Appropriate Clinical Management of Adult-Acquired Flatfoot Deformity. J Foot Ankle Surg. 2020 Mar-Apr;59(2):347-355.

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Smith C, Zaidi R, Bhamra J, et al. Subtalar arthroereisis for the treatment of the symptomatic paediatric flexible pes planus: a systematic review. EFORT Open Rev. 2021 Feb 1;6(2):118-129.

Suh DH, Park JH, Lee SH, et al. Lateral column lengthening versus subtalar arthroereisis for paediatric flatfeet: a systematic review. Int Orthop. 2019 Jan 30.

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

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

Clinical Evidence

A systematic review and meta-analysis regarding the state of renal sympathetic denervation (RSD) for management of patients with hypertension was published by Syed et al. in 2021. Eight studies, with a total of 1363 patients, were included. Mean age was 56 years of age± 2.6 years, and 29% of patients included were women. Data was pooled from randomized controlled trials (RCTs) and comparison of renal sympathetic denervation in the management of hypertension to sham procedures was performed. Median maximum follow-up was 6-month range (3-12 months). Data showed greater reduction in ambulatory systolic blood pressure (ASBP), ambulatory diastolic blood pressure (ADBP), office systolic blood pressure (OSBP) and office diastolic blood pressure (ODBP) with RSD. The authors concluded that the use of RSD for management of hypertension demonstrated reduced ambulatory and office blood pressure compared to sham procedure(s), however, additional high-quality RCTs of RSD are needed to assess impact on clinical outcomes and confirm safely and reproducibility. The studies by Desch,

et al. (2015), Bhatt, et al. (2014) Esler, et al. (2012), included in the previous versions of this policy are included in this systematic review and are no longer discussed in details below.

Kaltenbach et al. (2013) investigated the feasibility, safety, and effectiveness of renal sympathetic denervation in patients with recurrent mild hypertension despite treatment with ≥ 3 antihypertensive drugs. In a pilot study case series, consecutive patients with office systolic BPs of 140-160 mm Hg despite ≥ 3 antihypertensive medications treated with renal sympathetic denervation. Clinical evaluations were performed at baseline, 3, and 6 months to determine changes in office systolic blood pressure, 24-hr ambulatory blood pressure, and medication doses. Twenty patients treated with an average of 5.4 ± 1.5 antihypertensive drugs were treated with renal sympathetic denervation. The procedure was considered successful in all patients. There were no procedure- or device-related complications. The blood pressure reading at baseline was 148.4/83.0 ± 6.6/11.0 mm Hg and decreased by 5.7/0.6 ± 20.0/8.3 mm Hg (P = 0.2) and 13.1/5.0 ± 13.6/8.3 mm Hg (P < 0.01) at 3 and 6 months, respectively. Comparing baseline and 6-month follow-up, mean ambulatory 24 hr-BP was reduced by 11.3/4.1 ± 8.6/7.3 mm Hg (P < 0.01). Four patients were able to reduce antihypertensive medications prior to their 3-month visit. Study limitations included lack of comparison group and insufficient data to assess safety.

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

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

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

Reference(s)

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Syed M, Osman M, Alhamoud H, et al. The state of renal sympathetic denervation for the management of patients with hypertension: A systematic review and meta-analysis. Catheter Cardiovasc Interv. 2021 Mar;97(4): E438-E445.

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

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

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

Clinical Evidence

The National Comprehensive Cancer Network does not mention optical coherence tomography in their clinical practice guideline on breast cancer (April 2021).

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

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

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

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

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

Clinical Evidence

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

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

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

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

Fonseca et al. (2018) performed a study to investigate the validity of an eight-contact electrode 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, but that there is a need for an increased focus on the importance of improved standardization and its reporting in future studies.

Haverkort et al. (2015) conducted a systematic review to explore the variability of empirical prediction equations used in 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 a study utilizing three groups of six obese men to evaluate the accuracy of bioelectrical impedance spectroscopy (BIS) in measuring the following: fat mass (FM), total body water (TBW) and extracellular water (ECW) changes induced by different degrees of caloric deficit in obese men. Each group of men were instructed to participate in either (i) a total fast (for 6 days); (ii) a VLCD (2.5 MJ/day for 3 weeks); or (iii) LCD (5.2 MJ/day for 6 weeks). FM was measured using a 4-compartment (4-C) model. TBW and ECW were determined by dilution methods. TBW, ECW and FM were also assessed with BIS. Body weight loss in the fasting group was 6.0 ± 1.3 kg over 6 days; the VLCD group lost 9.2 ± 1.2 kg over 21 days and the LCD group lost 12.6 ± 2.4 kg over 42 days. BIS underestimated FM changes (bias = -3.3 ± 3.8 kg) and overestimated changes in TBW and ECW by +1.8 ± 4.8 kg and +2.3 ± 6.4 kg, respectively. The measurement error was consistently larger in the fasting group and the magnitude of the bias is greater with greater weight loss.

Widen et al. (2014) attempted to provide validation of bioelectric impedance analysis. The purpose of the study was to measure the total body water and percent body fat before and 12 months after bariatric surgery. The findings showed that the T0 to T12 median (IQR) change in deuterium TBW and 3C %fat was -6.4 L (6.4 L) and -14.8 % (13.4 %), respectively. There were no statistically significant differences between deuterium and BIA determined TBW [median (IQR) difference: T0 -0.1 L (7.1 L), $p = 0.75$; T12 0.2 L (5.7 L), $p = 0.35$; 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
0394T	High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed
0395T	High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed

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

Clinical Evidence

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

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).

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

Breast Cancer

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

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

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

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

Mehta et al. (2010) completed a phase IV prospective, non-randomized trial of 44 patients to evaluate the safety and device effectiveness of the Axxent electronic brachytherapy system. The study evaluated 44 patients. The subjects were over 50 years of age, had completely resected invasive ductal carcinoma or ductal carcinoma in situ and negative microscopic margins of equal to or greater than 1 mm. The treatment was completed with a balloon applicator with treatments twice per day for 5 days. Treatment was successfully completed in 42/44 patients. All 44 patients were followed up at one month, 43/44 followed up to 6 months and 36 of the 44 patients completed follow up at 1 year. No tumor recurrences were reported up to 1 year. The infection rate was high at 11%. Cosmetic evaluation was rated as good or excellent (minimal or no identifiable effects of radiation). The authors concluded that the electronic brachytherapy system performed as expected with similar acute toxicity profiles to other high-rate approaches in patients with resected, early breast cancer with no serious acute toxicities or serious AEs. This study is limited by small numbers, short-term follow-up and lack of randomization or comparison of outcomes to established radiation therapy techniques.

Skin Cancer

NCCN guidelines on basal cell and squamous cell skin cancers state that there are insufficient long-term safety and efficacy data to support the routine use of electronic surface brachytherapy (NCCN, 2021a; NCCN 2021b).

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

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

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

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

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

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

- Based on current evidence, surgical management remains the most effective treatment for basal cell and squamous cell carcinomas, providing the highest cure rates.
- Additional research is needed on electronic surface brachytherapy, particularly on long term outcomes.

- Electronic surface brachytherapy may be considered as a secondary option for the treatment of basal cell and squamous cell carcinomas, for use in special circumstances and after the benefits and risks of treatment alternatives have been discussed with the patient.

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

Delishaj et al. (2015) retrospectively evaluated 57 lesions in 39 elderly patients affected with nonmelanoma skin cancer (NMSC) treated with high-dose rate (HDR) brachytherapy using a Valencia applicator to estimate tumor control, toxicity and cosmetic outcomes. All lesions had a diameter ≤ 25 mm (median: 12.5 mm) and a depth ≤ 4 mm. Twelve lesions were treated as a supplementary therapy after surgery treatment. The total dose was chosen based on the lesion dimensions, age, and performance status. The dose prescription was delivered as two/three fractions a week, with a minimum interval of 48 hours between fractions. After 12 months median follow-up, 55 lesions (96.5%) completely regressed and only two lesions persisted. No recurrences were observed, and the treatment was very well tolerated with no Grade 3 or higher acute or late toxicities. The authors concluded that this treatment was safe and effective in elderly patients. The limitation of this study compared with studies of more established treatments for NMSC was the relatively short follow-up and small number of patients due to the age of the patients (mean age 84 years) as well as comorbidities.

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

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

Other Indications

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

An ECRI product brief found no clinical studies that assessed the Axxent electronic brachytherapy device for treating uterine, vaginal or vulvar cancer. One prospective (n=15) and 2 retrospective (n=41, n=6) case series reported on overall survival, toxicity, and adverse events in patients with various stages of endometrial or cervical cancer treated with mixed regimens (e.g., systemic chemotherapy, various forms of radiation therapy that included Axxent). Reported follow-up was 3 to 20 months. These studies had various limitations including small sample size and lack of randomization and control. Longer follow-up times are needed for outcome measures to determine safety and efficacy (ECRI, 2019c).

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

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

Clinical Evidence

Optical endomicroscopy also referred to as confocal endomicroscopy (CEM) or optical biopsy is an 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.

Park et al. (2019) conducted a randomized controlled trial assessing probe confocal laser endomicroscopy (pCLE) and if this new emerging procedure could increase the yield of endoscopic biopsy for gastric cancer compared with white light endoscopy (WLE). There was a total of 30 gastric cancers and 61 undifferentiated-type gastric cancers were examined in the pilot and confirmatory studies, separately. All lesions in the pCLE and WLE groups were initially evaluated through WLE. In the pCLE group, lesions were further examined through pCLE. In the pilot study, five and three biopsy specimens were obtained for histopathological examination and tumor marker analysis, respectively. In the confirmatory study, six biopsy specimens for histopathological evaluation were obtained. The proportion of cancer cells in biopsy samples of poorly differentiated adenocarcinoma or signet ring cell carcinoma was higher in the pCLE group than in the WLE group in both the pilot and confirmatory studies (pilot: median proportion, 65% vs 30%, P = 0.010; confirmatory: mean ± standard deviation, 49.5 ± 29.3 vs 29.3 ± 13.7, P = 0.002). The expression ratio of tumor markers including carcinoembryonic antigen, GW112, HOX transcript antisense RNA, and H19 tended to be higher in the pCLE group than in the WLE group. Although the proportion of cancer cells in biopsy samples was higher in the pCLE-targeted biopsy than in the WLE-targeted biopsy, the unsuccessful examination in two patients with small early gastric cancer, which had a very small amount of cancer, may demonstrate a limitation. Other limitations included different biopsy samples were used for histopathological examination of tumor markers and there may be a learning curve for the pCLE examination. Results will need to be validated with further studies on this new emerging technique.

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

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

A systematic review and meta-analysis was conducted by Fugazza et al. (2016), analyzing the current literature on CLE and evaluating the applicability and diagnostic yield of CLE in patients with GI and pancreatobiliary diseases. Both prospective and retrospective studies were eligible, identifying 102 studies for inclusion conducted in 16 different countries between 2004 and 2015 (n= 6943). The meta-analysis demonstrated that combining CLE with endoscopic retrograde cholangiopancreatography (ERCP) yields high sensitivity (90%) in the assessment of biliary strictures, demonstrating it as a useful tool for differentiating benign from malignant biliary strictures in individuals with biliary neoplasia. CLE for the surveillance of BE does not appear to be sensitive enough to replace current standard of care such as the Seattle biopsy protocol. For the stomach and duodenum, CLE demonstrated high sensitivity, specificity, accuracy, and positive and negative predictive values in comparison with both histopathology and other endoscopic techniques (e.g., white light endoscopy, narrow band imaging, and chromoendoscopy). However, these data were used with caution based on a limited number of publications. CLE is associated with a pooled sensitivity and specificity of 83% and 90%, respectively, in the detection of colorectal neoplasms and malignant foci in polypoid lesions. 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 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. 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).

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

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

Clinical Evidence

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

Essential Tremor

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

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

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

Halpern et al. (2019) published the 3-year results of the of the open-label extension study by Chang et al. (2018). The study assessed the effectiveness, durability, and safety of transcranial magnetic resonance-guided focused ultrasound (tcMRgFUS) thalamotomy for patients with medication refractory ET. Overall, the 3-year attrition from the treated patient cohort was 31%, with a loss of 23 patients. Scores at 36 months were compared with baseline and at 6 months after treatment to assess for efficacy and durability. Adverse events were also reported. Measured scores remained improved from baseline to 36 months (all $p < 0.0001$). Range of improvement from baseline was 38%-50% in hand tremor, 43%-56% in disability, 50%-75% in postural tremor, and 27%-42% in quality of life. When compared to scores at 6 months, median scores increased for hand tremor (95% confidence interval [CI] 0-2, $p = 0.0098$) and disability (95% CI 1-4, $p = 0.0001$). During the third follow-up year, all previously noted adverse events remained mild or moderate, none worsened, two resolved, and no new adverse events occurred. The investigators concluded that results at 3 years after unilateral tcMRgFUS thalamotomy for ET show continued benefit, and no progressive or delayed complications. Patients may experience mild degradation in some treatment metrics by 3 years, though improvement from baseline remains significant. Author noted limitations included the high dropout rate and the patient analysis differed from the cohorts present in the original RCT and the two-year follow-up. This study provides Class IV evidence that for patients with severe ET, unilateral tcMRgFUS thalamotomy provides durable benefit after 3 years.

Altinel et al. (2019) conducted a systematic review and meta-analysis evaluating randomized controlled trials of deep brain stimulation (DBS) and lesion surgery (LS) in the treatment of tremor. PubMed, Embase, and the Cochrane database were searched to include RCTs with either LS, deep brain stimulation, or controls. The outcomes were the change in tremor score, quality of life, cognitive function, and neuropsychiatric function. Fifteen trials, including 1508 patients, met eligibility criteria. No significant difference in change of tremor scale (SMD -0.07, 95% confidence interval [CI]: -0.38 to 0.24), quality of life (SMD -0.21, 95% CI: -0.69 to 0.27), cognitive function (SMD 0.06, 95% CI: -0.27 to 0.39), or neuropsychiatric function (SMD -0.15, 95% CI: -0.49 to 0.19) were observed between LS and stimulation surgery. Heterogeneity across studies was observed during indirect comparison of quality of life. The investigators identified a possible effect modifier: improvement in quality of life correlated with duration of disease ($P = 0.035$). The focused-ultrasound LS was associated with a 0.70 SMD increase ($P = 0.014$) in quality of life versus DBS in an exploratory subgroup analysis by separating 2 studies with focused-ultrasound LS from other LS studies. The investigators concluded that although the main analysis showed that LS and DBS were equally effective in the treatment of patients with tremor, an exploratory subgroup analysis indicated an improvement in quality of life with

noninvasive focused-ultrasound surgery. The investigators stated that focused ultrasound LS could be considered as a potential choice for tremor control, based on currently available evidence. However, additional evidence from randomized trials comparing stimulation with the focused-ultrasound approach is needed given the lack of direct comparison between the two in the literature and therefore in this meta-analysis. Authors Bond et al., 2017 and Elias et al., 2016 are included in this meta-analysis.

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

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

A systematic literature review was conducted by Langford et al. (2018) to identify and analyze evidence supporting the use of the emerging 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 with direct comparison. The study is limited by indirect comparison.

Mohammed et al. (2018) conducted a meta-analysis to analyze the overall outcomes and complications of 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 paresthesia's in 25.1% of the patients. At 12 months posttreatment, the ataxia had significantly recovered, and paresthesia's became the most common persisting complication, at 15.3%. The authors concluded that MRgFUS therapy for ET significantly improves the CRST scores and improves the QOL in patients with ET, with an acceptable complication rate. According to the authors, there are several limitations of this meta-analysis. Most of the included studies were retrospective case series; only 1 RCT (Elias et al., 2016) was included. Thus, the possibility of bias is high. Other

limitations include a short follow-up period and a small patient population. According to the authors, randomized trials comparing deep brain stimulation (the current standard surgical treatment for medication-refractory ET) to MRgFUS are the needed. Authors Elias et al., 2016; Kim et al., 2107; and Huss et al., 2015 are included in this meta-analysis.

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

A Health Quality Ontario (HQO) evidence-based guideline indicated that 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).

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

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

Parkinson Disease

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

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

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

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Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. Neurology. 2011 Nov 8;77(19):1752-5. Reaffirmed on April 30, 2014.

Code	Description
0408T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes
0409T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only
0410T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only
0411T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only
0412T	Removal of permanent cardiac contractility modulation system; pulse generator only
0413T	Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)
0414T	Removal and replacement of permanent cardiac contractility modulation system pulse generator only
0415T	Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)
0416T	Relocation of skin pocket for implanted cardiac contractility modulation pulse generator

Code	Description
0417T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system
0418T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system
K1030	External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only

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

Clinical Evidence

Cardiac contractility modulation (CCM) signals are nonexcitatory electrical signals delivered during the cardiac absolute refractory period (between beats) that enhance the strength of cardiac muscular contraction. CCM signals are provided by a pacemaker-like device that is connected to three standard pacemaker leads threaded through veins into the right ventricle. One lead is used to sense atrial activity, and the other two are used to sense ventricular activity and deliver the CCM signals. In contrast to a pacemaker or a defibrillator, the system is designed to modulate the strength of contraction of the heart muscle rather than the rhythm (Impulse Dynamics website).

The Optimizer™ implantable CCM system received FDA premarket approval (P180036) on March 21, 2019. Based on this FDA approval, the device is indicated to improve 6-minute hall walk distance, quality of life, and functional status of New York Heart Association (NYHA) Class III heart failure patients who remain symptomatic despite guideline-directed medical therapy, who are in normal sinus rhythm, are not indicated for cardiac resynchronization therapy, and have a left ventricular ejection fraction ranging from 25% to 45%. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180036. (Accessed May 19, 2021).

An ECRI clinical evidence assessment (2021) compared the Optimizer Smart System use with that of optimal medical therapy (OMT) in patients with heart failure (HF). The systematic review included four high-quality randomized controlled trials (RCT) and one study that was used as a comparison group to RCT. ECRI found the evidence to be somewhat favorable that the Optimizer is more effective than OMT for improving functional status and quality of life in patients with moderate to severe, chronic HF. The assessment found it was unclear whether Optimizer reduced mortality rates or HF-related hospitalization rates due to a high a risk of bias in 2 of the studies which had a single-center focus and /or lack of randomization and blinding. Longer term follow up comparing Optimizer with OMT with a focus on mortality and HF-related hospitalization is recommended.

Giallauria et al. (2020) conducted an individual data meta-analysis of all prospective RCTs of CCM versus control that measured functional capacity and/or quality of life questionnaires in patients with HF plus data from one single arm study. Peak oxygen consumption, 6 min walk test distance and quality of life measured by Minnesota Living with Heart Failure Questionnaire (MLWHFQ). Five trials were identified, 4 RCTs (n=801) for all endpoints of interest and one single arm study. The analysis of individual participant data revealed that compared with control, CCM significantly improved benefits in measures of functional capacity and HF-related quality of life. Limitations include relatively young and predominantly male cohorts, individuals with permanent atrial fibrillation were excluded, and the studies analyzed differed in design limiting the ability to define representative results across different individual subgroups. The authors recommend larger, well-conducted RCTs using parallel double-blind designs in order to determine the effect of CCM on mortality and morbidity outcomes before CCM can be widely recommended. Studies in less compromised HF patients, more women and older individuals are also encouraged. (Kadish et al., (2011), Borggrefe et al., (2008), and Neelegaru et al., (2006), which were previously cited in this policy, were included in this meta-analysis).

A Hayes (2019) health technology assessment reviewed the use of CCM with the Optimizer Smart System as an adjunct to OMT in patients with NYHA functional class III heart failure. Four fair quality RCTs, five poor-quality studies and one very poor-quality cohort study were identified that evaluated the safety and efficacy of CCM using the Optimizer Smart System for management of HF and were included in the review. The studies compared OMT alone with CCM therapy plus OMT. The review found there was a low-quality body of evidence suggesting that CCM with the Optimizer Smart System as an adjunct to OMT may improve outcomes related to cardiopulmonary stress tests, functional class severity and quality of life. The clinical significance of these

findings and whether the effect is significantly better than with OMT alone remains uncertain. In patients with HF and an ejection fraction of ≤ 25%, limited evidence suggests that CCM therapy may be less effective. Additional well-designed comparative studies are recommended to determine whether CCM with the Optimizer Smart System is safe and more effective than OMT alone. The authors conclude that the technology has potential but unproven benefit.

Kloppe et al. (2016) conducted a single center pilot evaluation study involving 19 medically refractory symptomatic patients with heart failure and reduced left ventricular function who underwent implantation of an Optimizer system. Patients were randomized into one of two treatment groups: 5 h/day CCM treatment or 12 h/day CCM treatment. Subjects and evaluating physicians were blinded to the study group. Subjects returned to the hospital after 12 and 24 weeks. Efficacy evaluations included changes from baseline to 24 weeks in Minnesota Living with Heart Failure Questionnaire score (MLWHFQ), maximal oxygen consumption in the cardio-pulmonary stress test (peak VO2), NYHA classification, 6-min walk distance (6MWD), and ejection fraction (EF). At the end of 24 weeks, clinical improvement was observed in the entire cohort in all efficacy measures. There were no significant differences, either clinically or statistically, between the groups receiving CCM for 5 h/day vs. 12 h/day. Given the small sample size, further studies are warranted. Additionally, the design of the study does not allow comparison of CCM to other approaches.

European Society of Cardiology guidelines for the diagnosis and treatment of heart failure state that the clinical evidence is insufficient to support specific recommendations for cardiac contractility modulation. The effect of CCM on HF morbidity and mortality remains to be established (Ponikowski et al., 2016).

Reference(s)

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Giallauria F, Cuomo G, Parlato A, et al. A comprehensive individual patient data meta-analysis of the effects of cardiac contractility modulation on functional capacity and heart failure-related quality of life. ESC Heart Fail. 2020 Oct;7(5):2922-2932.

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Kadish A, Nademanee K, Volosin K, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. Am Heart J. 2011 Feb;161(2):329-337.e1-2.

Kloppe A, Mijic D, Schiedat F, et al. A randomized comparison of 5 versus 12 hours per day of cardiac contractility modulation treatment for heart failure patients: A preliminary report. Cardiol J. 2016;23(1):114-9.

Neelagaru SB, Sanchez JE, Lau SK, et al. Nonexcitatory, cardiac contractility modulation electrical impulses: feasibility study for advanced heart failure in patients with normal QRS duration. Heart Rhythm. 2006 Oct;3(10):1140-7.

Ponikowski P, Voors AA, Anker SD, et al.; Authors/Task Force Members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129-200.

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

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

Clinical Evidence

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

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

Yoon et al. (2016) evaluated the safety and efficacy of cryoneurolysis in 22 individuals with refractory peripheral neuropathic pain through a prospective study performed from July 2011 to July 2013. All percutaneous ablations were performed using a PerCryo 17R device (Endocare/Healthtronics, Austin, Texas) with ultrasound imaging guidance. Pain levels were recorded using a VAS score before and at 1, 3, 6, 9, and 12 months after the procedure. A Wilcoxon rank-sum test showed a statically significant decrease between pre- and postprocedural pain scores, and no complications were reported. The authors concluded that US-guided cryoneurolysis of the peripheral nerve is safe and may be effective in controlling chronic refractory neuropathy, providing moderately long-term pain relief. Future studies with greater sample sizes would be able to quantify the amount of pain relief provided by the initial treatment versus each subsequent treatment with cryotherapy.

Prologo et al. (2015) evaluated the safety and efficacy of percutaneous CT-guided cryoablation of the pudendal nerve for the treatment of refractory pudendal neuralgia, selecting 11 patients following established diagnostic criteria. Using the Brief Pain Inventory questionnaires prior to treatment, the average level of pain on a scale from 0 (no pain) to 10 (worst pain imaginable) was 7.6, with pain described as "burning" (80%), "pulling" (37.5%), "crushing" (50%), "pressure" (84.5%), "throbbing" (50%), "knife-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.

Reference(s)

Prologo JD, Gilliland CA, Miller M, et al. Percutaneous Image-Guided Cryoablation for the Treatment of Phantom Limb Pain in Amputees: A Pilot Study. J Vasc Interv Radiol. 2017 Jan;28(1):24-34. e4.

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

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

Yoon JH, Grechushkin V, Chaudhry A, et al. Cryoneurolysis in Patients with Refractory Chronic Peripheral Neuropathic Pain. J Vasc Interv Radiol. 2016 Feb;27(2):239-43.

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

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

Clinical Evidence

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

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 Mydriasert insert (Théa Pharma) (0.28 mg of tropicamide and 5.4 mg of phenylephrine hydrochloride) placed in the inferior fornix of the eye. Pupil size before and after surgery, blood pressure, and heart rate were measured. Before surgery, pupil diameter was 9.44 ± 1.17 mm in Group 1 and 9.05 ± 1.54 in Group 2. Twenty-four hours after surgery, pupil diameter was 5.20 ± 1.54 mm in Group 1 and 3.33 ± 1.15 in Group 2. The authors concluded that the effect of the Mydriasert insert was similar to conventional mydriatic agents. The authors indicated that pupil size was restored to normal faster when using the Mydriasert insert compared with conventional mydriatic agents for pupil dilation. Study limitations included a small 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
0469T	Retinal polarization scan, ocular screening with on-site automated results, bilateral

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

Clinical Evidence

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

The U.S. Food and Drug Administration (FDA) awarded the Pediatric Vision Scanner, now being marketed as blinq™, market clearance through the "de novo" pathway in June 2016. For more information, refer to the following website: https://www.accessdata.fda.gov/cdrh_docs/reviews/den130051.pdf. (Accessed May 13, 2021).

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

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

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 anisometropic amblyopia as well as strabismus. The authors also followed patients during treatment to determine whether the improvements gained from treatment would be reflected in improved vision test results. 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 authors concluded that PVS identified children with amblyopia or strabismus with high sensitivity and specificity, while successful treatment restored normal BIN scores in amblyopic patients without strabismus. Study limitations again include small size, single center, and engagement of patients with known risk factors; it was also noted in this study that there was a lack of racial diversity with 74% of the participants identified as Caucasian.

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

Reference(s)

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

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

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

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

US Food and Drug Administration (FDA). De novo summary: Pediatric vision scanner. http://www.fda.gov. Published December 13, 2013. Accessed May 13, 2021.

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

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

Clinical Evidence

Choi et al. (2021) conducted a systematic review and meta-analysis to determine the efficacy of fractional CO2 lasers in treating burn scars, and to determine if laser therapy results in higher patient satisfaction and cost effectiveness. 15 articles published between 2012 and 2019, which were comprised of 3 randomized controlled trials (RCTs) and 12 observational studies totaling 778 patients were included. The median age was 22 years. All studies used ablative fractional CO2 lasers with a median of 2.5 treatments per patient, with a range of 1 to3 months between treatments. To measure response to therapy, two main observer description measures, the Vancouver scar scale (VSS) and patient/observer subjective assessment scale (POSAS) were commonly used. The results showed all studies, but one found a statistically significant ($P < 0.05$) improvement in overall and VSS component scores of pigmentation, vascularity, pliability, and height when comparing treatment groups and treatment versus control. The authors concluded that fractional CO2 lasers alone can result in clinical improvement of scars, with a notably decreased side effect profile compared to the more commonly used pulsed dye laser, and that even single treatments can result in statistically significant improvement in VSS and POSAS scores. Traditional burn scar management is time intensive, and has not demonstrated satisfactory improvement in scars, and burn practitioners should consider using laser therapy before attempting more invasive scar treatments such as surgical contracture release. (Levi et al. 2016, previously cited in this policy, is included in this systematic review).

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

Zhang et al. (2019) conducted a meta-analysis to evaluate the effectiveness of fractional carbon dioxide (CO2) laser for the treatment of burn scars. Fourteen studies were included and all except one retrospective study were prospective in design and were single arm evaluations. There was no significant publication bias identified. The results showed significant improvements in Vancouver Scar Scale (VSS), Patient and Observer Scar Assessment Scale (POSAS), and Scar Assessment Scale (SAS) scores after treatment especially with regards to pigmentation, vascularity, pliability, and height of scar. Pain and pruritis also improved with this treatment. However, scar thickness decreased statistically non-significantly and no improvement could be observed in scar firmness or elasticity, although lesser data were available to evaluate scar thickness, firmness and elasticity. This meta-analysis finds that 1 to 4 sessions of treatment of burn scars with fractional CO2 laser is associated with significantly improved outcomes. (El-Hoshy et al. 2017 and El-Zawahary et al. 2015, previously cited in this policy, are included in this systematic review).

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

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

Reference(s)

Choi KJ, Williams EA, Pham CH, et al. Fractional CO2 laser treatment for burn scar improvement: A systematic review and meta-analysis. Burns. 2021 Mar;47(2):259-269.

El-Hoshy K, Abdel-Halim MRE, Dorgham D, et al. Efficacy of fractional carbon dioxide laser in the treatment of mature burn scars: A clinical, histopathological, and histochemical study. J Clin Aesthet Dermatol. 2017;10(12):36-43.

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Oosterhoff TCH, Beekman VK, van der List JP, et al. Laser treatment of specific scar characteristics in hypertrophic scars and keloid: A systematic review. J Plast Reconstr Aesthet Surg. 2021 Jan;74(1):48-64.

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Seago M, Shumaker PR, Spring LK, et al. Laser Treatment of Traumatic Scars and Contractures: 2020 International Consensus Recommendations. Lasers Surg Med. 2020 Feb;52(2):96-116.

Zhang C, Yin K, Shen YM. Efficacy of fractional carbon dioxide laser therapy for burn scars: a meta-analysis. J Dermatolog Treat. 2019 Dec 22:1-6.

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

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

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

Clinical Evidence

Conventional diagnostic techniques for middle ear disorders include use of standard or pneumatic otoscopy to evaluate the surface of the tympanic membrane. Optical coherence tomography (OCT) is a non-invasive, non-contact optical imaging technology that can effectively reconstruct a depth-resolved high-resolution cross-sectional image of tissues (1-15 µm) using interferometry and a near-infrared light source (Cho et al., 2015).

Park et al. (2017) conducted a prospective study to examine the tympanic membranes (TMs) of 120 patients with middle ear conditions using a handheld optical coherence tomography-based otoscope (860 nm central wave length, 15 µm axial resolution, 15 µm lateral resolution, and 7 mm scanning range using relay lens). Both OCT and otoendoscope images were compared according to the clinical characteristics such as perforation, retraction, and postoperative healing process. The objective grade about the thickness of perforation margins and the accurate information about the extent of TM retraction that was not distinguishable by otoendoscopic exam could be identified using this system. The postoperative healing process of TMs could be also followed using the OCT device. The authors concluded that their findings suggest that the handheld OCT device would be another useful application.

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

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

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

Reference(s)

Cho NH, Lee SH, Jung W, et al. Optical coherence tomography for the diagnosis and evaluation of human otitis media. Journal of Korean Medical Science. 2015;30(3):328-335.

ECRI Institute. Hotline Response. Optical coherence tomography for aiding diagnosis of middle ear abnormalities. April 2018. Archived April 2021.

Nguyen CT, Robinson SR, Jung W, et al. Investigation of bacterial biofilm in the human middle ear using optical coherence tomography and acoustic measurements. Hearing research. 2013; 301:193-200.

Park K, Cho NH, Jeon M, et al. Optical assessment of the in vivo tympanic membrane status using a handheld optical coherence tomography-based otoscope. Acta Otolaryngol. 2017:1-8.

Code	Description
0487T	Biomechanical mapping, transvaginal, with report

Biomechanical mapping using vaginal tactile imaging techniques for assessment and treatment planning for vaginal conditions is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Biomechanical mapping is a diagnostic test used to assess conditions of the female pelvic floor to quantify tissue elasticity, pelvic support, and pelvic muscle functions. This may guide the optimal treatment for women with prolapse, incontinence, atrophy, and some forms of pelvic pain.

Lucente et al. (2017) developed a new approach for the biomechanical characterization of vaginal conditions, muscles, and connective tissues in the female pelvic floor. One hundred and thirty-eight women were enrolled in the study. The average age of this group of women was 60 ± 15 years and had normal pelvic support (stages I to IV). A set of 31 VTI parameters were transposed into a quantitative characterization of pelvic muscles and ligamentous structures. The authors concluded that VTI allowed biomechanical characterization of female pelvic floor structures and tissues in vivo, which may help to optimize treatment of the diseased conditions such as prolapse, incontinence, atrophy, and some forms of pelvic pain. The limitations identified during this study included image dependence on operator's skill level, contact conditions and probe size.

In an observational, case-controlled clinical study, Egorov and associates (2018) evaluated a new approach for quantitative biomechanical characterization of the vagina. Data were analyzed for 42 subjects with normal pelvic floor support. The average age was 52 years (range of 26 to 90 years). 8 new VTI parameters were introduced, including maximum resistance force to insertion, insertion work, maximum stress-to-strain ratio, maximum pressure at rest, anterior-posterior force at rest, left-right force at rest, maximum pressure at muscle contraction, and muscle contraction force. The investigators observed low to moderate correlation of these parameters with subject age and no correlation with subject weight. Six of eight parameters demonstrated a P value less than .05 for 2 subject subsamples divided by age (≤52 vs >52 years), which means six VTI parameters change with age. The authors concluded that further research with a more representative sample will show more comprehensive distributions and peculiar features for normal values. This study had 2 major drawbacks; its relatively small sample size (n = 42) and despite normal pelvic floor support (no prolapse), some analyzed subjects came to the urogynecologic office with some problematic conditions affecting the pelvic floor.

van Raalte and Egorov (2015) stated that VTI records pressure patterns during pelvic floor muscle (PFM) contractions and from vaginal walls under an applied tissue deformation. The investigators validated VTI and muscle contraction parameters (markers) sensitive to the female pelvic floor conditions. Twenty-two women with normal and prolapse conditions were examined by a VTI probe. Nine parameters were identified that were sensitive to prolapse conditions ($p < 0.05$ for 1-way ANOVA and/or $p < 0.05$ for t-test with correlation factor r from -0.73 to -0.56). The parameters included pressure, pressure gradient and dynamic pressure response during PFM at identified locations. The investigators concluded that these parameters may be used for biomechanical characterization of female pelvic floor conditions to support an effective management of pelvic floor prolapse. They also stated that further studies with larger sample sizes investigating a variety of other pelvic floor conditions, and use in the evaluation of interventions including physical therapy, conservative management options and surgical correction are needed to further explore diagnostic values of VTI.

Reference(s)

Egorov V, Murphy M, Lucente V, et al. Quantitative assessment and interpretation of vaginal conditions. Sex Med. 2018;6(1):39-48.

Lucente V, van Raalte H, Murphy M, et al. Biomechanical paradigm and interpretation of female pelvic floor conditions before a treatment. Int J Womens Health. 2017 Aug 3; 9:521-550.

van Raalte H, Egorov V. Tactile imaging markers to characterize female pelvic floor conditions. Open J Obstet Gynecol. 2015;5(9):505-515.

Code	Description
0491T	Ablative laser treatment, non-contact, full field and fractional ablation, open wound, per day, total treatment surface area; first 20 sq cm or less

Code	Description
0492T	Ablative laser treatment, non-contact, full field and fractional ablation, open wound, per day, total treatment surface area; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)

Ablative laser treatment (non-contact, full field and fractional ablation) for wound healing is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

While ablative laser treatment for open wound has been studied, the evidence is insufficient to support its routine use as proven in clinical practice.

In a systematic review, Suter et al. (2017) examined a potential benefit of laser use in the treatment of recurrent aphthous stomatitis (RAS). The primary outcome variables were pain relief, duration of wound healing and reduction in episode frequency. A PICO approach was used as a search strategy in Medline, Embase and Cochrane databases. After scanning and excluding titles, abstracts and full texts, a total of 11 studies (10 RCTs and 1 non-RCT) were included. Study selection and data extraction were carried out by 2 observers. Laser treatment included Nd:YAG laser ablation, CO2 laser applied through a transparent gel (non-ablative) and diode laser in a low-level laser treatment (LLLT) mode. Control groups had placebo, no therapy or topical corticosteroid treatment. Significant pain relief immediately after treatment was found in 5 out of 6 studies. Pain relief in the days following treatment was recorded in 7 studies. The duration of RAS wound healing was also reduced in 5 studies. However, criteria of evaluation differed between the studies. The episode frequency was not evaluated as only 1 study addressed this outcome parameter, but did not discriminate between the study (LLLT) and control (corticosteroid) groups. Jadad scores (ranging from 0 to 5) for quality assessment of the included studies ranged between 0 and 2 (mean = 1.0) for studies analyzing pain relief and between 0 and 3 (mean = 1.1) for studies evaluating wound healing. The use of lasers (CO2 laser, Nd:YAG laser and diode laser) to relieve symptoms and promote healing of RAS was a therapeutic option. The authors concluded that more studies for laser applications are needed to demonstrate superiority over topical pharmaceutical treatment and to recommend a specific laser type, wavelength, power output and applied energy (ablative versus photo-biomodulation).

Krakowski et al. (2016) stated that ablative fractional resurfacing (AFR) is an emerging therapy for chronic wounds. In a small case-series study, these researchers reported the successful use of AFR to facilitate the healing of chronic wounds in 2 pediatric patients. These patients had chronic wounds within scars that were treated with a micro-fractionated CO2 laser in a single pass at a pulse energy of 50 mJ and a treatment density of 5 %; 1 patient had 1 treatment and the other had 2 treatments 1 month apart. Ablative fractional laser resurfacing led to rapid healing of chronic wounds in both patients. The wounds remained epithelialized after 9 months in 1 patient and 4 months in the other. There were no complications. The authors concluded that the combination of tolerability and efficacy observed in these cases introduced AFR as a potential promising adjunct to existing treatments for chronic, non-healing wounds in the pediatric population. The study is however limited by lack of comparison group.

Phillips and colleagues (2015) stated that treating post-traumatic lower extremity wounds can be challenging, especially in elderly patients. Recently, the use of fractional carbon dioxide (CO2) laser has been shown to improve wound healing in scar-related wounds. These researchers used this treatment modality in post-traumatic wounds that were slow to heal in 3 elderly patients. Each wound underwent 1 fractional CO2 laser treatment. The wound base was treated at 30 mJ and 5 % density. The entire wound edge and 1 to 2 cm into the normal surrounding skin were treated at 50 mJ and 5 % density. One pass was completed at 150 Hz per treatment. Treatments were well-tolerated with only mild discomfort. Each wound healed by 60 % or greater within 3 weeks. No adverse events were reported aside from mild and transient erythema at site of treatment. The authors concluded that fractional CO2 laser treatment appeared to accelerate healing in each of these post-traumatic wounds; it may be a helpful adjunct in non-healing post-traumatic wounds. They also concluded that controlled studies are needed to further validate this modality as a second-line treatment for difficult-to-heal lower-extremity wounds.

Reference(s)

Krakowski AC, Diaz L, Admani S, et al. Healing of chronic wounds with adjunctive ablative fractional laser resurfacing in two pediatric patients. Lasers Surg Med. 2016;48(2):166-169.

Phillips TJ, Morton LM, Uebelhoer NS, et al. Ablative fractional carbon dioxide laser in the treatment of chronic, posttraumatic, lower-extremity ulcers in elderly patients. JAMA Dermatol. 2015;151(8):868-871.

Suter VGA, Sjölund S, Bornstein MM. Effect of laser on pain relief and wound healing of recurrent aphthous stomatitis: a systematic review. Lasers Med Sci. 2017 May;32(4):953-963.

Code	Description
0493T	Contact near-infrared spectroscopy studies of lower extremity wounds (e.g., for oxyhemoglobin measurement)
0640T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); image acquisition, interpretation and report, each flap or wound
0641T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); image acquisition only interpretation and report, each flap or wound
0642T	Noncontact near-infrared spectroscopy studies of flap or wound (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); interpretation and report only, each flap or wound

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

Clinical Evidence

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

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

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

Hill et al. (2020) conducted a cohort study to evaluate the capacity of NIR spectroscopy to detect clinically relevant differences in flap perfusion intraoperatively. Patients undergoing oncologic resection of breast cancer, sarcomas, and cutaneous tumors requiring flap reconstruction (local, regional, or free) between January 2018 and January 2019 were analyzed in this study. Clinicians were blinded to device tissue oxygen saturation (StO2) measurements taken intraoperatively after closure and at

follow-up appointments in the first 30 days. Measurements were categorized as (1) control areas not affected by the procedure, (2) areas at risk, and (3) areas of necrosis. These areas were retrospectively demarcated by 2 blinded assessors on follow-up images and transposed onto anatomically correlated intraoperative StO2 measurements. Forty-two patients were enrolled, and 51 images were included in the analysis. Oncologic procedures were predominantly breast (22), post-extirpative melanoma (13), and sarcoma (3) reconstructions. Flap reconstruction involved 30 regional skin flaps, 3 pedicled flaps, and 3 free flaps. Nine patients (20.9%) and 11 surgical sites developed skin flap necrosis (SFN). Mean intraoperative StO2 measurements for control areas, areas at risk, and areas of SFN were 74.9%, 71.1%, and 58.3%, respectively. Relative to control areas, mean intraoperative StO2 measurements were lower by 17.5% (P = 0.01) in ultimate areas of SFN and in areas at risk by 5.8% (P = 0.003). Relative to areas at risk, mean StO2 measurements from areas of ultimate SFN were lower by 8.3% (P = 0.04). The investigators indicated that these preliminary data suggest that measuring skin flap tissue oxygenation intraoperatively, with NIR spectroscopy, can differentiate objective variations in perfusion that are associated with clinical outcomes. According to the investigators, the relatively small sample size made analysis of the sensitivity and specificity of this device limited and not applicable in a clinical context.

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

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

Reference(s)

Hill WF, Webb C, Monument M, et al. Intraoperative near-infrared spectroscopy correlates with skin flap necrosis: a prospective cohort study. Plast Reconstr Surg Glob Open. 2020 Apr 22;8(4): e2742.

Lin BS, Chang CC, Tseng YH, et al. Using wireless near-infrared spectroscopy to predict wound prognosis in diabetic foot ulcers. Adv Skin Wound Care. 2020 Jan, Vol 33, No. 1, pp. 1-12.

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

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

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

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

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

Clinical Evidence

Najjar et al. (2016) studied ocular lens density and transmittance measurements of 43 subjects, obtained by an improved psychophysical scotopic heterochromatic flicker photometry (sHFP) technique. This was compared to the results obtained by

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

Reference(s)

Najjar RP, Teikari P, Cornut P, et al. Heterochromatic flicker photometry for objective lens density quantification investigative Ophthalmology & Visual Science March 2016, Vol.57, 1063-1071. doi: https://doi.org/10.1167/iovs.15-18642.

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

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

Clinical Evidence

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

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

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

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

Reference(s)

Finis D, Ackermann P, Pischel N, et al. Evaluation of meibomian gland dysfunction and local distribution of meibomian gland atrophy by non-contact infrared meibography. Curr Eye Res. 2015;40(10):982-9.

Johnson&Johnson website. Lipican Dynamic Mibomian Imager. Available at https://www.jnjvisionpro.com/products/lipiscan%E2%84%A2-dynamic-meibomian-imager. Accessed May 5, 2021.

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

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

Clinical Evidence

Currently, the diagnosis of osteoporosis is based on the measurement of bone mineral density (BMD), using axial dual energy X-ray absorptiometry (DXA) of the hip and/or the lumbar spine. Bindex® a pocket-sized tool for osteoporosis screening and diagnostics is used for measuring the cortical thickness of the tibia or radius. The results, combined with other patient data, are used to estimate the hip region's bone mineral density.

Nazari-Farsani et al. (2020) conducted a cohort study of postmenopausal women with primary hip osteoarthritis that underwent total hip arthroplasty with implantation of a parallel-sided femoral stem. The sixty-five participants were women between the ages of 60 and 85-year-old who were part of a single-center, double-blinded, placebo-controlled, randomized clinical trial. Preoperatively, subjects had multisite DXA measurement of bone mineral density (BMD) and pulse-echo ultrasonometry of the cortical-bone thickness using the Bindex mobile device. Measurements were conducted by two physiotherapists. Five successful repeated measurements in each location were taken and averaged. Patients then underwent a total hip replacement. The patients were randomly assigned to receive antiresorptive denosumab treatment (a subcutaneous injection of 60 mg every 6 months) or placebo for 1 year, which started 4 weeks before surgery. The authors found the measurement of cortical-bone thickness was challenging as the pulse-echo ultrasonometry (Bindex) only gave a rough estimate of bone thickness. Limitations of the trial included a study design that doesn't inform the use of this technology as a substitute to DXA for osteoporosis screening, a relatively small sample size along, with inclusion limited to postmenopausal women.

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

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

ultrasonometry shows promise as a tool for fracture risk assessment, but future prospective and randomized control studies are warranted.

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

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

The US Food and Drug Administration (FDA) approved the Bindex Osteoporosis Measurement device for diagnosing osteoporosis under 510(k) (K161971) on January 9, 2017. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/K161971.pdf. (Accessed April 20, 2021).

ClinicalTrials.gov identifies Bindex for Osteoporosis Diagnostics (NCT03878732) which focuses on the clinical validation of the ultrasound device (Bindex®) and Density Index (DI), a diagnostic parameter reported by Bindex. The study completion date is listed as February of 2020 with no posted results. Available at: https://www.clinicaltrials.gov/ct2/show/study/NCT03878732?term=NCT03878732&draw=2&rank=1. (Accessed April 20, 2021).

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

Multifocal electroretinogram (mfERG) is proven and medically necessary for chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy screening.

Multifocal electroretinogram (mfERG) is unproven and not medically necessary for all other indications 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 (PERG).

An ECRI report, Pattern Electroretinography for Detecting Central Retinal Damage from Glaucoma, states that evidence from 1 systematic review and 5 case-control studies (comprising 930 patients) suggests that changes in PERG waveform amplitude and latency may indicate retinal ganglion cell (RGC) damage in individuals with glaucoma. However, the evidence does not demonstrate that early detection of RGC damage would enable early therapeutic intervention, which would improve patient outcomes. The evidence were found to be inconclusive (2020).

Park et al. (2017) conducted a retrospective cohort 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 PERG (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 ($R^2 = 0.22$; $p<p\ 0.001$). 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 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. PERG 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 μm). 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 (AMD) 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 mfERG (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.

Tsang et al. (2015) conducted a systematic review to determine the validity of mfERG as a screening tool for detecting CQ and HCQ retinal toxicity in patients using these medications. Individual patient data (449 eyes of 243 patients) identified in 23 studies published from 2000-2014 were analyzed. Multi-focal ERG had the greatest proportion of positive test results, followed by AVF. The pooled sensitivity and specificity of mfERG were 90% and 52%, respectively. 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 a prospective study, Ambrosio et al. (2015) examined the role of mfERG for predicting visual acuity (VA) decline in early AMD with time. A total of 26 early AMD 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 (μV) 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.

Browning et al. (2014) conducted a retrospective case series analysis to determine the relative sensitivity and specificity of 10-2 visual fields (10-2 VFs), mfERG, and SD-OCT in the detection hydroxychloroquine retinopathy. A total of 121 patients taking hydroxychloroquine (n=119) or chloroquine (n=2) with 10-2 VF, mfERG, and SD-OCT test results were reviewed. Rates of test abnormality were determined. Retinopathy was present in 14 patients and absent in 107. Eleven of 14 (78.6%) patients with retinopathy were overdosed, defined as receiving hydroxychloroquine and chloroquine doses >6.5 mg/kg/day and >3.0 mg/kg/day, respectively. 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 authors concluded that 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, particularly in patients taking ≤6.5 mg/kg/day. This study is limited by its retrospective case series design and the small number of hydroxychloroquine and chloroquine retinopathy cases for which all three tests were available. Additional studies are needed with larger sample sizes to accurately determine the sensitivity and specificity of these tests.

Preiser et al. (2013) compared photopic negative response (PhNR) and PERG in different stages of the disease. Eleven eyes with pre-perimetric glaucoma (glaucomatous optic disc with normal field); 18 with manifest glaucoma; and 26 normal 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.

Banitt et al. (2013) conducted a longitudinal cohort study that included 107 adults (201 eyes) at risk of glaucoma and compared PERG amplitudes and 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 (≤ 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 RGC dysfunction in glaucoma suspects and patients with early primary open angle glaucoma (POAG) using 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 prospective study, Kandel et al. (2012) evaluated the effects of ethambutol therapy in visual functions of both eyes in 44 patients. Parameters evaluated included mfERG with Roland-RETI scan. Based on the results of the study, the authors concluded that visual acuity, contrast sensitivity, and mfERG 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.

Dale et al. (2010) compared the ability of the mfERG and frequency domain OCT (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 PERG to that of 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.

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

In a cross-sectional study of 71 patients, Bowd et al. (2009) obtained PERGLA recordings within 6 months of 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 PERGs 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.

The AAO revised recommendations for chloroquine and hydroxychloroquine retinopathy screening state that mfERG is a useful screening tool and provides objective corroboration for visual fields (Marmor et al., 2016).

The AAO's preferred practice pattern for POAG does not specifically mention ERG as a diagnostic tool (Prum et al., 2015).

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Code	Description
0515T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; complete system (includes electrode and generator [transmitter and battery])

Code	Description
0516T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only
0517T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; pulse generator component(s) (battery and/or transmitter) only
0518T	Removal of only pulse generator component(s) (battery and/or transmitter) of wireless cardiac stimulator for left ventricular pacing
0519T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter)
0520T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter), including placement of a new electrode
0521T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording, and disconnection per patient encounter, wireless cardiac stimulator for left ventricular pacing
0522T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, wireless cardiac stimulator for left ventricular pacing

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

Clinical Evidence

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

The WiSE (Wireless Stimulation Endocardially) CRT System (EBR Systems, Inc., Sunnyvale, CA) (formerly the WiCS-LV) is currently undergoing clinical trials. The WiSE CRT System is a wireless left ventricular (LV) pacing system that works with a conventional pacemaker and/or defibrillator for patients in whom CRT is indicated. The WiSE CRT system is comprised of an ultrasonic transmitter attached to a battery unit and a tiny wireless receiver which acts as a pacing electrode. The WiSE system allows for biventricular pacing while eliminating the need for a LV pacing wire in the coronary sinus. The system allows the provider to customize electrode placement to the optimal location for pacing, which varies among patients; this differs significantly from conventional LV pacing leads, which are limited by coronary sinus anatomy (Hayes, 2019; updated 2021).

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

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

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

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

Reddy et al. (2017) conducted a prospective multicenter case series (SELECT-LV), to assess the safety and performance of the WiSE-CRT system. Thirty-five patients who failed conventional treatment, underwent cardiac synchronization therapy. The patients were assessed out to 6 months post implant. The procedure was successful in 97.1% of attempted implants. The primary performance endpoint, biventricular pacing on the 12-lead electrocardiogram at 1 month, was achieved in 33 of 34 patients. Twenty-eight patients (84.8%) had improvement in the clinical composite score at 6 months, and 21 patients (66%) demonstrated a positive echocardiographic CRT response. There were no pericardial effusions, however serious procedure/device-related events occurred in 3 patients (8.6%) within 24 hours, and 8 patients (22.9%) between 24 hours and 1 month. The authors concluded that the SELECT-LV study demonstrates clinical feasibility of the WiSE-CRT system, providing benefit to a majority of patients that have not responded to conventional treatment. This study is limited by the small study population and lack of comparison group. NCT01905670

Auricchio et al. (2014) reported on the Wireless Stimulation Endocardially for CRT (WiSE-CRT) study. This multicenter, prospective, interventional study evaluated the feasibility, safety, and short-term outcomes of the WiSE-CRT System. Seventeen heart failure patients were enrolled and categorized as: (i) patients in whom attempted coronary sinus lead implantation for CRT had failed (n = 7); (ii) patients with a previously implanted CRT device, not responding to CRT (n = 2); and (iii) patients with previously implanted pacemakers or implantable cardioverter-defibrillator and meeting the standard indications for CRT (n = 8). System implantation was achieved in 13 patients (76.5%); mean R-wave amplitude was 5.6 ± 3.2 mV, and the mean pacing threshold was 1.6 ± 1.0 V, respectively. In one patient, no sufficient pacing thresholds were found; in three patients pericardial effusion occurred. Biventricular pacing was recorded in 83% and 92% of the patients at 1 month and 6 months, respectively. QRS duration was shorter during biventricular pacing compared with right ventricular pacing at 1 month (-41 ms; P = 0.0002) and 6 months (-42 ms; P = 0.0011), respectively. At the 6-month follow-up, two-thirds of the patients had at least one functional class change. Left ventricular ejection fraction significantly increased (P < 0.01) by 6 points at the 6-month follow-up. The authors concluded that despite the promising results for a novel technology, further study is required to definitively conclude the safety and the performance of the system. This study is limited by the small study population and lack of comparison group. NCT01294527

Reference(s)

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Singh JP, Walsh MN, Kubo SH, et al. Modified design of stimulation of the left ventricular endocardium for cardiac resynchronization therapy in nonresponders, previously untreatable and high-risk upgrade patients (SOLVE-CRT) trial. Am Heart J. 2021 May; 235:158-162.

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)

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

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

Clinical Evidence

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

The AngelMed Guardian System received U.S. Food and Drug Administration (FDA) premarket approval (P150009) on April 9, 2018. The AngelMed Guardian System is indicated for use in patients who have had prior ACS events and who remain at high risk for recurrent ACS events. The AngelMed Guardian System is indicated as an adjunct to patient recognized symptoms. The system detects potential ongoing ACS events, characterized by sustained ST segment changes, and alerts the patient to seek medical attention for those potential ACS events. Additional FDA information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P150009. (Accessed May 19, 2021)

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

Gibson et al. (2019) reported the results of the ALERTS (AngelMed for Early Recognition and Treatment of STEMI; NCT00781118) trial. The ALERTS trial was a multicenter, randomized trial of an implantable cardiac monitor that alerts patients with rapidly progressive ST-segment deviation. 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. Additionally, Holmes et al.

(2019) published previously unreported results from the ALERTS trial that focused on pre-hospital delays during ACS events. The study appears to include events collected after the randomization period, when all participants had the alarm on. The authors reported reduced delays, with 55% (95% confidence interval [CI]: 46% to 63%) of ED visits for ACS events <2 h compared with 10% (95% CI: 2% to 27%) in the Alarms OFF group ($p < 0.0001$) and shorter median pre-hospital delay for myocardial infarction: 12.7 h for Alarms OFF and 1.6 h in Alarms ON subjects ($p < 0.01$). The findings of this latest publication are limited by what appears to be inclusion of events outside of the randomization period, which results in breaking the randomization benefit and could introduce possible biases.

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

Reference(s)

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

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

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.

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

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

Clinical Evidence

Bone micro indentation 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).

Schoeb et al. (2020) conducted a systematic review of all clinical studies using IMI in vivo in humans also addressing practical aspects of the technique and differences in study design, which may impact outcome. Search data generated 38 studies showing that IMI can identify patients with primary osteoporosis and fractures, patients with secondary osteoporosis due to various underlying systemic disorders, and scarce longitudinal data also show that this tool can detect changes in bone material strength index (BMSi), following bone-modifying therapy including use of corticosteroids. However, this main outcome parameter was not always concordant between studies. This systematic review also identified a number of factors that impact on BMSi outcome. These include subject- and disease-related factors such as the relationship between BMSi and age, geographical region and the presence of fractures, and technique- and operator-related factors. Taken together, findings from this systematic review confirm the added value of IMI for the evaluation and follow-up of elements of bone fragility, particularly in secondary osteoporosis. Notwithstanding, the high variability of BMSi outcome between studies calls for age-dependent

reference values, and for the harmonization of study protocols. Prospective multicenter trials using standard operating procedures are required to establish the value of IMI in the prediction of future fracture risk, before this technique is introduced in routine clinical practice.

Rufus-Membere et al. (2018) conducted a cross-sectional analysis in a population-based study BMSi was measured using the OsteoProbe at the mid-tibia. Research using this minimally invasive technique is expanding yet, to-date, there have been no reports regarding its feasibility in the research setting. the feasibility and tolerability of using the OsteoProbe in men enrolled in the Geelong Osteoporosis Study. For 252 of 345 consecutive participants (aged 33 to 96 years), BMSi was measured using the OsteoProbe at the mid-tibia. Immediately following measurement, each subject used a visual analog scale (0 to 10) to rate the level of discomfort that was anticipated and experienced, their initial reluctance towards the measurement and their willingness to repeat measurement. Reasons for non-measurement in 92 men were needle phobia (n = 8), discomfort after 1st indentation (n = 5), skin infections (n = 21), excessive soft tissues around the mid-tibia region (n = 56), inability to provide informed consent (n = 2). Among 252 men who had IMI measures, the expectation for pain during measurement was low (1.54 ± 1.56), as was actual pain experienced (0.38 ± 0.71). Reluctance to undergo measurement was low (0.34 ± 0.93). All subjects indicated a willingness to have the measurement performed again. Mean (± SD) BMSi was 83.0 ± 6.4 (range of 62.3 to 93.0). The authors concluded that the procedure was well-accepted by subjects suggesting that IMI testing with the OsteoProbe was feasible in a research setting. These investigators stated that further assessment of the clinical utility of this technology for evaluating fracture risk is needed and is currently in progress. Limitations included the sample was selected at random and not on the basis of disease process and the findings but not be generalizable to women or other populations.

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 micro indentation, such as tip size, depth and method of analysis. Only two studies validated micro indentation 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 micro indentation has been used in various studies to assess bone stiffness, but only two studies with conflicting results compared micro indentation with traditional mechanical testing techniques. Further research, including more studies comparing micro indentation with other mechanical testing methods, is needed before micro indentation can be used reliably to calculate cortical bone stiffness.

Diez-Perez et al. (2010) assessed the validity results of micro indentation technique capable of directly testing the mechanical endurance of bone tissue in patients. The study reviews a device that performs bone micro indentation 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 micro indentation and other parameters measured by the RPI instrument to quantify the contribution of tissue mechanical properties to bone fracture risk.

Reference(s)

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

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

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

- Surgical planning
- Manufacturing of customized devices

Clinical Evidence

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

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

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

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

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

Moralidou et al. (2020) conducted a systematic review of the existing literature for the use of 3D pre-operative planning in primary total hip arthroplasty (THA). The review focused on (1) the accuracy of implant sizing, restoration of hip biomechanics and component orientation; (2) the benefits and barriers of this tool; and (3) current gaps in literature and clinical practice. A total of 43 full scientific articles were reviewed. Clinical studies have highlighted the accuracy of 3D pre-operative planning in

predicting the optimal component size and orientation in primary THAs. Component size planning accuracy ranged between 34-100% and 41-100% for the stem and cup respectively. The absolute, average difference between planned and achieved values of leg length, offset, center of rotation, stem version, cup version, inclination and abduction were 1 mm, 1 mm, 2 mm, 4°, 7°, 0.5° and 4° respectively. The benefits of 3D pre-operative planning include 3D representation of the human anatomy for precise sizing and surgical execution. The Barriers of 3D pre-operative planning include increased radiation dose and learning curve. According to the authors, the long-term evidence investigating this technology is limited. Emphasis should be placed on understanding the health economics of an optimized implant inventory as well as long-term clinical outcomes.

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

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

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

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

Langridge et al. (2018) performed a systematic review of the uses of 3D printing within surgical training and assessment. Overall, 49 studies were identified for inclusion in the qualitative analysis. Heterogeneity in study design and outcome measures used prohibited meaningful meta-analysis. 3D printing has been used in surgical training across a broad range of specialties

but most commonly in neurosurgery and otorhinolaryngology. The authors concluded that 3D printing technology has a broad range of potential applications within surgical education and training. Although the field is still in its relative infancy, several studies have already demonstrated its usage both instead of and in addition to traditional educational methods. The authors indicated that within the current literature review there is a lack of high-quality randomized control studies to assess the effectiveness of 3D printing within the preoperative planning setting. Most evidence related to the usage of 3D printing and their effect on clinical endpoints is an underexplored area with the majority of literature focusing on anecdotal case reports without assessing comparable clinical endpoints. The authors recommended that future studies should compare 3D printed models with current best surgical practice when measuring use within the preoperative planning setting. The implication of these findings on patient care is however unclear.

Diment et al. (2017) performed a systematic review to evaluate the clinical efficacy and effectiveness of using 3D printing to develop medical devices across all medical fields. Of the 3084 abstracts screened, 350 studies met the inclusion criteria. Only 21 studies were 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.

Reference(s)

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Malahias MA, Kostretzis L, Greenberg A, et al. Highly porous titanium acetabular components in primary and revision total hip arthroplasty: a systematic review. J Arthroplasty. 2020 Jun;35(6):1737-1749.

Moralidou M, Di Laura A, Henckel J, et al. Three-dimensional pre-operative planning of primary hip arthroplasty: a systematic literature review. EFORT Open Rev. 2020 Dec 4;5(12):845-855.

Tuncay V, van Ooijen PMA. 3D printing for heart valve disease: a systematic review. Eur Radiol Exp. 2019 Feb 15;3(1):9.

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

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

Clinical Evidence

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

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

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

Reference(s)

Femasys, Inc. website. Available at: http://www.femasys.com/. Accessed May 19, 2021.

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

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

Clinical Evidence

The National Comprehensive Cancer Network (NCCN) does not mention cryotherapy for the treatment of breast cancer in its clinical practice guidelines in oncology (NCCN, 2021).

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

Pusceddu et al. (2019) performed a systemic review of the available evidence on cryoablation in the treatment of solid tumors, including breast cancer. The authors stated that although this ablation method had the advantage of being a minimally invasive procedure, due to the small sample size of the available studies, reliable and definitive conclusions on the usefulness of cryoablation in patients with breast cancer could not be drawn. They further stated that other aspects of this technology, including technical issues, indications, efficacy, imaging follow-up, and possible advantages over other percutaneous ablative methods need to be clarified.

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

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

On August 2, 2019, The U.S. Food and Drug Administration (FDA) has cleared water vapor thermal therapy devices (e.g., the Rezūm™ Water Vapor Therapy system, (Boston Scientific Corp.) under 510(k) premarket notification for treatment of symptoms of benign prostatic hyperplasia (BPH), and treatment of the prostate with hyperplasia of the central zone and/or a median lobe. It is not approved for treatment of malignant prostate tissue. For additional information, see: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K191505 (Accessed April 16, 2021)

Reference(s)

Lowrance W, Breau R, Chou R, et al. Advanced prostate cancer: AUA/ASTRO/SUO guideline. 2020. Available at: https://www.auanet.org/guidelines/advanced-prostate-cancer. (Accessed January 7, 2021)

National Comprehensive Cancer Network (NCCN) (Clinical Practice Guidelines in Oncology. Prostate Cancer, v2 2021. February 17, 2021.

Sanda MG, Chen RC, Crispino T, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. 2017. Available at: https://www.astro.org/uploadedFiles/_MAIN_SITE/Patient_Care/Clinical_Practice_Statements/Content_Pieces/ClinicallyLocalizedProstateCancer.pdf. (Accessed April 16, 2021)

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

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

Clinical Evidence

The Tubes Under Local Anesthesia (Tula) System is intended to insert ear tubes (tympanostomy tubes) into the eardrum in young children and adults, using local anesthesia in a physician's office, to treat repeated ear infections (recurrent acute otitis media) or fluid in the ear (otitis media with effusion). The Tula® System consists of the Tula Iontophoresis System and the Tula Tube Delivery System. The Tula Iontophoresis System, which includes individually fitted disposable ear plugs and ear sets, delivers a local anesthetic solution, TYMBION™, to the eardrum resulting in numbness of the eardrum. The Tula Tube Delivery System is then used to place the ear tube in the eardrum. (FDA, Tula System – P190016).

In May 2020, Lustig et al. published the results of a prospective multi-center case series evaluating the safety, technical success, and tolerability of tympanostomy tube (TT) placement under local anesthesia in an office setting (OTTER study). A total of 337 children across 18 different sites, ages 6 months through 12 years of age, were included in the study. Lidocaine/epinephrine iontophoresis was the method used for anesthesia and tube placement was done using the Tula integrated, automated myringotomy and Tube Delivery System (TDS). Pain was rated by participants 5 to 12 years old using the Faces Pain Scale-Revised (FPS-R) tool, which is used to rate pain from 0 (no pain) to 10 (very much pain). Bilateral tubes were placed successfully in 85.8% of children less than 5 years of age and 89.2% of children 5 to12 years of age. For tube placement itself, mean FPS-R score was 3.30 (standard deviation [SD] = 3.39). 5-minute post-procedure mean FPS-R score was1.69 (SD=2.43). Authors note that an unexpected benefit of the in-office procedure was the avoidance of using additional medications that are often given in conjunction with general anesthesia during standard TT placement. 91.8% of implant tubes were still present at the 6 month follow up. Limitations include lack of comparison group, efficacy outcomes, or information about long-term tube retention as follow-up is ongoing. Additional high-quality evidence is needed to confirm the safety and efficacy of this technology.

In a 2020 Hayes Evidence Analysis Research Brief, quantity of existing peer-reviewed literature addressing in office, automated tympanostomy tube placement was assessed. Abstracts for 1 prospective comparative study and 2 prospective uncontrolled studies were located. Hayes concluded that there is an insufficient quantity of published peer-reviewed clinical data to evaluate this technology.

In 2019 The American Academy of Otolaryngology (AAC) published a Position Statement on in office TT tube placement. The statement notes that “although insertion of tympanostomy tubes in children is generally accomplished in the operating room under general anesthesia, insertion in the clinic in appropriately selected patients using shared decision making between clinicians and families can be appropriate.”

Cofer et al. (2017) noted that insertion of tympanostomy tubes is a common elective pediatric surgical procedure and is typically performed under general anesthesia in an operating room setting, and that a tympanostomy tube system has been developed to allow tympanostomy tube placement in a single pass on conscious patients under moderate sedation. A prospective study was conducted at 4 U.S. centers involving 128 children and 253 tympanostomy tube placements. The outcome of the study showed an 88.3 % success rate in performing the procedure under moderate sedation with adverse effects (AEs) within normal rates. The authors concluded that the feasibility of doing tympanostomy tube placement in an office setting using moderate sedation offered additional choices to physicians and parents. This study was limited by lack of a control group.

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

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

Reference(s)

AAO-HNS Position Statement. In-Office Placement of Tubes in Pediatric Patients While Awake. Available at: In-Office Placement of Tubes in Pediatric Patients While Awake - American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) (entnet.org) Accessed May 17, 2021.

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Cohen LL, Martin SR, Gamwell KL, et al. Behavioral techniques to optimize success of in-office pediatric tympanostomy tube placement without sedation. Int J Pediatr Otorhinolaryngol. 2015;79(12):2170-2173.

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U.S Food & Drug Administration (FDA). Recently Approved Devices Tula® System - P190016 | FDA. Accessed May 17, 2021.

Zeiders JW, Syms CA, Mitskavich MT, et al. Tympanostomy tube placement in awake, unrestrained pediatric patients: A prospective, multicenter study. Int J Pediatr Otorhinolaryngol. 2015;79(12):2416-2423.

Code	Description
0584T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; percutaneous
0585T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; laparoscopic
0586T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; open
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: Solid Organ Transplantation.

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

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

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

Clinical Evidence

Lablanche et al. (2018) conducted a multicenter, open label, randomized controlled trial to assess the efficacy and safety of islet transplantation compared with insulin therapy in patients with type 1 diabetes. Eligible patients had severe hypoglycemia or hypoglycemia unawareness, or kidney grafts with poor glycemic control. Fifty patients were randomly assigned to immediate

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

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

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

Hering et al. (2016) evaluated the effectiveness and safety of a standardized human pancreatic islet product in patients in whom impaired awareness of hypoglycemia (IAH) and severe hypoglycemic events (SHEs) persisted despite medical treatment. A multicenter, single-arm, phase 3 study of the investigational product purified human pancreatic islets (PHPI) was conducted at eight centers in North America. Forty-eight adults with type 1 diabetes (T1D) for >5 years, absent stimulated C-peptide, and documented IAH and SHEs despite expert care were enrolled. Each patient received immunosuppression and one or more transplants of PHPI. The primary end point was the achievement of HbA1c <7.0% at day 365 and freedom from SHEs from day 28 to day 365 after the first transplant. The primary end point was successfully met by 87.5% of subjects at 1 year, and by 71% at 2 years. The median HbA1c level was 5.6% at both 1 and 2 years. Hypoglycemia awareness was restored, with highly significant improvements in Clarke and HYPO scores. No study-related deaths or disabilities occurred. Five of the patients experienced bleeds requiring transfusions, and two had infections attributed to immunosuppression. Glomerular filtration rate

decreased significantly on immunosuppression, and donor-specific antibodies developed in two patients. The authors concluded that transplanted PHPI provided glycemic control, restoration of hypoglycemia awareness, and protection from SHEs in subjects with intractable IAH and SHEs. Safety events occurred related to the infusion procedure and immunosuppression, including bleeding and decreased renal function. They further state that islet transplantation should be considered for patients with T1D and IAH in whom other, less invasive current treatments have been ineffective in preventing SHEs. This is a single-arm study and further investigation is needed before clinical usefulness of this procedure is proven.

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

The American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2021) states that islet auto transplantation should be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes. Both patient and disease factors should be carefully considered when deciding the indications and timing of this surgery. Surgeries should be performed in skilled facilities that have demonstrated expertise in islet auto transplantation.

Reference(s)

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Morgan KA, Lancaster WP, Owczarski SM, et al. Patient selection for total pancreatectomy with islet auto transplantation in the surgical management of chronic pancreatitis. J Am Coll Surg. 2018 Apr;226(4):446-451.

Code	Description
0596T	Temporary female intraurethral valve-pump (i.e., voiding prosthesis); initial insertion, including urethral measurement
0597T	Temporary female intraurethral valve-pump (i.e., voiding prosthesis); replacement

The insertion of a temporary intraurethral valve-pump is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The inFlow Intraurethral Valve-Pump and Activator is a replaceable urinary prosthesis that is intended for use in females who have incomplete bladder emptying due to impaired detrusor contractility (IDC) of neurologic origin. The device must be replaced every 29 days (or less) and allows women with IDC to urinate, without the need to catheterize daily or be attached to a urine drainage bag. Early studies for the inFlow device show promising results, but further large randomized controlled studies are needed to confirm these findings.

In a multi-center single-arm crossover study, Chen et al. (2005) compared the safety, effectiveness and patient satisfaction of the In-Flow device against the current standard of care of a clean intermittent catheterization (CIC) for 77 females with hypo

contractile or acontractile bladder. The study started with 273 females, however a large withdrawal of participants occurred due to initial discomfort of the device and leakage. The authors found the InFlow™ device appeared to be a viable alternative to CIC.

Lynch et al. (2003) evaluated the benefits of the Inflow intraurethral device for managing acontractile bladders in women. Twenty females with acontractile bladders who had been unsuccessfully managed by other methods were recruited and asked to complete a quality-of-life (QoL) questionnaire which included 34 questions along with urine flowmetry assessments and urine culture. There was a decrease in the QoL score from a mean of 59.6 before insertion to means of 11.2, 8.8, 6.3 and 5.0 at 1, 3, 6 and 12 months afterward. Three patients had temporary asymptomatic bacteriuria and two experienced a single infection after the device was inserted that was treated with antibiotics. The authors concluded the Inflow device provides an effective method for bladder drainage, with few side-effects and a significant improvement in QoL. One limitation was the small sample size and authors indicated cost-effectiveness studies should be conducted in the future.

Madjar et al. (2000) performed a study to exam the long-term follow-up of women treated with the InFlow™ device for periods longer than 1 year. Data was collected for 92 patients on urodynamic diagnosis, complications, and satisfaction. Discontinuation of the device was recorded for 71 patients and only 21 patients were followed for more than one year. Complications for those patients followed included device migration into the bladder, asymptomatic bacteriuria, and symptomatic UTIs. All patients were satisfied with the device and preferred it to previous treatment modalities. The authors concluded the In-Flow™ intraurethral insert can serve as a long-term treatment for the management of women with voiding difficulties, however further studies are needed comparing this treatment with other modalities.

The U.S. Food and Drug Administration (FDA) approved the InFlow™ device in October of 2014 as a de novo device which is a low- to moderate-risk device that is ineligible for 510(k) review because it is not substantially equivalent to a predicate device. The evidentiary threshold for a de novo device is lower than the threshold required for a PMA. Refer to the following website for additional information:

- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN130044
- https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN130044.pdf

(Accessed April 26, 2021)

Reference(s)

Chen TY, Ponsot Y, Carmel M, Bouffard N, Kennelly MJ, Tu LM. Multi-center study of intraurethral valve-pump catheter in women with a hypocontractile or acontractile bladder. Eur Urol. 2005;48(4):628–633.

Lynch WJ, Testa GA, Bell DF. The subjective and objective benefits of a remote-controlled intraurethral device for managing the female acontractile bladder. BJU Int. 2003;92(9):960–963.

Madjar S, Halachmi S, Wald M, et al. Long-term follow-up of the in-flowtrade mark intraurethral insert for the treatment of women with voiding dysfunction. Eur Urol. 2000;38(2):161–166.

Code	Description
0598T	Noncontact real-time fluorescence wound imaging, for bacterial presence, location, and load, per session; first anatomic site (e.g., lower extremity)
0599T	Noncontact real-time fluorescence wound imaging, for bacterial presence, location, and load, per session; each additional anatomic site (e.g., upper extremity) (List separately in addition to code for primary procedure)

Noncontact real-time fluorescence wound imaging for bacterial presence is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

MolecuLight i:X® is a handheld fluorescence imaging device for real-time detection of bacteria in wounds; the violet light illumination captures and documents the presence of bacteria in the wound and surrounding areas. The device provides clinicians with information about the fluorescent characteristics of a wound to assist them in making improved diagnostic and treatment decisions. Despite FDA approval, additional robust clinical studies need to be completed to determine the safety and efficacy of this device. While some evidence exists for the predictive characteristics of the method compared to conventional wound cultures, the clinical significance of the method in improving care and patients' outcomes is unclear.

A clinical evidence assessment by ECRI suggests the evidence for the use of the MolecuLight i:X Fluorescence Imaging System is inconclusive. While the evidence might suggest the MolecuLight i:X Fluorescence Imaging System may be helpful for identification of wounds with bacterial loads, additional RCTs are needed to confirm the safety and efficacy of the device (ECRI 2021).

Le et al. (2020, included in ECRI report above), conducted a prospective multicenter observational study on the use of MolecuLight i:X for 350 participants. Wounds underwent clinical signs and symptoms (CSS) assessment using the International Wound Infection Institute (IWII) checklist immediately followed by fluorescent imaging with the MolecuLight device. CSS assessment missed approximately 85% of bacterial loads that were greater than 10^4 CFU/g which can be indicative of infection. The authors found the use of the MolecuLight device resulted in higher sensitivity and accuracy of the detection of the bacteria. Limitations of the study included underreporting of bacteria diversity with the culture analysis, limited experience by clinicians in using the MolecuLight device and funding of the study by MolecuLight, Inc. The authors recommend the MolecuLight device be used in combination with CSS assessment and that evidence from larger longitudinal studies would be beneficial.

Farhan and Jeffery (2020) conducted a single-center observational study to assess the MolecuLight i:X device for efficacy in pediatric burn wounds and the overall feasibility of the device. Ten patients were recruited, and the device was utilized on sixteen different wounds to assess for the presence or absence of clinical signs and symptoms of infection; swabs were obtained to confirm the findings. The authors found the device demonstrated ability to visually identify significant bacterial growth and high compliance for use of the device. These findings may pave the way for including bacterial fluorescence imaging use into the pediatric burn population.

A pilot study performed by Pijpe et al. (2019) compared the detection of bacteria in burn wounds between an bacterial fluorescence imaging device MolecuLight i:X and standard microbiological swabs. A total of 14 patients with 20 wounds participated in the study. Wounds were swabbed three times: once with a standard swam, once with a high-fluorescent area swab, and a finally with a non-fluorescent (nF) area swab. Proportion agreement of the microbiological results was calculated and the accuracy of the device to detect relevant bacteria was assessed. The diagnostic accuracy of the bacterial fluorescence imaging device to detect relevant bacteria in burn wounds was moderate and the reliability was equal to standard swabbing. Further research in larger sample sizes is needed for safety and efficacy of the fluorescence imaging device.

Raizman et al. (2019) conducted a study aimed to assess the accuracy, clinical incorporation and documentation capabilities of a handheld bacterial fluorescence imaging device (MolecuLight *i:*X). In a clinical trial, trained clinicians digitally measured and captured fluorescence images to assess for presence moderate to heavy loads of bacteria in 50 wounds. The results showed wound measurement was accurate 95%. A positive signal for bacterial fluorescence was demonstrated 72%. Sampling of wounds was found to under-report bacterial loads relative to fluorescence-guided curettage samples.

In a pilot study, Serena et al. (2019) evaluated 19 wounds for diagnostic accuracy of wound bacteria when bacterial fluorescence imaging (MolecuLight i:X) was used in combination with clinical evaluation of signs and symptoms (CSS). CCS criteria for wounds to determine the presence or absence of moderate-to-heavy bacterial loads was done using the NERDS (non-healing, exudate, red and bleeding surface or granulation tissue, debris and smell) and STONEES (size, temperature, osteomyelitis, new areas, exudate, erythema, and smell) method. Then fluorescence images of the wound were acquired along with determination of bacterial presence or absence. Biopsies were obtained under local anesthetic and sent to lab for confirmation; all lab staff was blinded to the wound's assessment outcomes. 4 out the 19 patients (21%) were identified as positive (for moderate-to-heavy bacterial loads) based on clinical signs and symptoms alone. The use of fluorescence imaging in combination with CSS assessment led to 2.5–3.2-fold improvements in reported diagnostic accuracy measures as compared with CSS assessment alone. The authors concluded the data in this pilot study suggests that current standard of care assessment for wounds fails to identify many wounds with moderate-to-heavy bacterial loads, leaving patients with undetected and untreated bacteria. The addition of bacterial fluorescence imaging improved sensitivity and accuracy of assessments for detecting moderate-to-heavy bacterial loads. Limitations of this study included small sample size thus not statistically significant and lack of follow-up. Future larger sample studies are needed.

In a prospective observational study, Hurley et al. (2019) swabbed 43 wounds from 33 patients. The authors wanted to establish the accuracy of the wound imaging device at detecting bacteria. All data was collected in the outpatient wound care clinic setting. Patients over 18 were recruited with a variety of wounds; participants on antibiotics for wound infection were excluded. Images from the wounds were captured with the handheld fluorescent device; upon visualization of bacteria, areas of red or cyan fluorescence indicating bacteria were swabbed and sent to the lab for culture and sensitivity testing. Of the swabs taken,

95.4% were positive for bacteria growth and nine different species of bacteria were identified. Limitations included device incompatibility for wounds with active bleeding, dressings that contained silver (a potent antimicrobial) and sample size. Despite these limitations, the authors concluded the device as safe, effective and accurate for use. Further research should be directed to its application in other environments such as preoperative and perioperative settings.

Twenty patients with burn wounds were photographed under both a standard light and violet light illumination to compare presentations of obvious infection signs and symptoms. Microbiology swab samples were obtained; the fluorescence images were used to guide swabs to where the bacteria were collecting. Four patients did not have bacterial contamination based on their images and swab results, sixteen patients showed growth of Staphylococcus aureus, Pseudomonas aeruginosa, or other bacteria and nine of the patients, by definition, had infections. Blumenthal and Jeffery (2018) found the pilot study to show the efficacy of the MolecuLight i:X is evident due to the microbiology results correlating to the images. With these early results and guidance of swab samples, the MolecuLight i:X may be able to detect bacterial load before an infection and subsequent graft failure, thereby shortening lengths of hospital stay and improving overall healing. Further research is needed to test the device in terms of being an early intervention tool.

Rennie et al. (2017, included in the ECRI report above) conducted a clinical trial where 60 lower chronic limb wounds were imaged for bacterial fluorescence using the MolecuLight i:X imaging device. Point-of-care bacterial fluorescence imaging illuminates a wound with 405nm light, triggering bacteria to produce red fluorescence and enabling real-time bacterial concentration. Regions positive for red fluorescence were sampled by either biopsy or curettage for bacterial presence and analysis. The authors found fluorescence imaging of wounds offers clinicians' real-time information on the wound's bacteria which can potentially influence treatment decisions.

The U.S. Food and Drug Administration (FDA) cleared The MolecuLight i:X® device 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/pdf19/K191371.pdf. (Accessed April 12, 2021)

For information on current clinical trials studying the use of MolecuLight i:X and bacterial growth, go to www.clinicaltrials.gov. (Accessed April 12, 2021)

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Serena TE, Harrell K, Serena L, et al. Real-time bacterial fluorescence imaging accurately identifies wounds with moderate-to-heavy bacterial burden. J Wound Care. 2019;28(6):346–357.

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

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

Hyperspectral imaging is a noninvasive assessment that provides color coded maps of oxygenated tissue, allowing qualitative and quantitative measurements with high spectral resolution (Sen, 2018).

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

Several techniques have been recently introduced that may enable tissue perfusion measurements in the lower extremity. Studies with non-invasive techniques include hyperspectral imaging (HSI), laser Doppler perfusion imaging (LDPI), laser speckle contrast imaging (LSCI), near-infrared (NIR) spectroscopy (NIRS), spectrophotometry, transcutaneous oxygen measurements (TcPO2) and vascular optical tomography imaging (VOTI). Ma et al. (2019) conducted a systematic review which provided an overview of these current diagnostic techniques to determine tissue perfusion in patients with PAD and healthy controls. Twenty studies describing 10 different techniques were found. The authors identified two publications related to HIS, both of which described in detail below. The authors found while using contact-free methods, such as hyperspectral imaging (HIS), laser speckle contrast imaging (LSCI), or MRI, may be preferable, especially when patients have foot ulcers, newer diagnostic techniques, such as HIS and LSCI require additional larger prospective cohort trials to fully assess the effectiveness.

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

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

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

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

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

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

The US Food and Drug Administration (FDA) approved the PUMA-G system for gastrostomy insertions under 510(k) (K183057) on April 10, 2019. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm (Accessed April 1, 2021).

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

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

Clinical Evidence

Geropoulos et al. (2021) performed a systematic review and meta-analysis looking at magnetically controlled capsule endoscopy (MCCE) versus conventional gastroscopy. The aim of this study is to systematically review the performance of

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

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

Rauya, et al. (2019) in a narrative yet systematic review methodology evaluated the efficacy and safety of magnetic guided capsule gastroscopy in gastric diseases. Conventional standard gastroscopy is the screening method of choice. Other screening methods have evolved with limited effectiveness. Magnetic guided capsule gastroscopy is a non-invasive screening tool which allows complete visualization of the gastric wall. It offers two rotational and three translational kinds of motion which can get closer to the mucosa for a clearer view. In this narrative review, the focus was on the recent advances in MGCG including technical issues, ideal gastric preparation, indications and contraindications, available evidences regarding the use of magnetic guided capsule gastroscopy in clinical practice and highlighted further technical advancements which are needed to make MGCG as a potential diagnostic tool. MGCG faces challenges of shortage of air sufflation, suction, obtaining tissue samples, provision of drugs on the site of pathology and ability to treat therapeutically. After review, it was noted that the magnetic guided capsule gastroscopy is a safe tool and would be a promising alternative examination equipment for gastric diseases. Large randomized controlled trials are needed which would focus on procedure preparation, focus on disease specifics and the safety of MGCG on patients with metal body parts and/or implanted devices.

In a comparative study, Liao et al (2016) compared the performance of MCE with conventional gastroscopy in detecting gastric lesions. The author notes, it is impossible to visualize the entire stomach with the passive capsule currently used in practice because of the large size of the gastric cavity. A magnetically controlled capsule endoscopy (MCE) system has been designed to explore the stomach. A multicenter blinded study comparing MCE with conventional gastroscopy in 350 patients (mean age, 46.6 y), with upper abdominal complaints scheduled to undergo gastroscopy at a tertiary center in China from August 2014 through December 2014. All patients underwent MCE, followed by conventional gastroscopy 2 hours later, without sedation. The sensitivity, specificity, positive predictive value, and negative predictive value of detection of gastric focal lesions by MCE was calculated, using gastroscopy as the standard. MCE detected gastric focal lesions in the whole stomach with 90.4% sensitivity (95% confidence interval [CI], 84.7%-96.1%), 94.7% specificity (95% CI, 91.9%-97.5%), a positive predictive value of 87.9% (95% CI, 81.7%-94.0%), a negative predictive value of 95.9% (95% CI, 93.4%-98.4%), and 93.4% accuracy (95% CI, 90.83%-96.02%). MCE detected focal lesions in the upper stomach (cardia, fundus, and body) with 90.2% sensitivity (95% CI, 82.0%-98.4%) and 96.7% specificity (95% CI, 94.4%-98.9%). MCE detected focal lesions in the lower stomach (angulus, antrum,

and pylorus) with 90.6% sensitivity (95% CI, 82.7%-98.4%) and 97.9% specificity (95% CI, 96.1%-99.7%). MCE detected 1 advanced gastric carcinoma, 2 malignant lymphomas, and 1 early-stage gastric tumor. MCE did not miss any lesions of significance (including tumors or large ulcers). Among the 350 patients, 5 reported 9 adverse events (1.4%) and 335 preferred MCE over gastroscopy (95.7%). There are study limitations including, the MCE preparation is slightly longer than conventional gastroscopy and it takes longer to perform an MCE (approx. 30 minutes). Lastly, the preference of MCE over gastroscopy observed in this study might be biased because the gastroscopy was performed without sedation. The author notes that this novel MCE has a high diagnostic accuracy and is a promising alternative for patient-friendly screening for gastric diseases. Larger studies are needed to confirm the efficacy of this novel technique.

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

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

Clinical Evidence

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

On June 28, 2017, the Nevisense™ (SciBase III, Stockholm, Sweden) device received FDA clearance through the premarket approval process. This device is indicated for use on cutaneous lesions with one or more clinical or historical characteristics of melanoma, when a dermatologist chooses to obtain additional information when considering biopsy. Refer to the following for complete information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150046 (Accessed May 13, 2021).

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

which is histopathology. Instead, it can be used to support early clinical diagnosis. Additional prospective trials with larger numbers of tumors are required to test the sensitivity and specificity of this method.

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

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

For information on current clinical trials on the use of the Nevisense device, go to https://www.clinicaltrials.gov/ (Accessed May 14, 2021).

American Academy of Dermatology (AAD)

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

National Comprehensive Cancer Network (NCCN)

In the 2021 practice guideline for cutaneous melanoma, the NCCN states that patients presenting with a suspicious pigmented lesion should undergo an excisional biopsy (elliptical, punch or saucerization). If excisional biopsy is inappropriate due to the location or the lesion is very large, a full thickness incisional or punch biopsy of the thickest portion is an acceptable option. In the common follow up recommendations for all patients, this guideline states that the available, noninvasive pre- diagnostic imaging technologies (including electrical impedance spectroscopy) have not been prospectively compared for diagnostic accuracy, and may enhance early detection of new primary melanoma in patients with a high mole count and/or the presence of clinically atypical nevi.

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Code	Description
0664T	Donor hysterectomy (including cold preservation); open, from cadaver donor
0665T	Donor hysterectomy (including cold preservation); open, from living donor
0666T	Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor
0667T	Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor
0668T	Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary
0669T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each
0670T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each

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

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

Fronek and colleagues (2021) reported results on ten patients receiving uterus transplantation (UTx) which is a rapidly evolving solution for women with uterine infertility and a growing field of study. The study compared the efficacy of UTx from five

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

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

In a 2018 committee opinion, the American Society for Reproductive Medicine (ASRM) states uterus transplantation is an experimental procedure for the treatment of AUFI.

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

Clinical trials for uterus transplantation are currently ongoing. See the following website for more information: https://clinicaltrials.gov/ct2/home.

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Code	Description
0672T	Endovaginal cryogen-cooled, monopolar radiofrequency remodeling of the tissues surrounding the female bladder neck and proximal urethra for urinary incontinence
53860	Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence
53899	Unlisted procedure, urinary system
58999	Unlisted procedure, female genital system (nonobstetrical)

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

Clinical Evidence

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

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

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

In the VIveve Treatment of the Vaginal Introitus to Evaluate Effectiveness (VIVEVE I) randomized controlled trial (RCT), Krychman et al. (2017) evaluated the safety and efficacy of surface-cooled, monopolar radiofrequency therapy for the treatment of vaginal laxity. The prospective, single-blinded, sham-controlled study involved 186 women treated in nine study centers in Canada, Italy, Spain and Japan. The active treatment group included 108 women who completed the study while the sham group included 56 women who completed the study. No vaginal laxity was achieved by 43.5% of the treated group and 19.6% of the control group and the treated group also showed greater improvement in sexual function. The authors concluded that a single treatment of CMRF was found to be safe and was associated with improved vaginal laxity and improved sexual function. Limitations of the study noted by the authors include the small sample size, the short (6 month) follow up period, the lack of a control for multiplicity of secondary end points and that the number of participants was not consistent with two of the sites contributing the majority of the subjects.

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

takes up to 90 days to fully complete and that further controlled study is needed to confirm the data. Limitations of the study include the small sample size, the short follow-up period and the lack of a control group.

The U.S. Food and Drug Administration (FDA) approved the Viveve® System under its 510(k) premarket notification process as substantially equivalent to predicate devices for use in general surgical procedures for electrocoagulation and hemostasis. See the following website for more information (use product code GEI): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm (Accessed August 25, 2021).

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

Reference(s)

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Code	Description
0692T	Therapeutic ultrafiltration
37799	Unlisted procedure, vascular surgery (when used to report aquapheresis (ultrafiltration))
90999	Unlisted dialysis procedure, inpatient or outpatient (when used to report aquapheresis (ultrafiltration))

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

Clinical Evidence

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

In 2016, Constanzo et al. conducted the Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial. The authors tested the theory that heart failure patients treated with UF would have a longer period of time to their first heart failure event within 90 days of discharge than those who had received adjustable intravenous loop diuretics (ALD). Secondary outcomes were classified as efficacy, clinical, and safety variables. Out of 224 patients, 110 were randomized into a group receiving UF and 114 into a group receiving ALD; three patients withdrew before the study started. The Aquadex FlexFlow System was utilized for the UF group and received UF at an average rate of 138 ± 47 ml/h for an average of 80 ± 53 hours. The ADL group of participants received an average dose of furosemide-equivalent intravenous loop diuretic of 271.26 ± 263.06 mg for an average of 100 ± 78 hours. After 90 days, out of 221 patients, 165 completed the study, 31 died, 9 were lost to follow-up, 3 withdrew consent, 7 were removed due to medical reasons identified by their physician and 6 did not finish due to other causes. Analysis of the data showed the UF group tended to have a longer first time to a heart failure event but experienced a larger number of adverse events. The results should be interpreted with caution as the study was prematurely terminated by the sponsor before its completion against the opinion of the study's Steering Committee. Furthermore, serious adverse events deemed to be related to study therapy occurred in a higher number of patients in the aquapheresis than in the diuretic group (16 [14.6%] vs. 6 [5.4%]; p = 0.026), raising concerns about the safety of this therapeutic approach.

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

In the UNLOAD trial, Constanzo et al. (2010) analyzes UF against standard intravenous (IV) diuretics in hospitalized patients with volume overloaded heart failure (HF). Two hundred participants with heart failure were randomized into two groups; one group received IV diuretics and the other UF (Aquadex System 100). Furthermore, the diuretic group was split into two: one group received continuous IV diuretics and the other IV bolus diuretics. Primary outcomes were weight loss and dyspnea assessment forty-eight hours after randomization. Secondary endpoints included fluid loss at 48 hours, functional capacity, rehospitalizations, and unscheduled visits in 90 days. The authors found that more patients treated with UF had successful results, as indicated by fewer rehospitalizations and unscheduled office or ED visits. Another key finding was that hypokalemia occurred less frequently in the UF group versus those treated with continuous IV diuretic infusion. Limitations included number of participants, lack of blinding thus introducing bias along with inadequacy of dosing of the diuretics for patients. The authors concluded that even though UF was associated with less rehospitalizations, additional randomized studies are needed. https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192756.pdf

Clinical trials of aquapheresis and ultrafiltration are currently ongoing. See the following website for more information: https://clinicaltrials.gov/ct2/home

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

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

A recent ECRI report states that Aquadex SmartFlow™ (previously FlexFlow) is a blood ultrafiltration system to provide life support by replacing renal function in patients with critical kidney failure or fluid overload (ECRI 2021). The findings are however inconclusive due to too few data on outcomes and comparisons in addition to high risk of bias due to lack of controls.

On February 24, 2020, the FDA granted premarket approval for the Aquadex FlexFlow® System (K192756) for continuous ultrafiltration therapy for temporary or extended use in adult and pediatric patients weighing 20 kilograms or more whose fluid overload is unresponsive to medical management, including diuretics. Additional information is available at:

Reference(s)

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Code	Description
0693T	Comprehensive full body computer-based markerless 3D kinematic and kinetic motion analysis and report

Comprehensive full body computer-based markerless 3D kinematic and kinetic motion analysis is unproven and not medically necessary for all indications due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

There is limited published evidence regarding the efficacy of full body computer-based markerless 3D kinematic and kinetic motion analysis. The evidence does not demonstrate that patient management decisions based on computer-based marker less 3D kinematic and kinetic motion analysis positively impact patient care or outcomes.

In March 2019, the FDA granted 510(k) clearance to the DARI Health system (Scientific Analytics, Inc.). DARI Health is a markerless, three-dimensional human motion capture and analytical software system that uses off-the-shelf video cameras, off-the-shelf computer hardware, off-the-shelf motion analysis software, and proprietary DARI Health Software (consisting of DARI Connect, DARI Capture plug-in, DARI Insight Engine) to collect, quantify, and document full-body human kinematic and kinetics during patient movement. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf18/K180880.pdf (Accessed September 8, 2021).

Hurley et al. (2021) compared leg length measurements (LLM) and varus/valgus knee measurements (VVM) performed clinically, radiologically and using markerless motion analysis (MMA) in patients being assessed for potential total knee replacement (TKR). Twenty-three patients awaiting unilateral primary TKR were included in the study. According to the authors, the most important finding of this study was that significant differences were reported between results obtained for calculating LLM and VVM clinically, radiologically and using MMA. As much of the literature has previously validated the use of clinical and radiological in obtaining LLM, this study poses the question as to whether the results obtained using MMA for LLM and VVM can be utilized.

van Kersbergen et al. (2021) investigated whether a consumer depth camera can capture changes in gait features of Parkinson's patients. The dataset consisted of 19 patients (tested in both a practically defined OFF phase and ON phase) and 8 controls, who performed the "Timed-Up-and-Go" test multiple times while being recorded with the Microsoft Kinect V2 sensor which records Red-Green-Blue (RGB)-depth data and tracks 25 anatomical landmarks in 3D space without the need for body-attached sensors or markers. Camera-derived features were step length, average walking speed and mediolateral sway. Motor signs were assessed clinically using the Movement Disorder Society Unified Parkinson's Disease Rating Scale. The authors were able to detect group differences in gait features between people with PD and healthy controls using the Kinect depth camera. However, the current task setup and analysis approach lacks sensitivity to detect small intra-individual changes in symptom severity. According to the authors, limitations of this study include the small sample size, subjects with relatively mild symptoms and a not complete age match with the control population. The standard outcome for the TUG (task duration) could not be analyzed because of missing frames at the beginning of the recording.

In a clinical case study, Schroeder et al. (2020) evaluated whether a markerless system for three-dimensional motion capture from Red-Green-Blue (RGB) depth sequences using a whole-body infant model can serve as the basis for automated General Movement Assessment (GMA). The 29 high risk infants that were included in the study were assessed at their clinical follow-up at 2-4 month corrected age (CA). Their neurodevelopmental outcome was assessed regularly up to 12-31 months CA. GMA was used as the study outcome measure. The GMA was completed by one of the study authors and by a masked GMA-expert of conventional and computed 3D body model ("SMIL motion") videos of the same general movements (GMs). Agreement between both GMAs was tested using dichotomous and graded scaling with Kappa and intraclass correlations, respectively. Sensitivity and specificity to predict cerebral palsy (CP) at ≥12 months CA were assessed. Agreement of the two GMA ratings was moderate-good for general movement (GM)-complexity (κ = 0.58; ICC = 0.874 [95%CI 0.730; 0.941]) and substantial-good for fidgety movements (FMs) (Kappa = 0.78, ICC = 0.926 [95%CI 0.843; 0.965]). Five children were diagnosed with CP (four bilateral, one unilateral CP). The GMs of the child with unilateral CP were twice rated as mildly abnormal with FMs. GM-complexity and somewhat less FMs, of both conventional and SMIL motion videos predicted bilateral CP comparably to

published literature. The authors concluded that this study demonstrates that the amount of motion details captured by the SMIL motion video (based on a Kinect recording and the KineMAT tool) enables accurate GMA at fidgety age. According to the authors, this implies that the Skinned Multi-Infant Linear Model (SMIL) motion video adequately catches the movement characteristics needed for GMA of infants with movements ranging from a normal to a definitely abnormal quality, turning it into an attractive tool for automatic GMA. The authors indicated that study limitations included a small sample size, the inclusion of high-risk infants only, and short follow-up. There is no evidence from this study that the markerless motion capture system will impact patient management.

Pantzar et al. (2018) evaluated a 2-dimensional markerless (2D ML) assessment of knee joint flexion/extension angles of the gait cycle in children and young adults with cerebral palsy (CP). Eighteen individuals, mean age 15 years (6.5-28), participated in the study. A total of 11 had bilateral, 3 unilateral, 3 dyskinetic, and 1 ataxic CP. In the Gross Motor Function Classification System, 6 were at level I, 11 at level II, and 1 at level III. The authors compared 2D ML, using a single video camera with computer processing, and 3D gait analysis (GA). The 2D ML method overestimated the knee flexion/extension angle values by 3.3 to 7.0 degrees compared with 3D GA. The reliability within 2D ML and 3-dimensional gait analysis (3D GA) was mostly good to excellent. The investigators concluded that despite overestimating, 2D ML is a reliable and convenient tool to assess knee angles and, more importantly, to detect changes over time within a follow-up program in ambulatory children with CP. This study does not demonstrate that 2D ML alters clinical management or improves clinical outcomes.

In a systematic review, Puh et al. (2019) evaluated the validity and reliability of using the Kinect camera (a markerless motion capture system) as an assessment tool for transitional movement and balance. A total of 21 research articles, published from 2012 to 2018, were included in the analysis and qualitative synthesis. Many of the included studies reported validity and did not report reliability, which limited the application to practice. According to the authors, the translation into practice for Kinect is also limited by lack of redundancy among studies and access to the software to implement the tests.

Knippenberg et al. (2017) conducted a systematic review to investigate 1) which markerless motion capture systems (MCS) are used as training devices in neurological rehabilitation, 2) how they are applied, 3) in which target population, 4) what the content of the training and 5) efficacy of training with MCS. A computerized systematic literature review was conducted in four databases (PubMed, Cinahl, Cochrane Database and IEEE). The Van Tulder's Quality assessment was used to score the methodological quality of the selected studies. The descriptive analysis is reported by MCS, target population, training parameters and training efficacy. Eighteen studies were selected (mean Van Tulder score = 8.06 ± 3.67). Based on methodological quality, six studies were selected for analysis of training efficacy. The most commonly used MCS was Microsoft Kinect, training was mostly conducted in upper limb stroke rehabilitation. Training programs varied in intensity, frequency, and content. None of the studies reported an individualized training program based on client-centered approach. The investigators concluded that markerless motion capture systems have the potential in neurological rehabilitation to increase the motivation during training and may assist improvement on one or more International Classification of Functioning, Disability and Health (ICF) levels. Future technological developments should take up the challenge to combine markerless MCS with the principles of a client-centered task-oriented approach and prove efficacy using randomized controlled trials (RCTs) with long-term follow-up. According to the investigators, because there are few RCTs and controlled clinical trials and few studies with long-term follow-up, it is difficult to prove efficacy of markerless MCS based on the studies included in this review.

Springer and Seligmann (2016) evaluated the literature describing the concurrent validity of using the Kinect as a gait analysis instrument. The Kinect consists of an array of sensors, including a camera and a depth sensor, enabling the Kinect to track and record 3-D human motion without using controllers or markers. An online search of PubMed, CINAHL, and ProQuest databases was performed. Included were studies in which walking was assessed with the Kinect and another gold standard device and consisted of at least one numerical finding of spatiotemporal or kinematic measures. The search identified 366 papers, from which 12 relevant studies were retrieved. The results demonstrate that the Kinect is valid only for some spatiotemporal gait parameters. Although the kinematic parameters measured by the Kinect followed the trend of the joint trajectories, they showed poor validity and large errors. The authors concluded that Kinect may have the potential to be used as a tool for measuring spatiotemporal aspects of gait, yet standardized methods should be established, and future examinations with both healthy subjects and clinical participants are required in order to integrate the Kinect as a clinical gait analysis tool.

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

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

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

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

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

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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).

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, 2021).

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).

TARGIT-A

Vaidya et al. (2010) conducted the TARGIT-A trial, a multicenter, phase III, randomized trial of breast cancer patients undergoing breast conserving surgery to determine whether a single dose of targeted intraoperative radiotherapy (IORT) would be non-inferior to a conventional course of post-operative external beam radiotherapy (EBRT). Eligible patients were 45 years or older with invasive ductal carcinoma up to 3.5 cm in diameter and suitable for breast conserving surgery. Patients were randomly assigned in a 1:1 ratio to receive IORT or whole breast external beam radiotherapy. Trial participants were divided into three strata based on timing of delivery of IORT: pre - pathology entry (patients who were randomized before the definitive surgical removal of the tumor), post pathology entry/IORT as a second procedure (patients who were randomized for entry to the trial after the pathological characteristics of the tumor had been reported) and contralateral breast cancer (patients who were suitable for participation and had a history of previous contralateral breast cancer). The Intrabeam, an IORT device, delivers low energy x-rays to tissues that are at high risk of local recurrence. Patients received a typical dose of 20 Gy to the surface of the tumor bed that would attenuate to 5–7 Gy at 1 cm depth. The comparator, EBRT, was given with a typical dose of 40- to 56 Gy, with or without a boost of 10- to 16 Gy to the tumor bed. This study's risk-adapted protocol recommended that if patients who had received IORT were found to have high risk factors postoperatively, they would also receive EBRT, and the IORT would serve as the tumor bed boost. The investigators published early results with a median follow-up period of approximately 2 years however, given that the cumulative incidence of in-breast recurrence rises slowly over time (e.g., 10 years, Colleoni 2016) the investigators continued the study and published an updated report.

In Vaidya et al. (2014) the primary endpoint was local recurrence in the conserved breast, and an absolute difference of 2.5% was the prespecified non-inferiority margin. Secondary endpoints included complications and mortality. A total of 3,451 patients were enrolled with a median follow-up of 2 years and 5 months (interquartile range, 12–52 months). Of those, 1,721 were randomized to the IORT group and 1,730 to the EBRT group. Sixty-seven percent (n=2,298) were randomized before lumpectomy (pre - pathology group) and 33% (n=1,153) were randomized after lumpectomy (post - pathology group). Among

those who received the allocated treatment, the IORT group comprised a total of 1,571 patients (1,332 received IORT and 239 received IORT and EBRT) and 1,590 received EBRT. The 5-year risk for local recurrence in the conserved breast was higher in the IORT group compared with the EBRT group (3.3% versus. 1.3%; p=0.042). Due to high risk factors identified during surgery or seen on post - pathology, 21% of patients who receive IORT in the pre - pathology arm also received 50 Gy of EBRT. The pre - pathology group (n=2,298) achieved the trial's noninferiority margin of 2.5% while the post - pathology group (n=1,153) did not. Grade 3 or 4 radiotherapy-related skin complications were lower in the IORT group than the EBRT group (0.2% versus 0.8%, p=0.029). There was no difference in breast cancer mortality or overall mortality between the groups however, there were fewer non-breast-cancer deaths with IORT compared with EBRT (1.4% 95% CI 0.8–2.5 versus. 3.5% 95% CI 2.3–5.2; p=0.0086). The authors concluded that concurrent IORT and lumpectomy, within a risk-adapted approach, should be considered for select breast cancer patients as outlined in the TARGIT-A trial protocol. However, there are study limitations, including lack of blinding, and these results should be interpreted with caution. For example, the pre-specified non-inferiority margin was an absolute difference of 2.5% however, this was based on an estimated 5-year locoregional reoccurrence rate of 6% and since that trial (Clark, 1992) rates have improved and it may no longer be as applicable, the short median follow-up period of only 2.4 years, 21.6% of patients who received IORT in the pre - pathology group also receive 50 Gy of EBRT, and the pre - pathology group met the trial's noninferiority threshold of 2.5% however, the post - pathology group did not. Additional results with complete 5-year follow-up of the TARGIT-A trial confirmed the conflicting findings on recurrence and mortality (Vaidya et al. 2016). Confirmatory randomized trials with carefully selected patients and longer follow-up are still needed to demonstrate the equivalence of IORT and EBRT in light of these conflicting findings.

Vaidya et al. (2020) reported long-term results of the TARGIT-A study (median 8.6 years, maximum 18.90 years) and found no statistically significant difference for local recurrence-free survival, distant disease-free survival, overall survival, and breast cancer mortality. Extended study follow-up will include further investigation into the nature of local recurrences.

ELIOT

Veronesi et al. (2013) conducted ELIOT, a single-institution randomized trial among women with early breast cancer to determine whether intraoperative radiotherapy (IORT) was non-interior to postoperative external radiotherapy (EBRT) in local recurrence and overall survival (OS). Eligible patients were women aged 48–75 years with early breast cancer with a maximum tumor diameter up to 2.5 cm and suitable for breast-conserving therapy. 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 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. Equivalence was prespecified and defined as a 5-year local recurrence rate that did not exceed 7.5% in the IORT group. The primary endpoint was occurrence of ipsilateral breast tumor recurrence (IBTR); overall survival was a secondary outcome. A total of 1,305 patients were randomized, with 654 patients in the EBRT group and 651 in IORT group and a median follow-up of 5.8 years. The 5-year IBTR rate was higher in the IORT group compared with the EBRT group (4.4% versus. 0.4%; p<0.0001). OS did not differ between the groups. Based on the increased harm with IORT, the authors concluded that improved selection of patients may reduce the rate of recurrence with IORT with electrons and that the advantage of not having to undergo radiation therapy over many weeks must be weighed against the possibility of an increased risk of local recurrence. Additional randomized trials are still needed to further clarify the subgroup of breast cancer patients who may benefit from IORT.

Orecchia et al. (2021) examined the planned long-term recurrence and survival outcomes from the ELIOT trial. In the ELIOT group, the 10-year rate was 8.1% (6.1–10.3), and the 15-year rate was 12.6% (9.8–15.9). In the WBI group, the 10-year rate was 1.1% (0.5–2.2), and the 15-year rate was 2.4% (1.4–4.0). At final follow-up on March 11, 2019, 193 (15%) women had died from any cause, with no difference between the two groups (98 deaths in the ELIOT group versus 95 in the WBI group; HR 1.03, 95% CI 0.77–1.36, p=0.85). In the ELIOT group, the overall survival rate was 96.8% (95% CI 95.1–97.9) at 5 years, 90.7% (88.2–92.7) at 10 years, and 83.4% (79.7–86.4) at 15 years; and in the WBI group, the overall survival rate was 96.8% (95.1–97.9) at 5 years, 92.7% (90.4–94.4) at 10 years, and 82.4% (78.5–85.6) at 15 years. The authors confirmed there was a higher rate of IBTR in the ELIOT group compared to the WBI group, without any differences in overall survival. Limitations include absence of long-term toxicity data, especially cardiac toxicity and difficultly gathering long-term outcome data.

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Code	Description
23929	Unlisted procedure, shoulder [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]
64624	Destruction by neurolytic agent, genicular nerve branches including imaging guidance, when performed
64999	Unlisted procedure, nervous system [when used to report cooled radiofrequency ablation]

Due to insufficient evidence of safety and/or efficacy, radiofrequency ablation (RFA), using any RFA method, is unproven and not medically necessary for the treatment of joint pain, including but not limited to hip, knee or shoulder pain.

This policy does not apply to RFA treatment of facet joint or sacroiliac pain. For information on RFA for spinal indications, see Ablative Treatment for Spinal Pain.

Clinical Evidence

RFA uses an electrode-tipped probe to deliver radiofrequency energy to nervous tissue, creating heat lesions that inactivate the nerve pathway that sends pain signals to the brain. Conventional RFA uses heat that is concentrated at the probe tip, while cooled RFA (e.g., Coolief) transmits thermal radiofrequency energy using water-cooled electrodes/probes (Avanos Medical website; ECRI, 2021).

Hip

An ECRI report (2021) evaluated cooled RFA for treating hip pain and found that the evidence is too limited in quantity and quality to permit conclusions. Randomized controlled trials (RCTs) assessing cooled RFA compared with other treatments for chronic hip pain (e.g., corticosteroid injections) are needed.

A Hayes report evaluated cooled RFA for treating pain associated with hip osteoarthritis (OA). Only one small study was identified in the clinical literature, and it provided minimal support for the use of cooled RFA in treating hip OA. No systematic reviews or clinical practice guidelines were identified to support the use of cooled RFA for hip OA (Hayes, 2020a).

In a small retrospective case series, Kapural et al. (2018) described technique and evaluated initial outcomes of patients who underwent ablation of the femoral and obturator nerves of the hip using cooled RFA guided by ultrasound (US) and fluoroscopy. Data was collected on 52 ablations of the hip in 23 consecutive patients. Change in pain scores went from the baseline 7.61 ± 1.2 to 2.25 ± 1.4 after the RFA ($p<0.01$). There were no reported adverse events, except one case of neuritis that

resolved within a week after the procedure. Opioid use did not decrease significantly. Study limitations include retrospective design, small patient numbers, lack of blinding, and no comparison group.

Knee

Evidence from low-quality studies suggests that cooled RFA of genicular nerve structures may improve pain, knee function, and quality of life compared with either a single intra-articular injection of hyaluronic acid or corticosteroid. The studies reported higher procedure-related adverse event rates in patients who received cooled RFA than in those who received an injection. RCTs with longer follow-up are needed to determine how cooled RFA compares with nonsurgical procedural treatments for knee OA (ECRI, 2020).

A Hayes report (2020c) concluded that a low-quality evidence base suggests that RFA of the genicular nerves may result in improvements in pain and function in patients with treatment-refractory pain associated with knee OA. Substantial uncertainty exists as to the consistency of clinically significant improvements in pain and the duration of effect of RFA on knee OA-related pain. The evidence was limited by inconsistency in treatment procedures across studies, limited follow-up, and individual study limitations.

Chen et al. (2020) conducted a systematic review comparing genicular nerve RFA to other nonsurgical treatments for the treatment of knee OA. Seven studies were included in the review. The authors concluded that RFA of the knee (cooled and conventional) provided better results than intra-articular steroid injections or other comparators. RFA improved pain, function, and composite scores compared with sham, oral analgesics, and intraarticular steroid or hyaluronic acid injections for up to 3 to 6 months. Further studies with longer follow-up are needed to confirm these findings.

A Hayes report evaluated cooled RFA for treating pain associated with knee OA. The report concluded that a very-low-quality evidence base is insufficient to draw conclusions regarding the effectiveness of cooled RFA in patients with pain associated with knee OA that is refractory to conservative treatment. Substantial uncertainty exists as to the clinical significance, comparative effectiveness, and the duration of effect of cooled RFA of the genicular nerves. In addition, a very-low-quality and small evidence base limits conclusions regarding the effectiveness of cooled RFA prior to total knee arthroplasty (TKA) (Hayes, 2020b)

The results of one multicenter RCT comparing cooled RFA with intra-articular steroid injections for the management of OA-related knee pain were published in three publications. Davis et al. (2018, included in the Hayes 2020b report cited above) randomized 151 patients with chronic (≥ 6 months) knee pain that was unresponsive to conservative therapies to cooled RFA (Coolief) (n=76) or intra-articular steroid injection (n=75). Participants were followed-up at 1, 3, and 6 months after the intervention. The primary efficacy end point was the proportion of subjects whose knee pain was reduced by 50% or greater from baseline. At 6 months, cooled RFA reduced index knee pain by at least 50% in 74.1% of treated participants compared with 16.2% in the intra-articular steroid group. The cooled RFA group consistently experienced greater pain relief throughout the study, with a mean Numeric Rating Scale (NRS) reduction of 4.9 compared with 1.3 in the intra-articular steroid group. There were no procedure-related serious AEs. At 12 months, Davis et al. (2019, included in the Hayes 2020b report cited above) reported that 65% of the original cooled RFA group had pain reduction 50% or greater, and the mean overall drop was 4.3 points on the NRS. Hunter et al. (2020, included in the Hayes 2020b report cited above) conducted an extension study using a subset of patients from the original study. Of the 33 patients enrolled, 25 were evaluated at 18 months after cooled RFA treatment. The mean NRS score was 3.1 ± 2.7, with 12 patients reporting ≥50% pain relief compared to baseline. At 24 months, 18 patients reported a mean NRS score of 3.6 ± 2.8, with 11 demonstrating ≥50% pain relief. Functional improvement, measured by the Oxford Knee Score, continued to be present, with an overall mean change from baseline of 26.0 ± 9.6 points at 18 months and 29.9 ± 10.4 points at 24 months. In this small subset of patients, cooled RFA provided sustained pain relief, improved function, and perceived positive effect through 24 months. Additional RCTs with longer reported outcomes are needed to further evaluate cooled RFA for the treatment of knee pain due to OA.

Kapural et al. (2019, included in the Hayes 2020b report cited above) evaluated the clinical effectiveness of cooled RFA in the treatment of chronic knee pain from both OA and post-TKA as part of a retrospective case series. Data was analyzed for 183 patients who received cooled RFA. Results demonstrated 65% of patients receiving cooled RFA reported more than 50% pain relief and the mean duration of >50% pain relief was 12.5 months. Fourteen percent of patients reported no pain at all after the cooled RFA. A subgroup of 21 patients were treated with cooled RFA for chronic knee pain post TKA and demonstrated no difference in the degree of pain or duration of pain relief. Use of opioids did not change significantly despite reduced pain scores. The study is limited by lack of comparison group.

McCormick et al. (2017, included in the Hayes 2020b report cited above) assessed outcomes of cooled RFA of the genicular nerves for the treatment of chronic knee pain due to OA. Thirty-three patients (52 discrete knees) met the inclusion criteria. After 6 months, the study reported that genicular cooled RFA demonstrated a success rate of 35% based on a combination of patient-reported outcome measures. Nineteen percent of patients experienced complete pain relief. Reports of 80% or greater relief from diagnostic blocks and duration of pain of less than five years were predictors of treatment success. Further prospective studies are needed to optimize the patient selection protocol and success rate of this procedure. The findings of this study are limited by the lack of comparison group.

Gupta et al. (2017, included in the Hayes 2020b report cited above) conducted a systematic review of studies investigating conventional, pulsed, or cooled RFA for the treatment of chronic knee pain. The seventeen studies included were a mix of small RCTs, retrospective or prospective case series and case reports. Four of the included publications (1 RCT, 1 case series, and two case reports) used cooled RFA. Overall, the studies showed promising results for the treatment of severe chronic knee pain by RFA at up to one year with minimal complications. The majority of the studies reported 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. The authors also reported a low level of certainty in supporting the superiority of any specific RFA procedure modality.

Shoulder

No clinical studies evaluating cooled RFA for treating shoulder pain were identified.

Reference(s)

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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.

Melese et al. (2020) identified 18 trials through a systematic review that evaluated the effectiveness of KT in reducing pain and increasing knee function for patients with knee osteoarthritis (OA). A total of 876 patients with OA were identified. Out of the 18 studies, participants in16 of them reported significant improvement of their knee pain with the use of KT when compared to the control group. Ten of the 18 studies assessed functional status and only one of these trials showed that KT had no significant effect on physical status. Although the systematic review found KT having a positive effective for the participant, the psychological and supporting effects were not considered which might constitute further benefits of the taping. Limitations varied amongst the studies including dropout rates of patients in follow up, variation of measurements with KT use and unclear long-term effects.

Pinheiro et al. (2020) conducted a randomized controlled trial of 45 women older than 60 years of age with OA to evaluate the short-term effects of KT (with or without tension). The primary outcome assessed was pain along with several other secondary outcomes. Pain assessment was done via the 10-point Numerical Pain Rating Scale (NPRS) and assessed at start for baseline and again 3 days later. Although a lower pain score was achieved in the participants with KT, the mean estimate did not reach the threshold for clinical significance. The authors concluded that the short-term use of KT in older women with OA had no benefits for their pain. Limitations included lack of binding and small sample size.

Ghozy et al. (2019) conducted a systematic review and network meta-analysis on the clinical effectiveness of kinesio taping for the treatment of shoulder pain. The research resulted in 12 studies with a total of 555 participants. Five studies compared the effectiveness of kinesio taping with a placebo, two studies compared kinesio taping with steroid treatment, and four studies compared kinesio taping plus exercise with exercise alone. The included studies assessed shoulder pain using a visual analogue scale (VAS) and for shoulder disability two scores were used: range of motion (ROM) and the Shoulder Pain and Disability Index (SPADI). The authors found that kinesio taping did not produce better results than placebo and concluded there was insufficient evidence to support the use of kinesio taping in the clinical practice as a treatment for shoulder pain. Limitations included lack of detailed reporting of the technique for application of kinesio tape, short duration of follow-up, low quality of some studies, and use of self-reported scales which resulted in response bias.

Macedo et al. (2019) investigated the effects of KT on chronic non-specific low back pain (LBP) with an assessor-blinded prospective randomized controlled trial. 108 women with chronic non-specific LBP were evaluated prior to, at 3- and 10-days post intervention of KT. Participants were randomized into four different groups: KT with tension group (KTT) applied KT® with tension in the region of the erector spinae muscles; KT no tension group (KTNT) applied KT® with no tension in the same region; Micropore group (MP)applied Micropore® tape on the erector spinae muscles; and the control group (CG) that did not receive any intervention. Participants in the experimental groups were instructed to leave the tape applied to the area for 3 days until re-evaluation. The primary outcome was pain sensation, measured by numerical pain rating scale, however secondary outcomes included disability, ROM, strength and electromyography. The authors concluded the KTT group and KTNT group had improvement with relief of pain 3 days after its application. Limitations lack of participants blinding, multiple comparisons, included female participants only and short-term follow-up; additional studies including long-term results are necessary to assess clinically significant benefit.

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 the 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.

Araujo et al. (2018) investigated the effectiveness of KT in patients with CLBP. 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. One item to point out was the vast age range in the participant selection from 18 to 80 years in age. 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.

To determine the effects of KT on pain, function, gait and neuromuscular control concerning patients with knee osteoarthritis (OA) Rahlf et al. (2018 included in the Melese systematic review above) 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 $p\leq0.001$) 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 and that KT might be an adequate conservative treatment for the symptoms of knee OA. The study is however limited by the short follow-up.

To investigate the effects of KT for patients with stroke and hemiplegic shoulder pain (HSP), Huang et al. (2017) conducted a double-blind, placebo-controlled clinical trial. Twenty-one patients with stroke and 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, included in the Melese systematic review above) 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, included in the Melese systematic review above) 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 elderly patients 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.

A systematic review was performed by Nelson (2016) to summarize the results of 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.

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.

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, included in the Melese systematic review above) 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. The authors concluded that 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
30117	Excision or destruction (e.g., laser) of intranasal lesion; internal approach [when used for nasal septal swell body reduction]
30999	Unlisted procedure, nose [when used for nasal septal swell body reduction]

Nasal septal swell body (NSB) 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 located in the nasal cavity that cleanse and humidify air that passes through the nostrils before it reaches the lungs. They are made by a bony structure surrounded by vascular tissue and a mucous membrane, 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.

The NSB is a thickened mucosa of the anterior nasal septum superior to the inferior turbinate and anterior to the middle turbinate. The NSB is often described within medical literature using various terminologies including nasal septal turbinate (NST), septal turbinate, Kiesselbach's body, septal swell body (SSB), nasal septal body, septal body, nasal swell body, swell body, septal erectile body, septal cavernous body, anterior septum tuberculum, and intumenscentia septi nasi anterior (Meng, 2021). The nasal vestibular body (NVB) is also described as a dynamic swell body present in the inferolateral internal nasal valve (Ibrahim, 2020). It is claimed that the NSB can contribute towards nasal resistance due to its location in the internal valve area. (Kim, 2016).

Meng et al. (2021) conducted a systematic review of the existing knowledge on recent NSB developments. The review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Embase, Web of Science, Ovid, Cochrane Library, and Google Scholar were used for the literature search. Of the 345 journal articles that were initially obtained in the literature search, 28 were included in the review. Three articles evaluated NSB treatment outcomes: Yu et al., Kim et al., and Catalano et al.

Yu et al. (described in detail below) conducted a prospective randomized controlled study that suggested a microdebrider-assisted procedure for inferior turbinate and NSB hypertrophy was superior to turbinoplasty alone. The review notes the limitations of Yu et al. were a small sample size (26 patients) and a short follow-up period. Kim et al. (described in detail below) conducted a study on using coblation to treat patients with an abnormally thickened NSB. The review notes Kim et al. demonstrated that coblation is an effective treatment option for NSB hypertrophy. Catalano et al. treated 60 patients with a prominent NSB using radiofrequency ablation (RFA). Nose obstruction symptom evaluation scores and NSB size scores were assessed at 3 and 6 months postoperatively. Patients reported satisfactory results and improved nasal congestion. One patient developed septal perforation which required attention.

The authors concluded that it is still unclear if surgical intervention of the NSB for nasal obstruction improves the long-term therapeutic effect. Minimally invasive surgical intervention of the NSB is recommended when performed, to avoid injuring the surrounding anatomy and causing postoperative complications. Surgical intervention of the NSB should not be performed simultaneously with septoplasty to minimize the risk of septal perforation. Patients who undergo septoplasty should wait at least 3 months before undergoing surgical intervention of the NSB. Performing surgery on both sides of the NSB increases the risk of septal perforation. Additional evidence on NSB surgical intervention is needed.

Ibrahim et al. (2020) conducted a retrospective cohort study to study the NVB, persistent nasal obstruction, and the effects of treatment with RFA. The review included 35 patients with recalcitrant nasal obstruction. Twenty-five patients (48 sides) had NVBs reduced with RFA. Another cohort of ten patients (20 sides) had untreated NVBs. Follow-up included an assessment of healing and complications post-RFA at two timepoints, early (<1 month) and late (mean, 7.3 months). A subset of patients who underwent RFA (18 of 25 patients) were compared with the 10 untreated patients using the 22-item Sino-Nasal Outcome Test (SNOT-22) and subdomain scoring. NVBs were found successfully reduced in all 35 patients (48 of 48 sides) who had NVBs reduced with RFA at both the early and late time-points. Early sequelae of RFA, including local crusting (22 of 23 patients) and bone exposure (4 of 23 patients), resolved with complete remucosalization (23 of 23 patients) by the late timepoint. No persistent pain, sensory loss, or pyriform aperture stenosis was observed in any patient. There were significant differences in reductions between mean pre- and postoperative SNOT-22 and individual subdomain scores observed in patients who had NVBs reduced with RFA (-24 and -2) compared to the reductions in patients who had untreated NVBs (-8 and -1). The authors concluded that treatment of the NVB using RFA is safe and effective and that RFA treatment of the NVB provides complete swell body reduction and significant improvement in nasal airway function with only transient local morbidity. The study is limited by the observational nature of the retrospective design, concurrent treatments, including septoplasty and turbinate reduction in many cases, and lack of adjustment for possible confounding factors.

Moss, et al. (2019) conducted a systematic review of the NST to summarize and assess existing research and to evaluate its potential as a treatment target. The review was performed using the PRISMA guidelines. Medline, Embase, Web of Science, and Cochrane databases were used for the literature search. Of the 1,069 journal articles that were initially obtained in the literature search, 24 were included in the review. Four articles evaluated NST treatment outcomes: Haight et al., Catalano et al., Kim et al. and Yu et al.

Haight et al. conducted a prospective non-randomized study of 28 patients who underwent inferior turbinate reduction alone and 28 patients who underwent inferior turbinate reduction in conjunction with NST reduction. Both cryosurgery and cautery were utilized. At 10 to 16 weeks postoperatively, there were no differences in patient symptoms or rhinometry between the two

patient groups. Catalano et al. conducted a prospective study of NST RFA in 60 patients who had a history of a failed prior septoplasty and turbinate reduction. There were statistically significant reductions in nasal obstruction symptom evaluation (NOSE) scores: 41.6 at pre-treatment, 17 at month 3, and 21 at month 6. There were also statistically significant improvements in endoscopic middle turbinate visualization. There were three minor infections, one small, asymptomatic septal perforation, and five patients who required multiple treatments. Kim et al. (described in detail below) retrospectively reviewed nasal obstruction scores in 8 patients who underwent NST coblation. Utilizing a visual analog scale, an average pre-treatment score of 7.63 was reduced to 3.88 (month 3) 4.16 (month 6), and 4.63 (month 12). There were no complications reported. Yu et al. (described in detail below) conducted a prospective randomized controlled study of 51 patients. Of those patients, 25 underwent a microdebrider submucous turbinate reduction alone and 26 underwent a concurrent NST reduction. At 3 months postoperatively, there were multiple statistically significant advantages in the NST group, including larger nasal obstruction score improvements (2.02 versus 1.43) and pronounced improvement in total nasal volume on rhinometry (0.83 mL versus 0.36 mL). Olfaction, rhinorrhea, and sneezing were similar between both treatment groups. There were no complications found related to NST reduction.

The authors concluded that evaluating the NST as a treatment target is encouraging, as 3 of the 4 treatment studies found significant benefits to surgical intervention. There was no benefit with NST cautery or cryosurgery. NST RFA, coblation, and submucosa reduction were safe and effective. However, the studies included in the review have some limitations. Haight et al. was non-randomized and included multiple treatment modalities. Yu et al. was the only prospective randomized controlled trial. Kim et al. was retrospective and included only a small sample size. Study follow-up in these studies was rarely longer than 3 to 6 months, limiting conclusions about long-term results. Future prospective studies evaluating NST treatment as an isolated and adjunct treatment are needed.

In a retrospective, case-series study, Kim and associates (2016) presented the results of coblation 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, lacking a comparison group.

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. The study design did not however allow for evaluation of the long-term efficacy and safety of the procedure.

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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

A systematic review and meta-analysis evaluating the effectiveness of rhinophototherapy for treatment of allergic rhinitis (AR) was published by Costa et al. in 2021. Searches were conducted via Web of Science, Scielo, PubMed, SCOPUS, PEDro, and LILACS databases. Terms used included ‘‘intranasal irradiation’’, ‘‘phototherapy’’ and ‘‘allergic rhinitis’’. Ultimately, 12 articles had all necessary data to perform statistical evaluation. Of note, both randomized and non-randomized studies were included in the review because the same questions were addressed in both trial types and, per the authors, limitation to only randomized trials would provide an incomplete summary of assessed treatments. All studies assessed the effectiveness in reduction of nasal symptoms related to AR and/or the quality-of-life score of the sample, evaluated before and after treatment, and/or related to control group, placebo or antihistamine. The meta-analysis results showed overall positive effects of photorhinotherapy for treatment of AR. Nasal symptoms decreased after phototherapy: rhinorrhea (ES = −1.35; $p < 0.0001$; I2 = 91.84%), sneezing (ES = −1.24; $p < 0.0001$; I2 = 91.43%), nasal pruritus (ES = −1.10; $p < 0.0001$; I2 = 91.43%), and nasal obstruction (ES = −1.11; $p < 0.0001$; I2 = 91.88%). More significant effects were noted in perennial allergic rhinitis than in the seasonal type. According to the authors, based on the statistical significance and effect size attained in this study, rhinophototherapy appeared to be an effective treatment for reducing nasal symptoms related to AR. Significant limitations of this study include the small number of articles with randomized clinical trials for evaluation and the high risk of bias in most of the studies included. Further robust randomized controlled trials are needed to establish safety and efficacy. Study by Alyasin et al. that was included in previous versions of this policy was part of this systematic review and meta-analysis and is thus no longer discussed in the details below.

Kennedy and Robertson (2020) compared the efficacy of the phototherapy device on the relief of a range of symptoms provoked by indoor and outdoor allergens in 64 participants. Phototherapy was compared to a placebo device which did not emit light on two groups of allergic rhinitis sufferers. A controlled environment test chamber was used in the studies during exposure to allergens. The authors concluded that rhinophototherapy improved nasal symptoms of allergic rhinitis arising from exposure to indoor and outdoor allergens. The difference in the intensity of symptoms scored at the baseline, and at the final visit for the group using the photoperiod device was significantly lower. Most of the group differences were, however, not statistically significant. According to the authors, phototherapy could potentially help improve the quality of life for allergy sufferers. These results need to be replicated in a larger clinical trial with long-term follow-up.

Jiang and Wang. (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 (Rhinosinusits Disability Index, Visual Analogic Scale of symptom severity) and objective scores (rhinomanometry, olfactory thresholds, nasal Nitic 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.

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).

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Code	Description
30468	Repair of nasal valve collapse with subcutaneous/submucosal lateral wall implant(s)
30999	Unlisted procedure, nose [when used to report the insertion of an absorbable nasal cartilage support implant]
L8699	Prosthetic implant, not otherwise specified [when used to report an absorbable nasal cartilage support implant]

Absorbable nasal cartilage support 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 and Accessory Delivery Device and is composed of a PLLA-PDLA copolymer.

The predicate device, INEX Absorbable Nasal Implant (Spiros®), 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 27, 2021)

According to the manufacturer's website, the Latera implant 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).

Kim et al. (2020) conducted a systemic review and meta-analysis on the effectiveness of using the Latera bioabsorbable implant to treat nasal valve collapse in patients with nasal obstruction. Five databases (PubMed, SCOPUS, EMBASE, Web of Science, and the Cochrane Database) were independently reviewed by two researchers. The review started at the earliest time point recorded in the database to September 2019. The inclusion criteria were studies that scored endoscopic lateral wall movement and nasal obstruction related to quality of life (QOL) postoperatively before and after bioabsorbable nasal implants and those that compared the outcomes of nasal implants (treatment group) with outcomes of sham surgery (control group). Five studies (396 patients) met the inclusion criteria, four of which being case series and one including a comparison group described in detail below (Stolovitzky et al. 2019). The authors found that bioabsorbable nasal implants significantly reduced endoscopic lateral wall motion compared to pretreatment values and also improved QOL at 12 months postoperatively. Most adverse effects were reported with a 5% incidence rate following nasal implant and included skin or mucosal reaction, infection, or implant retrieval. All adverse outcomes resolved without significant sequelae. In one study, compared with the sham surgery (control group), patients receiving bioabsorbable nasal implants (treatment group) significantly improved disease specific QOL. The authors concluded bioabsorbable nasal implants may reduce nasal wall movement and subjective symptom scores compared to preoperative status. However, more randomized clinical trials should be conducted to further verify the effectiveness of bioabsorbable nasal implants. This systematic review and meta-analysis is limited by lack of comparison group undergoing a different therapeutic approach in most of the included studies.

Sidle, et al, (2019, included in Kim [2020] systematic review above) performed a prospective multicenter case series to examine 12-month outcomes for in-office treatment of dynamic nasal valve collapse (NVC) with a bioabsorbable implant. One hundred sixty-six patients with severe-to-extreme class of Nasal Obstruction Symptom Evaluation (NOSE) scores were enrolled at 16 U.S. clinics (November 2016–July 2017). Patients were treated with a bioabsorbable implant (Latera, Spirox Inc., Redwood City, CA) to support the lateral wall, with or without concurrent inferior turbinate reduction (ITR), in an office setting. NOSE scores and Visual Analog Scale (VAS) were measured at baseline and 1, 3, 6, and 12 months postoperatively. The Lateral Wall Insufficiency (LWI) score was determined by independent physicians observing the lateral wall motion video. Using a disease-specific quality-of-life instrument and objective physical examination, the study shows that an in-office, minimally invasive procedure to stabilize the nasal wall with an absorbable implant significantly improves NAO symptoms in patients with dynamic NVC. The authors concluded that at12 months, the Latera implant is safe and efficacious for selected patients in whom dynamic NVC is a main contributor to their NAO. Longer follow-up is needed to determine efficacy beyond 12 months. Limitation of this study is lack of comparison with a group of participants receiving a treatment other than the Latera implant.

Stolovitzky et al. (2019, included in Kim [2020] systematic review above) conducted a multicenter, single-blinded randomized control study to evaluate the safety and effectiveness of a bioabsorbable implant (Latera) to support the lateral nasal wall in nasal valve collapse. 137 patients from 10 clinics were randomized into 2 arms: treatment arm (70 patients) and sham control arm (67 patients). Outcome measures were followed through 3 months after the procedure. The primary endpoint was the responder rate (percentage of patients with reduction in clinical severity by ≥1 category or ≥20% reduction in Nasal Obstruction Symptom Evaluation [NOSE] score). There were no statistically significant differences in patient demographics and nasal obstruction symptom measures between the 2 arms. Three months after the procedure, responder rate was significantly higher for the treatment arm compared to the control (82.5% vs 54.7%, $p = 0.001$). Patients in the treatment arm also had a significantly greater decrease in NOSE score (-42.4 ± 23.4 vs -22.7 ± 27.9, $p < 0.0001$) and significantly lower visual analogue scale (VAS) scores (-39.0 ± 29.7 vs -13.3 ± 30.0, $p < 0.0001$) than the sham control arm. Seventeen patients reported 19 procedure/implant-related adverse events, all of which resolved with no clinical sequelae. The authors concluded that the study did show the safety and effectiveness of the bioabsorbable implant in reducing patients' nasal obstruction symptoms. However, there are limitations of this study. This study reports short-term follow-up data up to 3 months only. However, previous studies of the bioabsorbable implant have shown that patients' response to treatment stabilized at 3 months and were consistent with data observed at 12-month, 18-month, and 24-month follow-up. This is a single-blinded study in which all patients were blinded but physicians were aware of the assignment, which may have introduced risk of bias. Additionally, 8 participants in the implant group (11%) were excluded after randomization due to protocol deviation and implant retrieval and the data are analyzed per protocol rather than using intent-to-treat, which could have introduced biases in the findings.

Stolovitzky et al. (2018, included in Kim [2020] systematic review above) reported 6-month outcomes from a prospective, multicenter, single-blinded (blinded assessor) case series 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. Some participants appear to overlap with these of Sidle, et al (2020) discussed above. 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. This study was also limited by lack of comparison group that did not receive the studied implant.

San Nicolo et al. (2017, included in Kim [2020] systematic review above) conducted a prospective case series 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 post procedure. 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 post procedure. Three implants in three subjects required retrieval within 30 days post procedure 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 post procedure. Well-designed randomized clinical trials with larger patient populations and longer follow-up periods are needed to further assess absorbable nasal implants. This study is limited by lack of comparison group.

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.

Reference(s)

American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS). Position statement: the use of biomaterials in sinonasal procedures. September 2015.

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Sidle DM, Stolovitzky P, Ow RA, et al. Twelve-month outcomes of a bioabsorbable implant for in-office treatment of dynamic nasal valve collapse. Laryngoscope. 2020;130(5):1132-1137. doi:10.1002/lary.28151.

Stryker website. Available at: https://ent.stryker.com/medical-devices/nasal-implant/latera. April 27, 2021.

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.

Stolovitzky P, Senior B, Ow RA, Mehendale N, Bikhazi N, Sidle DM. Assessment of bioabsorbable implant treatment for nasal valve collapse compared to a sham group: a randomized control trial. Int Forum Allergy Rhinol. 2019;9(8):850-856.

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

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

Clinical Evidence

A retrospective study of 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.

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

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

West et al. (2007) conducted a meta-analysis of six case series to address whether bronchoscopic or other minimal access approaches to the closure of BPFs were effective compared to a conventional re-thoracotomy. There was a 30% cure rate using a range of bronchoscopic techniques including cyanoacrylate or fibrin glue application, YAG laser therapy, injection of the vein sclerosant polidocanol and racheo-bronchial stenting. The mortality was 40% in these patients reflecting the very high mortality with BPFs. Many patients required multiple bronchoscopic procedures and further drainage procedures. The authors noted that, at the time, bronchoscopic treatment for BPF's had so far only been reported in small case series but may offer further treatment options in patients too unwell to undergo re-thoracotomy.

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

- Closure of BPFs should be attempted with a combination of primary closure and buttressing with a well vascularized transposed soft-tissue pedicle.

- Transposition of the omentum is preferred over skeletal muscle flaps or mediastinal soft tissue, and this should be attempted after the purulent fluid has been drained completely and the pleural cavity has a surface of granulation tissue. (Shen et al., 2017).

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

Reference(s)

Cardillo G, Carbone L, Carleo F, et al. The rationale for treatment of post re-sectional bronchopleural fistula: analysis of 52 patients. Ann Thorac Surg 2015; 100:251–7.

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.

Shen R, Bribriesco 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.

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
33267	Exclusion of left atrial appendage, open, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)
33268	Exclusion of left atrial appendage, open, performed at the time of other sternotomy or thoracotomy procedure(s), any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip) (List separately in addition to code for primary procedure)
33269	Exclusion of left atrial appendage, thoracoscopic, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)
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
33999	Unlisted procedure, cardiac surgery

Implantable cardiac devices for percutaneous endovascular closure (occlusion) of the left atrial appendage (LAA) are proven and medically necessary to reduce the risk of stroke when using a U.S. Food and Drug Administration (FDA) approved device, and all of the following criteria are met:
- Device is used according to FDA labeled indications, contraindications, warnings and precautions
- Diagnosis of nonvalvular atrial fibrillation
- Moderate to high risk of embolic stroke (CHA_2DS_2-VASc score ≥2 in men or ≥3 in women)
- Documented medical contraindication to long-term anticoagulation

Open or thoracoscopic closure (occlusion) of the LAA using any method (e.g., excision, isolation via stapling, oversewing, ligation, plication, clip) is unproven due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

The CHA_2DS_2-VASc score assigns a point value for the following categories:
- Congestive heart failure –1 point
- Hypertension –1 point
- 65–74 years of age –1 point; ≥75 years of age –2 points
- Diabetes –1 point
- Stroke/transient ischemic attack (TIA) –2 points
- Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) –1 point
- Female sex – 1 point

A score of 0 is low risk, a score of 1 is moderate risk and a score of 2 or more is considered high risk (Meschia et al., 2014).

The European Society of Cardiology guidelines for the management of atrial fibrillation (AF) make the following recommendations regarding LAA occlusion (Hindricks, et al., 2021):

- LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g., intracranial bleeding without a reversible cause).
- Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery. Multiple observational studies indicate the feasibility and safety of surgical LAA occlusion/exclusion, but only limited controlled trial data are available.

National Institute for Health and Care Excellence (NICE) guidelines make the following recommendations:

- Consider LAA occlusion if anticoagulation is contraindicated or not tolerated and discuss the benefits and risks with the individual (NICE, 2021; NICE, 2014).
- Do not offer LAA as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated (NICE, 2014).
- Current evidence on the safety and efficacy of thoracoscopic exclusion of the LAA for nonvalvular AF for the prevention of thromboembolism as an adjunctive procedure to surgical ablative techniques is inadequate in quantity and quality; therefore, this procedure should only be used as an adjunct to surgical ablation with special arrangements for clinical governance, consent and audit or research (NICE, 2011).
- Current evidence suggests that percutaneous occlusion of the LAA is efficacious in reducing the risk of thromboembolic complications associated with nonvalvular 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).

Joint guidelines from the American Heart Association, the American College of Cardiology and the Heart Rhythm Society make the following recommendations regarding LAA occlusion (January et al., 2014; January et al., 2019):

- Percutaneous closure of the LAA may be considered in patients with AF at increased risk of stroke with contraindications to long-term anticoagulation. (Class IIb; Level of Evidence B-NR)
- Surgical closure of the LAA may be considered in patients with AF undergoing cardiac surgery, as a component of an overall heart team approach to the management of AF. (Class IIb; Level of Evidence B-NR). Data on LAA occlusion at the time of concomitant cardiac surgery reveal a lack of clear consensus because of the inconsistency of techniques used for surgical excision, the highly variable rates of successful LAA occlusion and the unknown impact of LAA occlusion on future thromboembolic events.

An Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review update of invasive treatments for AF, including LAA closure devices, noted the evidence remains sparse in terms of stroke prevention. Observational studies comparing different LAA closure devices have suggested no statistically significant differences in risk of stroke, thromboembolism or mortality among the different devices; however, those studies were limited by small sample sizes and short follow-up. Based on these observational studies, LAA shows a trend toward a benefit over warfarin for all strokes and all-cause mortality. Although LAA with percutaneous closure results in less frequent major bleeding than warfarin, it is also associated with a higher rate of adverse safety events such as pericardial effusion and device embolization. Further studies are needed to determine if and how anticoagulation strategies should be modified in patients receiving these procedures (Sanders et al., 2018).

The Society of Thoracic Surgeons clinical practice guidelines for the surgical treatment of AF state the following (Badhwar et el., 2017):

- It is reasonable to perform LAA excision or exclusion in conjunction with surgical ablation for AF for longitudinal thromboembolic morbidity prevention. (Class IIA, Level C limited data)
- At the time of concomitant cardiac operations in patients with AF, it is reasonable to surgically manage the LAA for longitudinal thromboembolic morbidity prevention. (Class IIA, Level C expert opinion)

Watchman

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 September 24, 2021).

On July 21, 2020, the FDA approved an expanded indication to include patients deemed by their physicians to be suitable for anticoagulation therapy and have an appropriate rationale to seek a non-pharmacologic alternative to anticoagulation therapy. This next-generation device (Watchman FLX) was approved with supplement S035. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130013S035. (Accessed September 24, 2021).

An ECRI report comparing Watchman and Watchman FLX with other LAA closure devices or warfarin for thrombosis and stroke prevention concluded that the evidence is somewhat favorable in support of the Watchman devices. The assessment found no head-to-head RCT comparisons of Watchman to other devices. Based on two RCTs, Watchman devices reduce all-cause mortality compared to warfarin, but all-stroke or systemic embolism and major bleeding did not differ statistically between groups at 5-year follow-up. No studies were included that compared Watchman or Watchman FLX to novel oral anticoagulation methods that have less adverse events than warfarin (ECRI, 2021a).

The prospective, multicenter case series PINNACLE FLX study (n=400) evaluated the safety and effectiveness of the next-generation Watchman FLX LAA closure device in patients with nonvalvular atrial fibrillation in whom oral anticoagulation is not contraindicated, but who have an appropriate rationale to seek a nonpharmaceutical alternative. The primary safety end point was the occurrence of one of the following events within 7 days after the procedure or by hospital discharge: death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring cardiac surgery. The primary effectiveness end point was the incidence of effective LAA closure (peri-device flow ≤5 mm), as assessed by transesophageal echocardiography. At one-year, effective closure was seen in 100% of patients who had a Watchman FLX successfully implanted, and the incidence of the primary safety end point was 0.5%. Device-related thrombus was reported in 7 patients, no patients experienced pericardial effusion requiring open cardiac surgery, and there were no device embolization's. This study is limited by lack of comparison group, in particular, one that uses contemporary OACs. Additionally, the study was not designed to evaluate non-inferiority or superiority of the Watchman FLX device versus long-term anticoagulation in terms of mortality and stroke (Kar et al., 2021). NCT02702271. A clinical trial is in progress to compare the safety and efficacy of the Watchman FLX device to novel oral anticoagulants. NCT04394546

A Hayes report compared the safety and efficacy of percutaneous LAA closure devices with OAC medications, and with each other, to reduce stroke risk in patients with nonvalvular 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; updated 2020).

Both the PROTECT-AF and PREVAIL studies noted below had accompanying registries designed to continue accrual of data on longer-term outcomes. These registries, CAP (Continued Access to PROTECT-AF) and CAP2 (Continued Access to PREVAIL]) represent the largest number and longest follow-up of patients implanted with the Watchman device. Holmes et al. (2019) reported on the final 5-year total experience of CAP and the 4-year follow-up of CAP2. The nonrandomized CAP registry included 566 patients who continued follow-up through their 5-year visit or until study exit. The nonrandomized CAP2 registry enrolled 578 patients with follow-up data available through 4 years on all patients remaining in the trial. CAP2 patients were significantly older and had higher CHA2DS2-VASc score scores (4.51 versus 3.88; $p < 0.001$). Procedural success was similar in both (94%). The primary composite endpoint occurred at a rate of 3.05 per 100 patient-years in CAP and 4.80 per 100 patient-years in CAP2. Events contributing to this endpoint were most commonly cardiovascular/unexplained death (1.69 per 100 patient-years for CAP and 2.92 per 100 patient-years for CAP2). Hemorrhagic stroke was significantly less than ischemic stroke (0.17 per 100 patient-years in CAP and 0.09 per 100 patient-years in CAP2), and total stroke rates were significantly less than predicted by CHA2DS2-VASc score (78% reduction with CAP, 69% reduction with CAP2).

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 OACs other than warfarin in patients with AF, and to assess advantages for those with contraindications to anticoagulation.

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 embolization's (0.24%) (6 requiring surgical removal); and 3 procedure-related deaths (0.078%).

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 versus 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.

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 OACs.

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 three groups investigated were novel OACs, 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 RCTs (n=73,978) were included in the analysis. There was a significant difference favoring novel OACs 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 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% likely to be noninferior 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, the authors concluded that 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).

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.

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.

PREVAIL

The PREVAIL study (Holmes et al., 2014) is a multicenter, prospective RCT 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/TIA) 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 and the prespecified criteria noninferiority was not achieved for this outcome. 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.

ASAP

In the ASAP trial, Reddy et al. (2013a) conducted a multicenter case series 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 OAC.

Amulet

The Amulet™ LAA closure device (Abbott) received FDA premarket approval (P200049) on August 14, 2021. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P200049. Accessed September 16, 2021.

The multicenter Amulet IDE Trial (Lakkireddy et al., 2021) evaluated the safety and effectiveness of the dual-seal mechanism of the Amulet LAA occluder compared with the Watchman device. A total of 1878 patients with nonvalvular AF at high risk of stroke were randomly assigned (1:1) to undergo percutaneous implantation with the Amulet occluder or Watchman device. The

primary endpoints included safety (composite of procedure-related complications, all-cause death, or major bleeding at 12 months) and effectiveness (composite of ischemic stroke or systemic embolism at 18 months) and the rate of LAA occlusion at 45 days. Pre-specified secondary endpoints included a composite of all stroke, systemic embolism, or cardiovascular/unexplained death at 18 months, major bleeding at 18 months, and superiority test of the three primary endpoints. The Amulet occluder was noninferior to the Watchman device for the primary safety endpoint (14.5% vs. 14.7%). Major bleeding and all-cause death were similar between groups (10.6% vs 10.0% and 3.9% vs 5.1%, respectively). Procedure-related complications were higher for the Amulet occluder (4.5% vs. 2.5%), largely related to more frequent pericardial effusion and device embolization. The rate of complications decreased with operator experience. The Amulet occluder was noninferior to the Watchman device for the primary effectiveness endpoint (2.8% vs. 2.8%), and the composite of stroke, systemic embolism or cardiovascular/unexplained death (5.6% vs 7.7%). The rate of major bleeding was similar between groups (11.6% vs. 12.3%). LAA occlusion was higher for the Amulet occluder compared with the Watchman device (98.9% vs. 96.8%). Patient follow-up will continue for up to five years. Clinicaltrial.gov NCT02879448.

In a systematic review and meta-analysis of observational studies, Basu Ray et al. (2020) compared the safety and efficacy of the Amplatzer and Watchman LAA closure devices. Six studies, with 342 patients in the Watchman group and 274 patients in the Amplatzer group, were included in the meta-analysis. Of the six studies, two were prospective nonrandomized studies and four were retrospective studies. No RCTs were identified. Overall, both devices had relatively low complication rates. No significant differences between the devices were found in safety outcomes or in the rates of all-cause mortality, cardiac death, stroke/TIA, or device-related thrombosis. The total bleeding rate was significantly lower in the Watchman group, yet no significant differences were found when the bleeding rate was categorized into major and minor bleeding. Total peridevice leakage rate and insignificant peridevice leakage rate were significantly higher in the Watchman group. However, significant peridevice leakages were similar in both the devices. The authors noted that observations were limited by the small number of available studies. Furthermore, lack of randomization limits the validity of the findings.

Open or Thoracoscopic Closure of the Left Atrial Appendage

AtriClip

There are several FDA 510(k) premarket notifications for the AtriClip LAA occlusion system (AtriCure, Inc.). For additional information, search the following website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed September 24, 2021).

Evidence assessing AtriClip Flex-V and Pro-V is limited to reported clinical experiences on five patients that may not represent typical outcomes of LAA occlusion with these devices. Large clinical studies are needed to assess AtriClip Flex-V and Pro-V safety and effectiveness (ECRI 2021b).

A Hayes technology assessment concluded that a very low-quality body of evidence from single arm studies demonstrated a high rate of complete LAA occlusion; however, the specific impact of AtriClip on relevant clinical outcomes including stroke risk cannot be determined due to the lack of comparative studies and the confounding effect of concurrent cardiac interventions. Well-designed comparative studies with sufficient follow-up duration are needed to determine whether the AtriClip system is a safe and effective preventive measure for stroke (Hayes, 2021).

Toale et al. (2019) conducted a systematic review of 11 studies (n=922) evaluating the safety, efficacy and durability of LAA occlusion using the AtriClip device in the management of patients with AF. Rates of total LAA occlusion compared favorably to conventional surgical and percutaneous closure methods. No device-related adverse events were reported across the studies. The reported incidence of stroke or TIA post-procedure ranged from 0.2 to 1.5/100 patient-years. Four hundred and seventy-seven of 798 patients (59.7%) had ceased anticoagulation on follow-up. Limitations include heterogenous studies of differing design and methodology, use of various procedural approaches and inconsistent post-operative anticoagulation. Most of the included studies appeared to be case series without a comparator, limiting the conclusions that can be drawn from this review. The authors noted that future trials comparing AtriClip with established surgical and percutaneous methods of LAA closure are needed. Ellis et al. (2017) and Ailawadi et al. (2011), which were previously cited in this policy, are included in this systematic review.

Emmert et al. (2014) evaluated the AtriClip device in 40 patients with AF undergoing elective cardiac surgery with planned concomitant ablation. Early mortality was 10% due to non-device-related reasons; however, the remaining 36 patients were evaluated at 3, 12, 24 and 36 months. After imaging, clips were found to be stable, showing no secondary dislocation 36

months after surgery. No intracardial thrombi, LAA perfusion or LAA stump were detected. Apart from one unrelated TIA that occurred 2 years after surgery in a patient with carotid plaque, no other strokes and/or neurological events were reported. This study is limited by lack of randomization and small sample size.

Once published, findings from a completed RCT (NCT02701062) should provide additional evidence on the efficacy and safety of AtriClip.

Other Open or Thoracoscopic Methods

Ando et al. (2018) conducted a systematic review and meta-analysis of studies comparing patients who underwent open cardiac surgery with or without LAA closure. Seven studies were included in the analysis. There were 1,963 patients in the LAA closure group and 1,934 patients in the non-LAA closure group. Of the 7 studies, 3 were RCTs, 3 were propensity-matched studies and 1 was a case-matching study. At 30-day/in-hospital follow-up, LAA closure was significantly associated with decreased risk of mortality and cerebrovascular accident. The authors concluded that concomitant surgical LAA closure should be considered at the time of open cardiac surgery, particularly among those with preoperative AF. The benefit of LAA closure for patients without preoperative AF and for those undergoing nonvalvular surgery is still unclear. Additionally, the findings are mostly based on included observational studies, with the findings of the three RCTs being less conclusive. Further prospective investigations are indicated.

Atti et al. (2018) also conducted a systematic review and meta-analysis of studies comparing patients who underwent open cardiac surgery with or without LAA closure. There was some overlap in included studies with Ando et al. (2018), with the same three RCTs included. Five additional retrospective studies were included in this analysis. Combining findings of observational studies and RCTs, surgical LAA closure was associated with lower risk of embolic events and stroke, especially in participants with AF. There was no significant difference in the incidence of all-cause mortality, AF and reoperation for bleeding and postoperative complications. The included studies were limited by retrospective design, small sample size, a wide variation of surgical methods used and short-term follow-up. The findings are mostly based on included observational studies, with the findings of the three RCTs being less conclusive. The authors reported that the results support the safety of surgical LAA closure but acknowledge that RCTs are needed to evaluate long-term outcomes.

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

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

Clinical Evidence

Leadless pacemakers 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.

The Micra™ Transcatheter Pacemaker System (TPS) (Medtronic) received FDA premarket approval (PMA) (P150033) on April 6, 2016. On January 15, 2020 the FDA approved a supplement (S061) to the original PMA approving the Micra™ AV Transcatheter Pacing System. Additional information is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P150033. (Accessed May 25, 2021).

A Hayes report concluded that there is insufficient evidence and substantial uncertainty regarding the safety and efficacy of the Micra TPS, especially in relation to the alleviation of symptoms associated with bradycardia. Conclusions cannot be drawn from the very-low-quality body of evidence limited chiefly by lack of contemporaneous comparative evidence, limited number of studies, lack of long-term safety, and a general lack of studies demonstrating patient-centered outcomes of effectiveness. Well-designed and well-conducted 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 transvenous pacemakers (Hayes 2019; updated 2021).

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

Dar et al. (2020) reported a comparison of the retrieval process for Nanostim versus Micra transcatheter leadless pacemakers. The list of retrievals for the Micra TPS was obtained from Medtronic, whereas Nanostim data was obtained from centers that participated in the Leadless II study. Details of retrieval such as indication, days post implantation, complications, and post procedure device management were obtained from the manufacturer database for each site, and any missing details were obtained from individual operators. Extractions performed on the same day were labeled as “Early” and thereafter were labeled as “Late.” A total of 113 retrievals were attempted (73 in Nanostim and 40 in Micra TPS). The most common reasons for retrieval were battery advisory and inadequate pacing threshold ($n = 16$) for Nanostim and Micra, respectively. Success rate in Nanostim group was around 90% (66/73) compared with 100% in Micra group ($p = 0.049$). Late retrieval occurred in 50% of

Micra TPS cases (20/40) compared with 100% of Nanostim LP cases. Median time to extraction was 46 days for Micra TPS and 256 days for Nanostim LP ($p < 0.001$). Rate of serious adverse events with Nanostim extraction was 3% ($n = 2/73$). The authors concluded that overall, leadless pacemaker extraction is feasible and safe to perform irrespective of the duration and type of the device.

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

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., 2019).

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

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.

Duray et al. (2017) reported 12-month safety data and 24-month electrical performance compared to historical controls. 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 contemporary 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 historical controls traditional pacemaker group.

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. The findings are limited by lack of comparison group. Longer follow-up is needed to confirm these results (Roberts et al., 2017).

Using historical controls, 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 historical control patients. The authors concluded that the transcatheter pacemaker met the prespecified safety and efficacy goals and that the device had a safety profile similar to that of a transvenous system while providing low and stable pacing thresholds. The findings are limited by lack of contemporary comparison group.

Ritter et al. (2015) published an interim report on a case series of140 patients from 23 centers in 11 countries. Patients received the device to treat AV 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 or control and small patient numbers. Long-term safety and benefit of the device will be further evaluated in the trial.

LEADLESS II Trial

The LEADLESS II trial is a prospective, nonrandomized, multicenter case series 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.

Tjong et al. (2018b) conducted a 3-year follow-up to the LEADLESS trial. Patients implanted with a leadless cardiac pacemaker (LCP) (Nanostim, St. Jude Medical/Abbott) were retrospectively assessed to evaluate the safety and performance of this device with a minimum of 3 years of follow-up. Medical records were analyzed from June 2014 until May 2016 and evaluated for (1) serious adverse device effects (SADEs) and (2) electric performance of the LCP. Thirty-three patients (age 77±8 years, 67% male) were enrolled and were followed for a median duration of 38 months (range, 21–41 months). The authors found freedom from SADEs in 89.9% (95% confidence interval, 79.5%–100%) of patients at 40 months of follow-up. In total, 3 of 33 patients experienced device-related complications, of whom 2 patients had procedure-related SADEs (freedom from procedure-related SADEs is 93.9% [95% confidence interval, 86.1%–100%]). The electric performance of the LCP was adequate up to 36 months of follow-up. Pacing thresholds were at baseline, prehospital discharge, 3, 12, 24, and 36 months, respectively, 0.80±0.51, 0.41±0.20, 0.46±0.31, 0.43±0.30, 0.47±0.31, and 0.47±0.19 V at 0.4 ms pulse width. Similarly, the R-wave amplitudes were, respectively, 8.3±3.1, 9.7±2.7, 10.6±2.3, 10.3±2.2, 10.4±2.5, and 10.8±2.3 mV; and impedances were, respectively, 772±243, 719±196, 627±199, 627±209, 609±181, and 614±169 Ω. During follow-up in a substantial number of patients, the rate response feature was activated (61% at 12, 42% at 24, and 39% at 36 months). One battery issue–related complication occurred in the longer term, ultimately leading to the issuing of a battery advisory and redevelopment of battery components. This study is limited by lack of comparison group.

Reddy et al. (2016) conducted a multicenter case series 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. This study is limited by lack of comparison group.

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 without a comparison group 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.

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.

In the LEADLESS trial, Reddy et al. (2014) conducted a prospective, non-randomized, single arm case series 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 AV 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 lack of comparison groups, 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.

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Code	Description
53451	Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance
53452	Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance
53453	Periurethral transperineal adjustable balloon continence device; removal, each balloon
53454	Periurethral transperineal adjustable balloon continence device; percutaneous adjustment of balloon(s) fluid volume

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

Clinical Evidence

According to the manufacturer (Uromedica Plymouth, Minnesota), the ProACT system is used for the treatment of adult men who have stress incontinence arising from intrinsic sphincter deficiency of at least twelve months duration following radical prostatectomy or transurethral resection of the prostate (TURP), and who have failed to respond adequately to conservative therapy. The device consists of two adjustable balloon implants placed bilaterally at the bladder neck or at the apex of the prostatic remnant. The ACT® device is used for women, and the balloons are surgically placed on either side of the bladder neck, providing compression. The ACT device is currently in clinical trials and not available in the United States. A normal amount of effort is still required to urinate, and the pressure from the balloons will help guard against unintentional urine loss, such as during a sneeze or cough.

On November 24, 2015, the ProACT device received FDA Premarket Approval as a Class III device. Further information may be found at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P130018 (Accessed May, 26, 2021)

Munier et al. (2020) conducted a two center retrospective case series of 26 patients implanted with the ProACT device to treat persistent stress urinary incontinence after radical prostatectomy who had insufficient improvement from sub urethral slings. The primary endpoint was continence, defined as 0 pads per day (PPD). The secondary endpoints were 50% decrease in PPD and increases in the Incontinence Quality of Life score (IQOL). Refilling and complications were also reported. The mean follow-up was 36 months (±20; min 14-max 128). Five patients have had adjuvant radiotherapy (18%). All patients presented with persistent stress urinary incontinence, using 2.3 PPD (±1; min 1-max 6), and only one sling was removed due to infection. After ProACT with an average 3 mL refilling (±1.2 min 2-max 6), 18 patients (66.7%) were continent. Eight of the remaining patients

(29.6%) were improved; their number of PPD decreased from 2.6 to 1. The average IQOL score of those 8 patients increased by 20 points, from 53.4 up to 74.2 (P = .005). Overall 26 patients (96.3%) were improved. The remaining patient was not implanted because of an intraoperative urethral injury and is considered a failed case (3.7%). He had instead an artificial urinary sphincter implantation. Three patients (14.8%) needed peri-urethral balloon replacement. The authors concluded that ProACT implantations are effective and without significant complications. This study is limited by a small number of participants, and a lack of a comparison group.

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

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 sequalae. The authors concluded that these results confirm the long-term safety and efficacy of this newly FDA-approved therapy, showing significant improvements in both objective and subjective measures of SUI in mild, moderate, and severely incontinent male patients. They also note that the implant procedure is minimally invasive, and complications are generally mild and easily resolvable. These findings are limited by the lack of a comparison group and a large loss to follow up.

Nordhoff et al. (2019) conducted a retrospective multicenter case series 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. These findings are limited by lack of comparison group and small sample size.

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 Invance Sling, 48.8% for Advance Sling, 64.2% for ProACT. The overall complication rate was 19.43% for AUS, 7.4% for Invance Sling, 12.3% for Advance Sling, 12.3% for ProACT. The authors concluded that due to the poor overall quality of available studies, it was not possible to identify or refute clinically important differences between the alternative surgical procedures. The data seems to suggest that while AUS has the highest efficacy in the treatment of SUI following RP it is also associated with the highest complication rate, but this may be due to the longest follow up. Larger rigorous trials are needed in order to support this evidence.

Venturineo et al. (2015) conducted a case series to evaluate the functional results, morbidity, and quality of life of the adjustable continence balloons ProACT for the treatment of male 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 refillments postoperatively. The baseline daily pad number decreased from a mean of 5.9 pads (range, 3-12 pads) to a mean of 1.7 pads (range, 0-5 pads) per day after refilling but increased to a mean of 3.9 (range, 0-10) at the last follow-up visit. After balloon adjustments, 4 patients (18%) were continent and 18 patients (82%) showed an improvement with a 95% rate of subjective satisfaction. Revision and explanation rates were 73% and 55%, respectively. At a median follow-up of 57 months, only 1 patient (4.5%) remained dry, and only 10 patients (45%) remained satisfied with the procedure, whereas 12 patients (55%) were unchanged and dissatisfied. The authors concluded that the ProACT device appears to be safe and efficacious in the short term, and that the postoperative readjustment allows the achievement of a short-term continence status. They also note that in the long term, the ProACT does not appear to be an ideal device for durable continence and patients' satisfaction. This study is limited by the lack of comparison group and small sample size.

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

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

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Code	Description
53899	Unlisted procedure, urinary system (when used to report UroCuff)
55899	Unlisted procedure, male genital system (when used to report UroCuff)

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.

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. While it is not a replacement for cystometry (which still remains the 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 II device and is 510(k) exempt. Further information can be found here using product code EXQ: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm?GMPPart=876#start (Accessed May 17, 2021).

In a 2020 observational cross-sectional study, Kaplan et al. reviewed the results of 50,680 men who received UroCuff testing on men with lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) to evaluate voiding characteristics and quantify changes in urodynamic parameters with age. Data was gathered from 103 urology practices across the country. Inclusion criteria required initial pressure flow study with subsequent tests excluded, voided volume 50 ml or greater, at least 1 cuff inflation and patient over age 20. Pressure, maximum flow rate, flow rate efficiency (maximum flow rate/Pcuff), voided volume and post-void residual were plotted by age and stratified by Newcastle Noninvasive Nomogram category. This study demonstrates that symptomatic patients enter urological practices at different urodynamic stages of bladder function and outlet obstruction, that Pcuff, maximum flow rate, voided volume, flow rate efficiency and post-void residual deteriorate with age, and that UroCuff is a sensitive evaluation of bladder performance. This evidence is limited by heterogeneity. Even if several noninvasive assessments of bladder outlet obstruction have shown promising results, invasive urodynamics remain the gold standard. The main limitation of the study is the lack of data about diagnosis, symptoms and treatment outcomes. Furthermore, the results cannot be extended to a general population considering that study included exclusively men with LUTS enrolled in urological outpatient visits. Further studies comparing UroCuff with validated predictive models as a control tool are needed to better define the clinical efficacy of this new test.

In 2019 evidence-based guideline, the Benign Prostatic Hyperplasia Guideline Panel of the American Urological Association (AUA) stated that for the evaluation and preoperative testing of patients presenting with LUTS that may be due to BPH, clinicians should take a medical history, utilize the AUA -Symptom Index and urinalysis, and that some patients may also require post-void residual, uroflowmetry, or pressure flow studies. They also state clinicians should consider uroflowmetry prior to surgical intervention for LUTS/BPH.

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).

Reference(s)

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Matulewicz RS, Hairston JC. The UroCuff test: a non-invasive alternative to pressure flow studies in adult males with lower urinary tract symptoms secondary to bladder outlet obstruction. Can J Urol. 2015 Aug;22(4):7896-901.

SRS Medical, North Billerica, MA. Website. (Accessed May 5, 2021).

Code	Description
63268	Laminectomy for excision or evacuation of intraspinal lesion other than neoplasm, extradural; sacral

Surgical treatment (e.g., laminectomy and sacral reconstruction) of a sacral Tarlov cyst is proven and medically necessary for individuals with the following:

- Pain directly attributable to the Tarlov cyst, or
- Neurologic conditions attributable to the Tarlov cyst (e.g., motor loss, urinary or fecal incontinence, cauda equina syndrome), and
- Radiologic evidence of a Tarlov cyst that by its anatomic location, size and compression or displacement or neural elements correlates to the neurologic signs and symptoms found on current evaluation.
- Failure to improve with non-surgical treatment for at least 12 weeks.

Clinical Evidence

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. 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 and have failed an appropriate course of non-operative treatments. (National Organization for Rare Disorders, 2015).

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), 2019).

Guo et al. (2007) investigated the microsurgical results of symptomatic sacral perineurial 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.

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.

Reference(s)

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Tanaka M, et. al. Surgical results of sacral perineural (Tarlov) cysts. Department of Orthopaedic Surgery, Okayama University Hospital. Acta Med Okayama. 2006 Feb;60(1):65-70.

Code	Description
64454	Injection(s), anesthetic agent(s) and/or steroid; genicular nerve branches, including imaging guidance, when performed

Due to insufficient evidence of safety and/or efficacy, genicular nerve block (GNB) is unproven and not medically necessary for treating knee pain.

Note: For information on radiofrequency ablation of the genicular nerve, see separate section above.

Clinical Evidence

In a GNB procedure, an anesthetic agent (and/or steroid) is injected on the genicular nerves of the knee. The procedure specifically targets the superior lateral, superior medial, and inferior medial genicular nerves. Once injected, the anesthesia numbs the nerves and inhibits the transmission of pain signals to the brain (Hayes, 2020).

Fonkoue et al. (2021) assigned 55 patients with chronic knee osteoarthritis (OA) in a double-blinded randomized controlled trial designed to compare the effectiveness of GNB using classical anatomical targets (CT) versus revised targets (RT). The groups received a GNB (using a fluid mixture of two milliliters of lidocaine 1% and 20 milligrams triamcinolone) with either classical targets (n=28) or revised targets (n=27). Numeric Rating Scale (NRS), Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index Score (WOMAC), Quantitative Analgesic Questionnaire (QAQ), and Global Perceived Effects Scale (GPES) were assessed at baseline, and at one-hour, 24-hours, one, four, and twelve-weeks post-intervention. The RT group had a greater reduction in NRS mean score at one-hour post intervention and a higher proportion of patients

achieving more than 50% knee pain reduction at each follow up interval. However, the differences were only statistically significant at one-hour post intervention. Both protocols resulted in substantial pain reduction and joint function improvement that lasted up to twelve-weeks post intervention. The authors concluded the revised technique resulted in more pain relief and a higher proportion of successful responders at one-hour post intervention. Limitations include the large volume injected for GNB which did not allow to clearly discriminate the effects of the anatomical precision of the targets in both techniques, patient highly subjective reported outcomes, and no sham-controlled trials performed to demonstrate the efficacy of therapeutic GNB.

A Hayes health technology assessment (2020), evaluated the use of GNB for the management of knee pain associated with pain following total knee arthroplasty (TKA) or OA of the knee. A total of four RCTs (n=33 to 80 patients) were reviewed. Three studies included patients with OA and one study consisted of patients with knee pain that persisted at least 6 months following TKA. Corticosteroids applied to the genicular nerves combined with GNB were evaluated in 3 studies. These three studies varied and included GNB alone, ultrasound-guided administration compared with fluoroscopy -guided administration and radiofrequency ablation. One RCT evaluated intra-articular corticosteroid injection (IACSI) combined with GNB compared to IACSI alone. Follow-up ranged from eight-weeks to twelve-months. No technology related adverse events were reported. While short-term results often demonstrated clinically and statistically significant improvements in pain from baseline, these results were not maintained at last follow-up. Three of four RCTs found statistically significant improvement in pain from baseline; however, none of these improvements achieved clinical significance. A statistically significant difference in pain was noted and favored IACSI over GNB followed by IACSI. No significant difference was noted between GNB combined with corticosteroid and RFA or GNB alone. No differences were observed between GNB combined with corticosteroid and RFA in quality-of-life scores. Additionally, no differences were noted between IACSI and GNB combined with IACSI at one-month follow-up; however, IACSI was favored at 3-month follow-up. The effect of GNB combined with a corticosteroid on function generally demonstrated an improvement from baseline with two of four studies also demonstrating a clinically significant improvement as well. No significant difference was found between GNB combined with corticosteroid and RFA or GNB alone. IACSI was favored over GNB followed by IACSI related to function. Based on the assessment, the body of evidence overall for GNB for knee pain was very low due to limiting and conflicting evidence, limited follow-up data, considerable heterogeneity in terms of comparators, and individual study quality limitations Additional studies to evaluate efficacy and any long-term benefit were recommended. Hayes noted the evidence does not consistently provide proof of benefit and substantial uncertainty remains due to conflicting evidence and limited follow-up.

In a prospective randomized design study, Kim et al. (2019) compared the efficacy of ultrasound versus fluoroscopy guided genicular nerve blocks. From July 2015 to September 2017, a total of 80 patients were enrolled and randomly distributed to groups U (ultrasound guided, n=40) and F (fluoroscopy guided, n=40). The NRS, WOMAC, GPES, and complications were evaluated pre-procedure, one, and three months after genicular nerve block. No differences were observed between the two groups at baseline or during the follow up period. The authors concluded ultrasound and fluoroscopy guided GNB had similar results in pain relief, functional improvement and safety. However, considering radiation exposure, ultrasound guidance maybe be superior to fluoroscopic guidance. The authors noted that GNB with an adjuvant corticosteroid improved knee functionality and alleviated pain intensity until one-month post procedure. Limitations of this study include lack of blinding, short follow-up duration, and small sample size.

Kim et al. (2018) in a randomized, double-blinded, institutional study investigated the effects of combining corticosteroids and local anesthesia during ultrasound-guided GNB in patients with chronic knee OA. Patients were randomly assigned in groups of 24, one group received lidocaine alone and the other lidocaine plus triamcinolone before ultrasound guided GNB. Ultimately, 61 of the original patients were analyzed, the other nineteen patients did not receive the scheduled intervention, were lost to follow-up, or received other treatments. Visual analog scale (VAS), Oxford Knee Scores (OKS) and Global Perceived Effects Scale (GPES) were assessed at baseline, and at one, two, four and eight-weeks after the procedure. VAS scores were significantly lower in the lidocaine plus TA group than in the lidocaine alone group at two and four weeks after the procedure. A similar difference in OKS was observed at four-weeks. The authors concluded ultrasound- guided GNB when combined with a local anesthetic and corticosteroid can provide short-term pain relief. The clinical benefit of corticosteroid administration was not clear when compared with local anesthesia alone. The authors noted that the preliminary data regarding optimal steroid dose or type should be validated in future large-scale studies. Study limitations include small sample size, lack of placebo group and short follow-up duration.

In 2017, Qudsi-Sinclair et al. published a double-blind randomized clinical study comparing neurolysis using traditional radiofrequency (RF) to local anesthetic and corticosteroid block of the genicular nerves. The study included 28 patients who had TKA and continued to experience pain. The patients were divided in two groups, with fourteen on each treatment arm, and

were followed over a one-year period. A significant joint function improvement and reduction in pain was noted during the first three to six-month period, with similar results using both techniques. Results of the study indicated that both treatment groups had improvement in quality of life, disability, and a reduction in the need for analgesics. Limitations included subjective pain measurement tools and limited sample size. Additional clinical trials with a larger sample size and longer follow-up to confirm the efficacy and detect possible long-term adverse effects are recommended by the authors.

Reference(s)

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Kim DH, Lee MS, Lee S, et al. A prospective randomized comparison of the efficacy of ultrasound- vs fluoroscopy-guided genicular nerve block for chronic knee osteoarthritis. Pain Physician. 2019 Mar;22(2):139-146.

Qudsi-Sinclair S, Borrás-Rubio E, Abellan-Guillén JF, et al. A comparison of genicular nerve treatment using either radiofrequency or analgesic block with corticosteroid for pain after a total knee arthroplasty: a double-blind, randomized clinical study. Pain Pract. 2017 Jun;17(5):578-588.

Code	Description
68841	Insertion of drug-eluting implant, including punctal dilation 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. Dextenza® (dexamethasone ophthalmic insert) 0.4mg (Ocular Therapeutix™ Inc.) is inserted through the inferior punctum into the canaliculus of the eye. According to the manufacturer and the FDA, Dextenza is intended for the treatment of ocular inflammation and pain following ophthalmic surgery. Another drug-eluting insert, OTX-TP, a sustained-release travoprost intracanalicular insert, is being investigated to determine if it is effective for reducing intraocular pressure.

McLaurin et al. (2021) evaluated the efficacy and safety of a dexamethasone intracanalicular ocular insert for treatment of allergic conjunctivitis in a multicenter, randomized, double-masked, placebo-controlled, Phase 3 clinical trial. Subjects with allergic conjunctivitis were randomized 1:1 to dexamethasone insert or placebo insert to both eyes and evaluated using a modified version of the Ora-CAC® (conjunctival allergen challenge) model. After in-office insert placement, a series of 4 closely spaced post-insertion CACs at Weeks 1, 2, and 4 were conducted across approximately 30 days. Primary efficacy endpoints, assessed at Week 1 CAC Day 8, were subject-reported ocular itching at 3-, 5-, and 7-minutes post-CAC and investigator-evaluated conjunctival redness at 7-, 15-, and 20-minutes post-CAC. For the primary endpoints, dexamethasone insert showed statistically significantly lower mean ocular itch scores compared with placebo at all time points ($P<.001$), with differences favoring dexamethasone insert over placebo (0.86, 0.98, and 0.96 units at 3, 5, and 7 minutes, respectively), and statistically significantly lower conjunctival redness scores at 20 minutes ($P<.05$) but not at 7 or 15 minutes ($P\geq.05$). Results also showed statistically significantly less itching and conjunctival redness at 31 and 29 of 33 other time points, respectively ($P<.05$). There were no serious AEs; one subject had elevated intraocular pressure in both eyes. The authors concluded that this study demonstrates the potential for a single, physician-administered dexamethasone intracanalicular insert to provide relief of ocular itching for up to 4 weeks in subjects with allergic conjunctivitis, while maintaining a favorable safety profile. According to the authors, this study is limited because the CAC study design provides a strictly controlled environment of allergen exposures in which to study ocular allergy therapies, which is an advantage for research purposes, but it does not permit evaluation of therapeutic outcomes in the uncontrolled, real-world environment of allergen exposures. The study is also limited by the short follow-up period.

ECRI published a report for Dextenza (Dexamethasone Ophthalmic Insert) for treating pain and inflammation after eye surgery (ECRI, 2019). According to ECRI, the evidence is somewhat favorable based on evidence from 3 multicenter, randomized, placebo-controlled trials (Tyson et al., 2019; Walters et al., 2016; Walters et al., 2015). These studies indicated that Dextenza reduced ocular pain and inflammation better than no corticosteroid treatment after cataract surgery. According to ECRI, the randomized controlled trials were high quality: all were multicenter and double-blinded. The manufacturer funded all studies. To maintain blinding, Dextenza was not compared to standard of-care dexamethasone eye drops. ECRI indicated that studies of this comparison would be informative.

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.

Reference(s)

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Tyson SL, Bafna S, Gira JP, et al. Dextenza Study Group. Multicenter randomized phase 3 study of a sustained release intracanalicular dexamethasone insert for treatment of ocular inflammation and pain after cataract surgery. J Cataract Refract Surg. 2019 Feb;45(2):204-212.

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

In a health technology assessment from Hayes, the overall body of evidence for the use of eustachian tube balloon dilation (ETBD) for treatment of chronic ETD is considered to be of low quality. The literature search included four RCTs, one case control, one retrospective and five pre/post studies. The authors concluded that this approach has potential but unproven benefit. While recipients may have experienced symptom relief and improved function, additional studies are needed to confirm ETBD is better than standard care protocols (Hayes, 2021).

Alper et al. (2020) performed a prospective case series assessment in eleven adults for changes in eustachian tube (ET) function (ETF) with balloon dilation of eustachian tube (BDET). The participants had at least one ventilation tube inserted for chronic eustachian tube dysfunction and a history of otitis media with effusion. The changes in ETF after balloon dilation were measured by Forced Response Test (FRT), Inflation Deflation Test (IDT) and Pressure Chamber test. The test results showed positive results with pressure which suggested the BDET made it easier to open the ET and stay open longer. The authors concluded these adults with severe ETD may benefit from BDET however it may not completely resolve the patients' condition and ventilation tubes might still be required. The study is however limited by lack of comparison group.

Using data from a prospective, multicenter, randomized, controlled trial, Anand et al. (2019, included in Hayes report above) analyzed and investigated the durability of BDET for obstructive eustachian tube dysfunction (OETD) plus medical management (MM) treatment outcomes through 52 weeks. Among subjects randomized to BDET + MM, the overall number with normalized tympanograms and ETDQ-7 scores (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. This particular publication however is limited to the analysis of one of the randomized arm and doesn't allow comparison to a different treatment approach.

Meyer et al. (2018, included in Hayes report above) compared eustachian tube balloon dilation versus continued medical therapy for treating persistent ETD in a prospective, multicenter, randomized controlled trial. Sixty participants were randomized to either a balloon dilation group or a control group; after 6 weeks, the control participants had the option to undergo balloon dilation if symptoms persisted. No complications were reported in either study group. Among participants with abnormal baseline assessments, improvements in tympanogram type and tympanic membrane position were significantly better for

balloon dilation than control. Technical success was 100% and most procedures (72%) were completed in the office under local anesthesia. Improvements in the 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. Another limitation is the short-term duration (six weeks) of the randomized portion of the study. The author's concluded balloon dilation is a safe and effective treatment for persistent ETD. Based on improved ETDQ-7 scores, balloon dilation is superior to continued medical management for persistent ETD. Symptom improvement is durable through a minimum of 12 months and procedures are well tolerated in the office setting under local anesthesia.

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

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

Huisman et al. (2018) conducted a systematic review to evaluate the success of balloon dilation in adult patients with 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. All 15 included studies were case series. A total of 1,155 patients were treated with balloon dilation with follow up ranging from just after therapy to 50 months later. Conclusions suggested that balloon dilation of the Eustachian tube can be a helpful treatment in patients with Eustachian tube dysfunction, however placebo-controlled trials are still warranted. The findings are however limited by lack of comparison groups in these case series.

Randtrup 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. Nine case series with a total of 443 patients were included. 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.

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

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

The U.S. Food and Drug Administration (FDA) approved the XprESS ENT Dilation System under 510(K) (K163509) on April 5, 2017. The device is intended for use in dilating the cartilaginous portion of the Eustachian tube for treating persistent Eustachian tube dysfunction. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K163509. (Accessed April 23, 2021).

The U.S. Food and Drug Administration (FDA) approved the Acclarent Aera Eustachian Tube Balloon Dilation System (Acclarent Inc.) under 510(k) (K171761) on January 16, 2018. The device use is intended to dilate the Eustachian tube for treatment of persistent Eustachian tube dysfunction in patients ages 18 and older. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171761.pdf. (Accessed April 23, 2021)

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

The use of video fluoroscopy, 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 video fluoroscopy of the spine (also known as cineradiography) and digital motion X-ray. Video fluoroscopy 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 (video fluoroscopy), 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; Qu et al., 2019) 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).

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Code	Description
80145	Adalimumab
80230	Infliximab
80280	Vedolizumab
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)

Assa et al. (2019) performed a nonblinded, randomized controlled trial of 78 children to investigate whether proactive drug monitoring is associated with higher rates of clinical remission in pediatric patients with Crohn's disease (CD). The patients were randomly assigned to groups that received proactive monitoring (trough concentrations measured at weeks 4 and 8 and then every 8 weeks until week 72, n = 38) or reactive monitoring (physicians were informed of trough concentrations after loss of response, n = 40). In both groups, doses and intervals of adalimumab were adjusted to achieve trough concentrations of 5 μg/mL. The primary endpoint was sustained corticosteroid-free clinical remission at all visits (week 8 through week 72). The primary endpoint was achieved by 31 children (82%) in the proactive group and 19 children (48%) in the reactive group (P = .002). Sixteen patients in the proactive monitoring group (42%) achieved a composite outcome of sustained corticosteroid-free remission, C-reactive protein ≤0.5 mg/dL, and level of fecal calprotectin ≤150 μg/g compared with 5 patients in the reactive monitoring group (12%) (P = .003). By week 72 of treatment, 33 patients in the proactive monitoring group had received adalimumab intensification (87%) compared with 24 patients in the reactive monitoring group (60%) (P = .001). The authors concluded that proactive monitoring of adalimumab trough concentrations and adjustment of doses and intervals resulted in significantly higher rates corticosteroid-free clinical remission than reactive monitoring (measuring trough concentration after loss of response). Independent confirmation with larger sample sizes, longer follow-up, and a broader age range are necessary before these findings can be translated into routine clinical practice.

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

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

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

Karmiris et al. (2009) conducted an observational study of 168 patients with CD to assess the long-term clinical benefit of ADA in patients who failed to respond to infliximab (IFX), specifically focusing on the influence of trough serum concentration and antibodies against ADA on clinical outcome. Trough serum concentration and antibodies against ADA were measured at predefined time points using enzyme-linked immunosorbent assays. A total of 71% and 67% of patients responded by weeks 4 and 12, respectively; among them, 61.5% demonstrated sustained clinical benefit until the end of follow-up (median [interquartile range], 20.4 [11.7-30.0] months). Of the 156 patients receiving maintenance therapy, 102 (65.4%) had to step up to 40 mg weekly and 60 (38.5%) eventually stopped ADA therapy mainly due to loss of response. Significantly lower ADA trough serum concentrations were measured throughout the follow-up period in patients who discontinued therapy as compared with patients who stayed on ADA. Antibodies against ADA were present in 9.2% of the patients and affected trough serum concentration. Serious AEs occurred in 12% of the patients. The authors concluded that in this patient population, introduction of ADA after failure of IFX therapy resulted in a sustained clinical benefit in two thirds of patients during a median follow-up period of almost 2 years. Randomized controlled studies are needed to further evaluate these findings.

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)

Strik et al. (2021) conducted a randomized control, multicenter study to investigate the efficacy of dashboard driven Infliximab (IFX) dosing compared to standard dosing in a prospective trial for individuals. 80 individuals were randomly assigned to receive either dashboard driven IFX dosing (precision dosing group, PG) or continued IFX maintenance treatment without adjustments of the dose and/or treatment interval (conventional dosing group, CG). IFX is administered through intravenous infusions using weight-base (5 mg/kg) with an induction schedule at week 0, 2, 6 and followed by 8-weekly maintenance treatments with a goal to achieve and maintain remission in individuals with IBD. Recent studies showed that IFX serum concentrations ≥ 28 mcg/ml during the first 2 weeks of treatment and ≥15.0 mcg/ml between week 2 and 6 can be associated with higher mucosal healing rates in Ulcerative Colitis (UC). During maintenance treatment, an association was reported between IFX trough levels (TL) of 3 mcg/ml to correlate with improved clinical outcomes. After one year, 28/32 (88%) of individuals in the PG were in sustained clinical remission versus 25/39 (64%) of the CG individuals. The authors concluded that a higher percentage of individuals receiving dashboard guided IFX dosing maintained clinical remission during one year of follow-up compared to patients who did not receive proactive dose adjustments. In the majority of patients with TLs >3 mcg/ml dose reduction did not lead to clinical Loss of Response (LOR). However, a small proportion of patients may need higher target TLs depending on the specific treatment goal. Future trials should be performed to investigate dashboard guided dosing of IFX in individuals with IBD during induction treatment. Limitations of the study included lack of endoscopies performed due to the use of FCP as a reliable measurement of disease activity, use of drug-sensitive assay to detect glow ADA levels, but presence was clinically insignificant and a lower IFX target concentration which might not have been an optimal target.

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

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

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

Vande Casteele et al. (2013) identified that ATI may be transient and do not always lead to a worse clinical outcome. Sustained high levels of ATI, however, may lead to permanent loss of response. IFX trough and ATI levels were measured retrospectively in 1,232 consecutive serum samples of 90 (64 CD and 26 UC) patients, 57 with previously detected and 33 without antibodies with a new homogenous mobility shift assay. The results showed that patients with low IFX trough levels at week 14 are at risk for ATI formation and IFX discontinuation. The authors recommend that IFX trough levels be measured at week 14 and at the time of lack of response. When undetectable or low, ATI should be determined and if positive followed up on consecutive time points to rule out sustained ATI. Further studies are needed to validate these findings. In a prospective study (n=52), Paul et al. (2013) evaluated the efficacy of TDM in IFX treatment to predict mucosal healing (MH) in IBD. IFX trough levels, antibodies to IFX concentrations, C-reactive protein levels, and fecal calprotectin were measured before IFX optimization and at week 8. A proctosigmoidoscopy was performed on the day of first IFX optimization and at week 8 in all patients with ulcerative colitis (UC). MH was defined by fecal calprotectin <250 μg/g stools in CD and by an endoscopic Mayo score of 0 or 1 in UC. After IFX dose intensification, half of CD and UC patients achieved MH. Increase in IFX trough levels (called "delta IFX" in micrograms per milliliter) was associated with MH in both CD and UC (P = 0.001). A delta IFX >0.5 μg/mL was associated with MH (sensitivity [se], 0.88; specificity [sp], 0.77; P = 0.0001, area under the receiver operating characteristic curve, 0.89). On multivariate analysis, the only factor associated with MH after IFX optimization was a delta IFX >0.5 μg/mL (likelihood ratio = 2.02; 95% confidence interval, 1.01-4.08; P = 0.048) in patients with IBD. The authors concluded that TDM of IFX strongly predicts the likelihood of achieving MH following IFX dose intensification in both CD and UC. Further studies with larger patient populations are needed to establish the efficacy of TDM.

Afif et al. (2010) conducted a retrospective review of patients (n=155) with IBD who had human anti-chimeric antibodies (HACA) and IFX concentrations measured to determine whether the result affected clinical management. The main indications for

testing were loss of response to IFX (49%), partial response after initiation of infliximab (22%), and possible autoimmune/delayed hypersensitivity reaction (10%). HACAs were identified in 35 patients (23%) and therapeutic IFX concentrations in 51 patients (33%). In HACA-positive patients, change to another anti-tumor necrosis factor (TNF) agent was associated with a complete or partial response in 92% of patients, whereas dose escalation had a response of 17%. In patients with subtherapeutic IFX concentrations, dose escalation was associated with complete or partial clinical response in 86% of patients whereas changing to another anti-TNF agent had a response of 33%. Patients with clinical symptoms and therapeutic IFX concentrations were continued at the same dose 76% of the time and had no evidence of active inflammation by endoscopic/radiographic assessment 62% of the time. The authors' concluded that measurement of HACA and IFX concentration impacts management and is clinically useful. 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 µg/ml. The authors concluded that there is a significant difference between serum IFX levels in patients with IBD in remission, compared with those who relapse, and a trough threshold during maintenance > 2 µg/ml is associated with a greater probability of clinical remission and mucosal healing.

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

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 patient's 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 ≥ 23.2 mcg/ml at week 2 were associated with endoscopic remission at week 52 (OR 8.8 [95% CI 2.6-29.7], p < 0.001). VDZ concentrations during induction were associated with endoscopic remission at week 52. The authors concluded that interventional studies looking into improved efficacy with higher drug exposure are warranted.

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

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

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. $\alpha 4\beta 7$ 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 μg/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.

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 February 2021).

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

Fleischmann et al. (2021) compared the utility of the multi-biomarker disease activity (MBDA) score in assessing rheumatoid arthritis (RA) disease activity with that of the Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) and the Clinical Disease Activity Index (CDAI) in a multicenter, randomized, placebo-controlled trial of repository corticotropin injection (RCI) in patients with persistently active RA. Patients received 80 U of RCI twice weekly during a 12-week open-label period; those who achieved low disease activity at week 12 were randomly assigned to receive either 80 U of RCI or placebo twice weekly during a 12-week double-blind period. Changes in disease activity (measured by DAS28-ESR, CDAI, and MBDA) and

correlations between MBDA scores and both DAS28-ESR and CDAI scores were assessed. Changes from baseline in DAS28-ESR and CDAI scores suggested that RCI therapy led to clinically meaningful improvements in disease activity, but improvements from baseline in MBDA scores were below the minimally important difference threshold. For the DAS28-ESR and CDAI, correlations with total MBDA and individual component scores were generally low (r≤0.3), occasionally moderate (r>0.3 but <0.5). The investigators concluded that their results suggest overall MBDA scores are not sufficiently responsive for assessing RA disease activity after RCI therapy. These findings are consistent with those seen with other RA drugs and, although they are from a clinical trial, suggest the MBDA should not be a preferred disease activity measure in clinical practice.

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

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

Ma et al. (2020) used the multi-biomarker disease activity (MBDA) test to explore the role of biomarkers in predicting point remission and sustained remission. RA patients on > 6 months stable therapy in stable low disease activity (DAS28-ESR ≤ 3.2) were assessed every 3 months for 1 year. Baseline, intermittent (IR) and sustained (SR) remission were defined by DAS28-ESR, DAS28-CRP, simple disease activity index (SDAI), clinical disease activity index (CDAI) and ACR/EULAR Boolean criteria. Patients not fulfilling any remission criteria at baseline were classified as 'low disease activity state' (LDAS). Patients not fulfilling any remission criteria over 1 year were classified as 'persistent disease activity' (PDA). MBDA score was measured at baseline/3/6 months. The baseline MBDA score, the 6-month time-integrated MBDA score and MBDA biomarkers were used

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

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

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

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

Curtis et al. (2019a) compared the multi-biomarker disease activity (MBDA) score with the DAS28-CRP and CRP for predicting risk of radiographic progression in patients with rheumatoid arthritis. Published studies of the MBDA score and radiographic progression with ≥100 patients per cohort were evaluated. Patient-level data from studies having all three measures was pooled to: (1) determine a combined RR for radiographic progression in the high vs. not-high categories for each measure; and (2) compare the predictive ability of MBDA score vs. DAS28-CRP by comparing the rates of radiographic progression observed in subgroups created by cross-classifying the high and not-high categories of each measure. Five cohorts were identified for inclusion (total N=929). In each, radiographic progression was more frequent with increasing MBDA scores. Among the three cohorts with requisite data, PPVs were generally similar using categories of MBDA score, DAS28-CRP or CRP but NPVs were

greater for MBDA score (93-97%) than DAS28-CRP or CRP (77-87%). RRs for radiographic progression were greater when based on categories of MBDA score than DAS28-CRP or CRP and the combined RR was greater for MBDA score than DAS28-CRP or CRP. For patients cross-classified by MBDA score and DAS28-CRP, high vs. not-high MBDA score significantly predicted radiographic progression independently of DAS28-CRP. The authors concluded that high and not-high MBDA scores were associated with increased and low risk, respectively, for radiographic progression over one year. MBDA score was a better predictor of radiographic progression than DAS28-CRP or CRP. This study did not validate MBDA findings with improved treatment outcomes.

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

Johnson et al. (2018) performed a systematic review of the multi-biomarker disease activity (MBDA) and meta-analysis of the correlation between the MBDA and other rheumatoid arthritis (RA) disease activity measures. Twenty-two studies were identified in the systematic review, of which 8 (n=3,242 assays) reported correlations of the MBDA with RA disease activity measures. Pooling results from these eight studies in the meta-analysis, the MBDA demonstrated modest correlations with DAS28-CRP and DAS28-ESR with weaker correlations observed with SDAI, CDAI, and RAPID3. Correlations between change in MBDA and change in disease activity measures ranged from r = 0.53 (DAS28-ESR) to r = 0.26 (CDAI). The authors concluded that MBDA demonstrates moderate convergent validity with DAS28-CRP and DAS28-ESR, but weaker correlations with SDAI, CDAI, and RAPID3. While it appears to complement existing RA disease activity measures, further assessment of the MBDA's performance characteristics is warranted.

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

Bouman et al. (2017) evaluated the predictive value of the baseline multi-biomarker disease activity (MBDA) score in long-standing RA patients with low disease activity tapering TNF inhibitors (TNFi) for successful tapering or discontinuation, occurrence of flare and major flare, and radiographic progression. Dose REduction Strategies of Subcutaneous TNF inhibitors (Dutch Trial Register, NTR 3216) is an 18-month non-inferiority randomized controlled trial comparing tapering of TNFi until discontinuation or flaring with usual care (UC) in long-standing RA patients with stable low disease activity. MBDA scores were measured at baseline. Radiographs were scored at baseline and 18 months using the Sharp-van der Heijde score. The area under the receiver operating characteristic (AUROC) curve was used to analyze the capability of baseline MBDA score to

predict the above-mentioned outcomes. Serum samples and outcomes were available for 171 of 180 patients from Dose REduction Strategies of Subcutaneous TNF inhibitors (115 tapering; 56 UC). AUROC analyses showed that baseline MBDA score was not predictive for the above-mentioned clinical outcomes in the taper group, but did predict major flare in the UC group. Radiographic progression was minimal and was not predicted by MDBA score. The authors concluded baseline MBDA score was not predictive for successful tapering, discontinuation, flare, major flare or radiographic progression in RA patients who tapered TNFi.

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Code	Description
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).

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

Amengual, et al. (2017) reported that a task force of scientists at the International Congress regarding Antiphospholipid Antibodies. They recognized that phosphatidylserine-dependent antiprothrombin antibodies (aPS/PT) might contribute to a

better identification of APS. In the initial and replication studies, data was collected via retrospective cross-sectional review and multiple centers. Serum/plasma samples were tested for IgG aPS/PT at Inova Diagnostics (Inova) using two enzyme-linked immunosorbent assay (ELISA) kits. A replication study (five centers, five countries) was carried out afterwards. Results in the initial study reported a moderate agreement between the IgG aPS/PT Inova and MBL ELISA kits. IgG aPS/PT were more prevalent in APS patients (51%) than in those without (9%), OR 10.8, 95% CI (4.0-29.3). Sensitivity, specificity, positive (LR+) and negative (LR-) likelihood ratio of IgG aPS/PT for APS diagnosis were 51%, 91%, 5.9 and 0.5, respectively. In the replication study, a moderate/substantial agreement between the IgG aPS/PT results obtained with both ELISA kits was observed. IgG aPS/PT were more prevalent in APS patients (47%) than in those without (12%), OR 6.4, 95% CI (2.6-16). Sensitivity, specificity, LR + and LR- for APS diagnosis were 47%, 88%, 3.9 and 0.6, respectively. The authors concluded that IgG aPS/PT detection is an easily performed laboratory parameter that might contribute to a better and more complete identification of patients with APS.

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, βâ,,-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.

ACOG (2012, Reaffirmed 2017) criteria states that only three APS antibodies should be used to establish the diagnosis of APS: lupus anticoagulant, anticardiolipin, and anti-β_2-glycoprotein I. Other APS antibody tests are available, but not recommended, as these tests do little to improve the accuracy of APS diagnosis.

ASMR (2012) states that the most widely accepted diagnostic tests for APS are lupus anticoagulant, anticardiolipin antibody, and anti-β2 glycoprotein I. Other clinical assays for antiphospholipid antibodies are not standardized and the level of evidence does not warrant routine screening.

Reference(s)

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Code	Description
91113	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 May 28, 2021)

Hayes (2019) technology brief concluded that published evidence is insufficient to reflects very-low-quality evidence that is insufficient to draw conclusions regarding the clinical validity, clinical utility, and safety of CCE for screening for CRC in asymptomatic individuals at average risk of the disease. There is also uncertainty related to the accuracy of CCE versus CC and versus computed tomography colonography for diagnosis or surveillance in adults with signs or symptoms of colorectal cancer (CRC) and risk factors for the disease.

An ECRI report for PillCam Colon 2 capsule endoscopy system for detecting colon polyps indicates that the evidence is somewhat favorable. Despite the number of studies, there are limitations. Findings of a systematic review of diagnostic cohort studies are at risk of spectrum bias because authors looked at patients referred for routine screening and patients with positive fecal immunochemical test, who have a higher pretest probability. Therefore findings may not fully identify to either group. Longitudinal studies described diagnostic yields, which may not explain the clinical benefits because many polyps are benign and since colon cancers typically progress slowly which may be detected in subsequent colonoscopies. Larger more robust studies are needed comparing the PillCam Colon 2 to computed tomography colonography as a follow-up method for incomplete traditional colonoscopy. (ECRI, 2020).

Möllers et al. (2021) conducted an updated systematic review and meta-analysis evaluates the diagnostic accuracy of colon capsule endoscopy (CCE) compared to optical colonoscopy (OC) as the gold standard, adequacy of bowel preparation regimes and the patient perspective on diagnostic measures. A systematic literature search in PubMed, EMBASE and the Cochrane Register for Clinical Trials was performed. Results included 13 studies in the systematic review and up to 9 in the meta-analysis. CCE-2 had a high diagnostic accuracy for polyps ≥6mm (pooled sensitivities were 87 % with a 95% CI) and ≥10mm (pooled sensitivities were 87 % with a 95% CI). Most adverse events were mild and usually related to bowel preparation rather than the CCE examination itself and the rate of adequate bowel cleansing varied widely among studies. Limitations included a small number of studies in addition to a low number of new published clinical trials. This may be due to a possible new third generation capsule being introduced. Another limitation of the meta-analysis is the heterogeneity of specificities which does not allow for a clear conclusion on the patients perspective. Further research is needed with larger sample sizes in addition to findings on patient perspectives. (Authors Eliakim 2009, Hagel 2014, Kobaek-Larsen 2018, Morgan 2016, Rex 2015, Rondonotti 2014, Spada 2011 which were previously cited in this policy, are included in this systematic review).

Vuik et al. (2021) conducted a systematic review to provide an overview of the applicability of CCE as a CRC screening tool. A systematic search was conducted of literature published up to September 2020. Studies reporting on CRC screening by second-generation CCE in an average-risk screening population were included. Out of 582 studies, 13 were included, comprising 2485 patients. Eight studies used CCE as a filter test after a positive FIT result and five studies used CCE for the main screening. The polyp detection rate of CCE was 24 % - 74 %. For polyps > 6 mm, sensitivity of CCE was 79 % - 96 % and specificity was 66 % - 97 %. For polyps ≥ 10 mm, sensitivity of CCE was 84 % - 97 %, which was superior to computed tomographic colonography (CTC). The CRC detection rate for completed CCEs was 93 % (25/27). Bowel preparation was adequate in 70 % - 92 % of examinations, and completion rates varied from 57 % to 92 %, depending on the booster used. No CCE-related complications were defined. There are limitations that include the following; no meta-analysis could be performed due to the heterogeneity of the studies, the sensitivity could not be compared directly between the different studies because some studies performed per patient and others were per polyp, the differences between the diagnostic accuracy of CCE as a screening tool and that of a CCE filter text could not be distinguished, most videos were read by experienced readers and lastly, variations in polyps(size, type and location) were lacking. In spite of the diagnostic accuracy, further larger trials are

needed to determine the role of CRC population-based screening programs. (Authors Kobaek-Larsen 2018, Rex 2015, Rondonotti 2014 which were previously cited in this policy, are included in this systematic review).

Kjølhede et al. (2020) conducted a systematic review of the literature for studies investigating the diagnostic yield of second-generation CCE compared with standard colonoscopy. After a systematic literature search, 12 studies were included. Studies involved a total of 2199 patients, 1898 were included in analyses. The rate of patients with adequate bowel preparation varied from 40 % to 100 %. The rates of complete CCE transit varied from 57 % to 100 %. Our meta-analyses demonstrated that mean (95 % confidence interval) sensitivity, specificity, and diagnostic odds ratio were: 0.85 (0.73-0.92), 0.85 (0.70-0.93), and 30.5 (16.2-57.2), respectively, for polyps of any size; 0.87 (0.82-0.90), 0.95 (0.92-0.97), and 136.0 (70.6-262.1), respectively, for polyps ≥ 10 mm; and 0.87 (0.83-0.90), 0.88 (0.75-0.95), and 51.1 (19.8-131.8), respectively, for polyps ≥ 6 mm. No serious adverse events were reported for CCE. The completion rate requires improvement if this method was to be used for generalized screening. There is also a need on how to handle polyps between 6 and 9mm. While second generation CCE has a high sensitivity, larger studies are needed to address the incomplete CCE transit rate and issues with bowel preparation before CCE can be used as a standard screening utility. (Authors Eliakim 2009, Hagel 2014, Kobaek-Larsen 2018, Rex 2015, Spada 2011 which were previously cited in this policy, are included in this systematic review).

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 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.

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.

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 (≥6mm 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
93702	Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)

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

Clinical Evidence

Shah et al. (2021) conducted a systematic review and meta-analysis to evaluate the impact of monitoring techniques on the incidence of chronic breast cancer-related lymphedema (BCRL) among patients monitored by bioimpedance spectroscopy (BIS) and circumference measurement as compared to the expected incidence. A search, using predetermined terms, was conducted using PUBMED, CINAHL, and Google Scholar. BCRL incidence rates were classified by monitoring method: background (no standardized BIS or circumference assessments), BIS or circumference. A random-effects model was used to calculate a pooled annualized estimate of BCRL incidence while accounting for clinical and methodological heterogeneity. Known risk factors for BCRL were assessed via subgroup analyses. Sufficient data were available on the proportion of patients undergoing axillary lymph node dissection (ALND), sentinel lymph node biopsy (SLNB), and mastectomy. Other known risk factors not included due to a lack of data were body mass index (BMI), taxane chemotherapy, and regional nodal irradiation (RNI). Results were reported without transformation but were square root transformed. A total of 2,259 individual references were identified and screened and of those, 50 studies were included, representing 67,712 women. The annualized incidence of BCRL was 4.9% (95% CI: 4.3 to 5.5) for background studies (n=35), 1.5% (95% CI: 0.6 to 2.4) for BIS-monitored studies (n=7), and 7.7% (95% CI: 5.6 to 9.8) for circumference-monitored studies (n=11). The cumulative BCRL incidence rate in BIS-monitored patients was 3.1% as compared to 12.9% with background monitoring (69% reduction) and 17.0% with circumference-monitored patients (81% reduction). The authors concluded that monitoring with BIS allows for early intervention and thereby, significantly reduces the relative risk of chronic BCRL with a 69% and 81% reduction compared to the expected incidence and circumference-monitoring, respectively. They also stated that BIS should be considered for BCRL screening in order to detect subclinical BCRL and reduce rates of chronic BCRL, particularly in high-risk patients. However, a notable limitation of this study is that the investigators did not adjust for patient-related BCRL risk factors (e.g., BMI, taxane chemotherapy, and RNI) between the groups, and even after square-root transformation of the data, heterogeneity estimates remained high (>50%) as related to between-study differences as well as clinical risk factors e.g., ALND, and SLNB. Other differences between cohorts, such as level of BCRL and other confounding factors, significantly limit the conclusion that can be drawn from the indirect comparisons performed in this study. Additional studies evaluating the clinical utility of BIS as a monitoring tool for breast cancer-related lymphedema are still needed.

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

An ECRI report, SOZO Bioimpedance Spectroscopy for Diagnosing and Managing Lymphedema, states that there are too few data on important clinical outcomes and therefore, definitive conclusions cannot be made (2020).

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

Whitworth and Cooper (2018) conducted a single-center, case series analysis to evaluate the use of BIS to facilitate early detection and treatment of breast cancer-related lymphedema (BCRL). From April 2010 through November 2016, patients enrolled in the center's BCRL surveillance program and were followed prospectively using a standard protocol, which included BCRL education and preoperative and postoperative L-Dex U400 measurements. An elevated L-Dex score was defined as an increase of greater than 10 points from baseline. If an elevated was noted, the intervention was initiated, which consisted of complete decongestive physiotherapy (CDP) for 4 weeks and then, an L-Dex score re-evaluation. The study group was comprised of 596 participants (79.6% considered to be high risk), with a mean follow-up period of 17 months (range 0.2-80.4). Overall, 73 patients (12%) had an abnormal L-Dex score at some point during surveillance. Of the 73 patients, 55 (75%) patients' L-Dex scores returned to normal while 18 had L-Dex scores that did not return to baseline and required CDP. The authors concluded that the results (which represent the largest group of patients monitored in a structured program for early detection of BCRL using BIS) support the concept that prospective surveillance using BIS can detect subclinical BCRL, facilitating simple preemptive intervention and resulting in very low rates of chronic BCRL. Additional randomized controlled trials evaluating BIS to other detection modalities e.g., arm circumference measurement alone are underway and are still needed to determine the efficacy of BIS. This study was included in the Shah (2021) study.

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

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

Barrio et al (2015) 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 (2020). This study was included in the Shah (2021) study.

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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

The 2021 Global Initiative for Asthma (GINA) guidelines specific to children 5 years and younger state that, while no tests specifically and definitively diagnose asthma with certainty in children 5 years and younger, there are tests such as a therapeutic trial of treatment, allergy testing, and chest x-ray that may be useful adjuncts. Other tests such as lung function

testing, exhaled nitric oxide, and risk profiling tools are less frequently used. They state that, by 5 years of age, children are often capable of performing reproducible spirometry if coached by an experienced technician and with visual incentives.

An updated 2021 NICE asthma guideline addressing diagnosis and monitoring of suspected asthma states to treat symptoms based on observation and clinical judgement with regular follow up examinations for children under five. If the child is still symptomatic when they turn five, objective tests should be carried out. Asthma control should be monitored at each visit using spirometry or peak flow variability testing for all children aged five and older, young people and adults.

The American Thoracic Society (ATS) and European Respiratory Society (ERS) published an updated Technical Statement in 2019 of their 2005 technical standards for spirometry. The guideline indicates that, when the operator administering the spirometry has been specifically trained and is competent to work with young children, a child as young as 2.5 years old with normal cognitive and neuromotor function is able to perform acceptable spirometry when appropriate coaching is given. The guideline also indicates that one of the contraindications for performing spirometry is a patient's inability to understand the directions or the patient's unwillingness to follow the directions because the results will usually be submaximal. (Graham et al., 2019).

In a clinical guideline on the diagnostic evaluation of infants with recurrent or persistent wheezing, the 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).

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 into clinical care improves patient outcomes; such studies are urgently needed. They also stated that, 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 ERS, 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 National Heart, Lung, and Blood Institute (NHLBI) National Asthma Education and Prevention Program (NAEPP) Coordinating Committee Expert Panel Work Group 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).

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Code	Description
96999	Unlisted special dermatological service or procedure [when used to report multi-spectral digital skin lesion analysis]

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

Clinical Evidence

Farberg et al (2018) performed a meta-analysis to evaluate the impact of Multispectral digital skin lesion analysis (MSDSLA) on melanoma diagnosis, Multispectral digital skin lesion analysis (MSDSLA) is both sensitive and specific in the detection of malignant melanoma by dermatologists and non - dermatologists, and data have shown that MSDSLA can be a valuable tool in the evaluation of pigmented skin lesions (PSLs). This study aimed to aggregate data from 7 prior studies to provide a comprehensive overview and evaluate the consistency of the effects of MSDSLA when used in conjunction with clinical examination and dermoscopy to evaluate PSLs.

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 ((2021).

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National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Uveal Melanoma. v3 2020

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

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

Clinical Evidence

Robotic lower body exoskeletons (also referred to as reciprocating gait orthoses, powered orthoses, robotic orthoses, robotic gait assist devices, wearable exoskeletons, bionic legs, and computerized walking systems) are intended to assist some

patients with paraplegia as a result of spinal cord injury (SCI) to stand and move to improve their independence and QOL. Some early clinical trials have also evaluated versions of this technology in patients with other conditions including quadriplegia, stroke, multiple sclerosis, and Parkinson's disease.

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

Rodríguez-Fernández et al. (2021) completed a systematic review of 87 clinical studies that gathered information and measured the outcomes of wearable lower-limb exoskeletons while gait training overground for individuals with neuromuscular impairments. There were 25 exoskeletons included with only 6 containing FDA approval and/or commercially available. The results of the literature survey revealed that wearable exoskeletons have potential for a number of applications including early rehabilitation, promoting physical exercise, and carrying out daily living activities both at home and the community. Likewise wearable exoskeletons may improve mobility and independence in non-ambulatory people, and may reduce secondary health conditions related to sedentariness. However, the use of this technology is still limited by heavy and bulky devices, which require supervision and the use of walking aids. In addition, evidence supporting their benefits is still limited to short-intervention trials with few participants and diversity amongst clinical protocols. Wearable lower-limb exoskeletons for gait rehabilitation are still in the early stages of development and RCTs are needed to demonstrate their clinical efficacy.

A 2020 Hayes evidence analysis conducted on the ReWalk Personal System (ReWalk Robotics) for home use in patients with SCI included eight small prospective observational studies with less than 15 patients per study. While one author's conclusion suggest that ReWalk allows SCI patients to perform over-ground walking, there is an insufficient amount of peer-reviewed evidence and human clinical data to accurately evaluate the effectiveness and safety of the ReWalk Personal System in patients with SCI.

Awad et al. (2020) conducted a multi-site clinical trial that included 44 patients with post-stroke hemiparesis to study the safety, reliability and feasibility of the ReWalk Restore soft robotic exosuit for post-stroke gait rehabilitation. The patients trained for five days with the Restore soft exosuit and 16 patients required an assistive device (Ankle foot orthosis (AF0), cane, ankle brace, walker) on the treadmill and overground. During the five days of training, each visit consisted of 20 minutes of overground and 20 minutes treadmill walking practice while wearing the Restore exosuit motor at the waist as it transmitted mechanical forces to points located proximally attached around the calf and distally to a shoe insole. During the study eight patients dropped out for various reasons. Of the 36 patients that finished the study, they found the Restore soft exosuit clinically feasible, less than 10% had safety issues ranging from mild to severe, no falls, and the device malfunctioned for 11.6%. After five days of training 61% of the patients increased their maximum walking speed. The authors concluded that the ReStore soft exosuit is safe and reliable for using in post-stroke gait rehabilitation with the supervision of licensed physical therapist for support. These findings are motivation for further efficacy trials of soft robotic exosuits.

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

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.

Cheung et al. (2017) completed a systematic review and meta-analysis to investigate the effects of robot-assisted training on the recovery of people with SCI. The survey considered all randomized controlled trials (RCTs) and quasi-RCTs. Only studies involving people with SCIs were considered. Studies were included if the intervention involved robot-assisted training, including both upper limb robotic training and robot-assisted body-weight–supported treadmill training (BWSTT). 11 articles met the inclusion criteria. Four articles were identified as reporting investigations of the effect of robotic training on walking speed and walking endurance. Two studies provided sufficient data for analysis. Together they involved 158 participants. The robotic group showed no significant improvement in walking speed. The pooled mean difference (fixed effects model) was only .08 seconds. The robot-trained group showed improvements in endurance, which were highly significant in both statistical and practical terms. The pooled mean difference (fixed effects model) was 53.32m (95% CI, −73.15 to −33.48; $P \leq .00001$; $I^2 = 0\%$). 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.

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

Diagnosis Code	Description
F78.A1	SYNGAP1-related intellectual disability
F78.A9	Other genetic related intellectual disability
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
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

Diagnosis Code	Description
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, non - mosaicism (meiotic nondisjunction)
Q90.1	Trisomy 21, mosaicism (mitotic nondisjunction)
Q90.2	Trisomy 21, translocation
Q90.9	Down syndrome, unspecified
Q91.0	Trisomy 18, non - mosaicism (meiotic nondisjunction)
Q91.1	Trisomy 18, mosaicism (mitotic nondisjunction)
Q91.2	Trisomy 18, translocation
Q91.3	Trisomy 18, unspecified
Q91.4	Trisomy 13, non - mosaicism (meiotic nondisjunction)
Q91.5	Trisomy 13, mosaicism (mitotic nondisjunction)
Q91.6	Trisomy 13, translocation
Q91.7	Trisomy 13, unspecified
Q92.0	Whole chromosome trisomy, non - mosaicism (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, non - mosaicism (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

Diagnosis Code	Description
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 photo screening is proven and medically necessary for the following:

- As a mass screening instrument for children 1-5 years of age (ends on 6th birthday); or
- In individuals 6 years of age and older who are developmentally delayed and are unable or unwilling to cooperate with routine visual acuity screening

Instrument-based ocular photo screening 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 photo screening 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 photo screening 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 photo screens 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%. However, in the 6–11-month age group, the unreadable rate was 25.5%, the referral rate was 3.7%, and the overall positive-predictive value was 82.5%. 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 photo screening in children aged 1 year and older. They also note that photoscreens require some cooperation, and children <1 year of age have been previously shown to be difficult to screen and their photoscreens show a high unreadable rate.

In a cross-sectional study, Longmuir et al. (2010) reported on a cohort of preschool children screened by a photo screening program (using MTI PhotoScreener) over a 9-year period from a single, statewide vision screening effort. Children who failed the photo screening 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 photo screens to detect amblyopic risk factors at 9746 sites. Because of abnormal photo screen results, 6247 children (4.2%) were referred. The overall positive predictive value (PPV) of the MTI PhotoScreener was 94.2%. For those children <1 years of age, the unreadable rate was 21.2% and in those from 1 to 2 years of age group was 10.9%. The unreadable rate continued to decrease with increasing age, with an overall unreadable rate of 5.0%.

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 photo - screener 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 photo - screening and autorefraction, 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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Donahue S, Baker C. Committee on Practice and Ambulatory Medicine, Section on Ophthalmology, American Association of Certified Orthoptists, American Association for Pediatric Ophthalmology and Strabismus, American Academy of Ophthalmology. Visual system assessment in infants, children, and young adults by pediatricians. Pediatrics 2016b;137;1. Hayes, Inc. Medical Technology Directory Report. Photo screening for the Detection of Amblyopia Risk Factors in Children. Lansdale, PA: Hayes Inc.; October 2013. Updated September 2016. Archived November 2018.

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Longmuir SQ, Pfeifer W, Leon A, et al. Nine-year results of a volunteer lay network photo screening program of 147 809 children using a photo - screener in Iowa. Ophthalmology. 2010 Oct;117(10):1869-75.

U.S. Preventive Services Task Force (USPSTF). Final Recommendation Statement: Visual impairment in children ages 6 months to 5 years: screening. U.S. Preventive Services Task Force. September 2017.

Code	Description
B4105	In-line cartridge containing digestive enzyme(s) for enteral feeding, each

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 6, 2021).

An ECRI product brief, Relizorb Immobilized Lipase Cartridge for Facilitating Absorption of Enteral Formula Fats in Adults, indicates that the evidence is inconclusive. Relizorb's safety and efficacy in adults could not be determined due to the clinical trials pooling outcomes of adults and children and therefore, the findings may not generalize to either patient group individually. In addition, the trials used serum fatty acid levels as the primary efficacy outcome, which is insufficient to access nutritional status and risk of adverse events (ECRI, 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 2021 position paper on the medical management of chronic pancreatitis in children, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee states that the role of an organized lipid matrix and the efficacy of enteral in-line feeding cartridges in the management of exocrine pancreatic insufficiency is an area of much needed research. They also state that for patients with Cystic Fibrosis (CF)-associated exocrine pancreatic insufficiency (EPI), a high-fat diet is recommended, with >35% of total calories from fat, in conjunction with pancreatic enzyme replacement therapy (PERT), with routine monitoring for pubertal delay. Patients requiring continuous or nighttime enteral nutrition, inline lipase cartridges may be considered (Freeman et al., 2021).

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)

ECRI Institute. Custom Product Brief - Relizorb Immobilized Lipase Cartridge for Facilitating Absorption of Enteral Formula Fats in Adults. Plymouth Meeting, PA. June 2019.

Freedman S, Orenstein D, Black P, et al. Increased fat absorption from enteral formula through an in-line digestive cartridge in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr. 2017 Jul;65(1):97-101.

Freeman AJ, Maqbool A, Bellin MD, et al. Medical Management of Chronic Pancreatitis in Children: A Position Paper by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee. J Pediatr Gastroenterol Nutr. 2021 Feb 1;72(2):324-340.

Schwarzenberg SJ, Hempstead SE, McDonald CM, et al. Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines. J Cyst Fibros. 2016 Nov;15(6):724-735.

Stevens J, Wyatt C, Brown P, et al. Absorption and Safety with Sustained Use of RELiZORB Evaluation (ASSURE) Study in Patients With Cystic Fibrosis Receiving Enteral Feeding. J Pediatr Gastroenterol Nutr. 2018 Oct; 67(4):527-532.

Code	Description
G0429	Dermal Filler injection(s) for the treatment of facial lipodystrophy syndrome (LDS) (e.g., as a result of highly active antiretroviral therapy)

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

Human Immunodeficiency Virus

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

On December 22, 2006, the FDA approved Radiesse, an injectable (under the skin) implant to restore or correct signs of facial lipidatrophy, or fat loss, in people with human immunodeficiency virus (HIV). For additional information, refer to the following website: https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050052b.pdf (Accessed April 22, 2021)

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 22, 2021).

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

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

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

Vocal Fold Insufficiency

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

On March 7, 2007, the U.S. Food and Drug Administration (FDA) approved the Radiesse Laryngeal Implant, a sterile, non-pyrogenic injectable material consisting of calcium hydroxylapatite (CaHA) suspended in an aqueous formulation of USP grade pharmaceutical excipients consisting of sterile water, glycerin, and sodium carboxymethylcellulose, stabilized with a phosphate buffer. It is indicated for vocal fold medialization and vocal fold insufficiency that may be improved by injection of a soft tissue hulking agent. For additional information refer to the following: https://www.accessdata.fda.gov/cdrh_docs/pdf7/K070090.pdf (Accessed April 22, 2021).

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

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

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

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

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

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

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

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

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

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

Clinical Evidence

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

A Hayes Clinical Research Response (2021) did not identify any clinical studies, position statements or clinical practice guidelines addressing the PureWick system.

Eckert et al. (2020) conducted a quality improvement, single center study comparing the use of a female external urinary collection (FEUC) device with wall suction as an alternative to indwelling catheter (IDC). The outcomes were to determine if FEUCs reduced the risk of catheter-associated urinary tract infection (CAUTI) rates. The FEUC device was trialed September 2015 through December 2015, using 60 FEUC devices on 30 female patients. Data collection on these patients for one year period after use of FEUC. In 2015, before the use of the FEUC device, the baseline female IDC utilization rate was 31.7% (7181 IDC device-days/22,656 patient stay days) and the female CAUTI rate was 1.11 (8 cases/7181 IDC device-days) per 1000 stay days. After implementing use of the FEUC device both IDC utilization and CAUTI rates declined. In 2016, the IDC utilization rate was 29.7% (P = .000) and the CAUTI rate was 0% (P =.005). In 2017 there was a reduction in IDC utilization rates of 26% (P = .000) but the CAUTI rate of 0.90% was not significantly different from the prior year rate (P = .726). The authors concluded they need to continue to prioritize the use of FEUCs over IDCS. Limitations of this study include lack of consistent sample size, short follow-up and lack of equal comparisons of FEUC and IDC patient usage.

Warren et al. (2020) conducted a retrospective study analyzing the impact of a hospital-wide implementation of an external female urinary catheter. The investigators compared a 12-month period before and after device implementation to assess the impact on indwelling urinary catheter utilization and CAUTI rate. The study included female patients with a combined patient stay of 220,000 days,10,000 external urinary catheter days and 33,000 indwelling urinary catheter days. The authors concluded that an increase in external female urinary catheter utilization coincided with a decline in patient CAUTI rate, but only in intensive care units (ICUs). Limitations of this study included lack of documentation regarding the catheter type used by the patients and lack of direct correlation of CAUTI decline with use of FEUCs, especially outside of the ICU setting. Further studies are needed to correlate usage of FEUCs versus IDCs and the impact on the CAUTI rate.

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

A 2019 ECRI Product Brief states that the evidence on the PureWick system is inconclusive due to a lack of published relevant clinical studies.

The PureWick™ (C.R. Bard, Inc.) female external catheter and the PureWick™ urine collection system, used for the non-invasive, non-sterile collection of urine, received FDA 510(k) approval (K062061) on October 5, 2006. Product code NZU. Additional information available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K062061

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

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

Clinical Evidence

External upper limb tremor stimulators of the peripheral nerves of the wrist (e.g., the Cala Health, Inc., Cala Trio™) deliver non-invasive electrical stimulation to the peripheral nerves of the wrist (Cala Health, Inc. Cala Trio website).

Isaacson et al. (2020) performed a prospective, multi-center, open-label, post-clearance, single-arm study to evaluate the efficacy and safety of Transcutaneous Afferent Patterned Stimulation (TAPS) delivered by an FDA-cleared wrist-worn device (Cala Health, Inc.). A total of 263 subjects were enrolled at 26 study sites. Of those, 205 subjects completed the study. Subjects were instructed to use the wrist-worn device for 40 minutes, twice daily, for three months. The co-primary efficacy endpoints were clinician-rated Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) and (patient-rated Bain & Findley Activities of Daily Living (BF-ADL) dominant hand scores. These endpoints were considered met ($p \ll 0.0001$), with 62% (TETRAS) and 68% (BF-ADL) of "severe" or "moderate" subjects improving to "mild' or 'slight". Wrist-worn accelerometer recordings of tremor power showed that 92% of subjects improved and 54% of subjects experienced ≥50% improvement. Clinical Global Impression (CGI-I) scores showed that clinicians reported tremor improvement in 68% of patients. Patient Global Impression (PGI-I) scores showed 60% of subjects self-reported tremor improvement. Quality of Life in Essential Tremor (QUEST) surveys completed by subjects also showed improvement ($p = 0.0019$). Device-related adverse events occurred in 18% of subjects and included wrist discomfort, skin irritation, and pain. There were no device-related serious adverse events reported. The authors concluded that non-invasive neuromodulation therapy used at home over three months is safe and effective to treat patients with essential tremor (ET). This study had some limitations including the open-label, single-arm design; clinical raters were unblinded; while there were statistically significant reductions across the TETRAS and BF-ADL ratings, the extent of those reductions varied; and 58 subjects did not complete the study.

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

The U.S. Food and Drug Administration (FDA) cleared the Cala Health, Inc. Cala Trio device under its 510(k) premarket notification process as substantially equivalent to predicate devices. For additional information see the following: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K182706. (Accessed September 7, 2021)

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

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. (2020) in an experimental study evaluated the Unity elevated vacuum system on gait in high functioning individuals with transtibial amputation, while the vacuum was active and inactive. Twelve unilateral transtibial amputees were fit with the Ossur elevated vacuum suspension system (Unity) and Pro-flex XC foot. Temporal-spatial, kinematics, and kinetics were studied during level walking to understand the effect of the elevated vacuum, separate trials were completed with the vacuum active or inactive. Significant differences were found between vacuum conditions for some temporal-spatial gait parameters, but the differences were small and may not be clinically important. Changes between vacuum conditions on most kinetic and kinematic gait parameters were also low. Step length symmetry between intact and prosthetic limbs improved with active elevated vacuum. Limitations included four weeks of acclimations which was provided for the active Unity system but no acclimatation period was provided to the group with the suction system that was inactive. The socket fit may have varied if the system was off for a longer time. This study also included high functioning users (K3, K4) which may have affected results. The author noted that gait parameters were expected to change when walking on a level treadmill with the elevated vacuum system compared to walking with the vacuum off. While some of these gait parameters were statistically different, the differences were small and not clinically significant. Only step length symmetry between prosthetic and intact limbs improved when walking with the elevated vacuum system. Future research including added surfaces encountered in everyday living, such as slopes, are also needed to better determine the effects of active vacuum on gait parameters.

Young and Loshak (2020) in a review evaluated the clinical effectiveness of prosthetics with elevated vacuum suspension systems versus standard prosthetic systems for adults with amputation. Three relevant systematic reviews, five randomized controlled trials, and five non-randomized studies were identified regarding the clinical effectiveness of elevated vacuum suspension systems for adults (≥18 years of age) with amputation. While some of the identified literature indicated that elevated vacuum suspension systems may improve balance, physical capability, prosthetic pitoning, fear and risk of falling, socket comfort, residual limb volume, and skin health compared to non-vacuum suspension systems, there was variation in the results (i.e., in some instances studies did not detect statistically significant differences between vacuum and non-vacuum groups or reported significant improvements favoring non-vacuum suspension systems [e.g., the authors of one study observed that participants were less active and had decreased ambulation while using a VASS compared to pin-lock sockets]). There were no statistically noteworthy variances in measures of quality of life between users of VASS and non-VASS devices. The vagueness of these findings was reflected in the included evidence-based guidelines, Stevens et al. provided some support for vacuum-assisted devices; however, they recommended that vacuum-assisted suspension sockets are not universally indicated. The VA/DoD guidelines stated that there was insufficient evidence to recommend for or against any suspension system. Limitations included the following, limited number of participants, risk of performance bias due to a lack of blinding of participants and study personnel. The limitations affect the interpretation of the results. Additional research studying the clinical effectiveness of elevated vacuum suspension systems, especially with larger sample sizes and report long-term health outcomes is needed to support this system.

Gholizadeh et al. (2018) conducted a review to see if elevated vacuum suspension could benefit transtibial amputee gait for slope walking. Twelve people with unilateral transtibial amputation were fitted with the Unity elevated vacuum suspension system (Össur) and Pro-Flex XC foot. 3D motion analysis was performed for 7° incline, 7° decline, and level walking within a CAREN-Extended system virtual Park environment. Randomized and blinded walking trials were completed with the vacuum active or inactive. Findings indicated that active vacuum improved gait symmetry for incline walking, but the other differences between vacuum conditions were small and may not be clinically significant. Therefore, the Unity system approach for elevated vacuum suspension had a positive, but small, effect on walking and should maintain appropriate walking even with vacuum failure, until limb volume changes adversely affect socket fit (i.e., elevated vacuum helps control limb volume fluctuations over time).

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); whiles 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

pre - study 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.
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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

Custom craniofacial implants are used to repair skull bone defects after trauma or surgery. Cranial implants must fit precisely within all borders of a defect to restrict movement and successfully restore natural cranial shape. Currently, cranial implants are

designed and produced by third-party suppliers, which can be time consuming and expensive. Recent advances in additive manufacturing (3-D) make point of care fabrication of personalized implants feasible. (Li et al., 2021)

On February 18, 2013, Oxford Performance Materials (OPM) received 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 6, 2021).

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 6, 2021).

Maricevich et al. (2019) evaluated the symptomatic and aesthetic improvement of patients with cranial defects secondary to decompressive craniectomies after cranial reconstruction with customized polymethyl methacrylate (PMMA) prostheses produced by 3D impression molds. This prospective study included 63 patients who underwent cranioplasties that were performed using customized PMMA prosthesis produced by 3D impression molds. All patients underwent a functional and aesthetic evaluation questionnaire in the preoperative period and in the sixth postoperative month. The mean area of the defect was 147 cm^2. The mean postoperative follow-up of the patients was 21 months, ranging from 6 to 33 months. Fifty-five patients attended the 6-month postoperative consultation. All patients presented symptomatic improvement after reconstruction of the skull. The infection rate was 3.2%, 4.8% of extrusion, 1.6% of prosthesis fracture, 7.9% of extradural hematoma, 17.4% of reoperation, 5% of wound dehiscence, and 4.8% of removal of the prosthesis. The authors concluded that cranioplasty, with a customized PMMA prosthesis, improved the symptoms and aesthetic appearance of all operated patients. The use of prototypes to customize cranial prostheses facilitated the operative technique and allowed the recovery of a cranial contour very close to normal. Limitations of this study include its case series design, the use of simple direct questions by the team that performed the cranioplasties to assess cognitive, motor, and QOL rather than the use of validated assessment tools, and the short follow-up period. Additional prospective, randomized controlled trials with longer follow-up are needed to examine the safety and efficacy of 3D printed cranial implants.

Francaviglia et al. (2017) conducted a case series analysis to present their preliminary experience with a custom-made cranioplasty, using electron beam melting (EBM) technology, in ten patients. EBM is a new sintering method for shaping titanium powder directly in 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 its design, a small population and short follow-up period. Additional prospective studies with comparison groups, larger sample sizes and longer follow-up periods are needed.

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

advanced, it is becoming possible to manufacture custom-made 3D titanium implants for skull reconstruction. This study was limited by a small study population, lack of a comparison group, and short follow-up time.

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

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Code	Description
L8701	Powered upper extremity range of motion assist device, elbow, wrist, hand with single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated
L8702	Powered upper extremity range of motion assist device, elbow, wrist, hand, finger, single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated

The use of the upper limb orthotic known as the MyoPro™ is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

MyoPro™ is a powered orthosis (brace) designed to help restore function to arms and hands paralyzed or weakened by CVA stroke, brachial plexus injury, cerebral palsy or other neurological or neuromuscular disease or injury. It works by reading the faint nerve signals (myoelectric signals) from the surface of the skin (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 myoelectrical 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, 2020).

In a focused report on the use of the MyoPro™ Orthosis for improving upper extremity function and elbow range of motion in patients with infantile spastic cerebral palsy (CP), Hayes (2020) was unable to locate any abstracts of peer-reviewed literature in

the PubMed and Embase databases that were published in the last 20 years. The report concluded that the data is insufficient to evaluate the MyoPro™ Orthosis for use for this clinical indication.

A 2020 ECRI Custom Product Brief identified three case series with 28 participants examining the device MyoPro-G, as there were no published studies available on MyoPro2 devices. The report concluded that the evidence is insufficient to determine how well the MyoPro-G works or how it compares with alternative devices intended to improve arm and hand impairment. Controlled studies with larger sample sizes are needed to assess efficacy, provide longer-term results, assess home use and study use of the device in different clinical condition patient populations (ECRI, 2020) (Authors McCabe et al. (2019) and Peters et al. (2017)) which were previously cited in this policy are included in this study).

A single-blinded randomized controlled trial was conducted by Page et al. (2020) to compare the efficacy of myoelectric bracing (Myomo) and/or repetitive task-specific practice (RTP) in moderately impaired stroke patients. There were 34 participants all exhibiting chronic, stable, moderate upper extremity impairment. Each participant was selected randomly for therapy consisting of Myomo combined with RTP, RTP only or Myomo therapy only. All three groups were supervised by a therapist and were administered therapies targeting their hemiparetic upper extremities. The primary outcome measure was the upper extremity section of the Fugl-Meyer Impairment Scale (FM); the secondary measurement was the Arm Motor Activity Test (AMAT). The therapies were one hour in duration, occurring 3 days/week for eight weeks. Upon completion of the study, all three groups showed a Fugl-Meyer (FM) score increase of +2 points. On the secondary outcomes, the two groups that included Myomo had the same FM score increase of +1 and the group with RTP only had a FM score increase of +2.6. The authors concluded that outcomes in the group with Myomo and RTP were comparable to the RTP only group. Several limitations were identified by the authors, the device tested in the trial did not always work as expected and was somewhat cumbersome. Future studies would be strengthened by larger sample sizes.

A 2020 Hayes report focused on the use of MyoPro™ Orthosis for the treatment of stroke-induced upper extremity paresis or paralysis. Four abstracts were identified, including 2 randomized controlled trials, 1 prospective comparative study, and 1 retrospective uncontrolled trial. The review concluded that there is insufficient published evidence to assess the efficacy and impact on health outcomes or patient management associated with the use of MyoPro™ Orthosis for stroke induced upper-extremity paralysis or paresis (Hayes, 2020a).

A single-blinded randomized controlled pilot study was conducted by Park et al. (2020) to evaluate the differences in the clinical and kinematic outcomes between active-assistive and passive robotic rehabilitation among stroke survivors. Twenty stroke patients with upper extremity dysfunction were randomly assigned to the active-assistive robotic intervention (using an exoskeletal robot with robotic actuators; ACT) group or passive robotic intervention (using a passive exoskeletal robot without robotic actuators; PSV) group. Both groups completed 20 sessions of 30-minute robotic intervention, five days a week for four weeks. Each group received 30 minutes of conventional therapy of the affected upper limb five days a week for four weeks as well. In both the groups the Wolf Motor Function Test (WMFT) score and -time improved. The PSV group showed better improvement in participation and smoothness than the ACT group. The ACT group exhibited better improvement in mean speed. The authors concluded there was minimal measurable difference in outcomes such as improvement of patient impairments and activity between the ACT group and PSV group. For usability, the patients in the ACT group complained the device was “too heavy” and “bulky”. Further studies with larger populations and longer intervention periods are needed.

Willigenburg and colleagues (2017) examined the efficacy of an 8-week regimen combining repetitive task-specific practice (RTP) with a myoelectric brace (RTP+Myomo) on paretic upper extremity (UE; use in valued activities, perceived recovery, and reaching kinematics) in 12 patients. Seven were administered RTP+Myomo therapy, and 5 were administered RTP only. Both groups participated in individualized, 45-min therapy sessions occurring 3 days/week over an 8-week period. The arm, hand ability, activities of daily living, and perceptions of recovery subscales of the Stroke Impact Scale (SIS), as well as UE reaching kinematics, assessed before and after the intervention. The RTP+Myomo group showed greater improvements on all SIS subscales. Patients in the RTP-only group showed a greater increase in hand velocity in the reach up task, but no changes were observed in the range of shoulder flexion or elbow extension during reaching. None of the changes in kinematic outcome measures significantly correlated with any of the changes in SIS subscales. The authors concluded that RTP integrating myoelectric bracing may be more beneficial than RTP only in improving self-reported function and perceptions of overall recovery. The authors observed no changes in the range of elbow extension, and no relationship between self-reported improvements and changes in reaching kinematics. This study is limited by small sample size and short follow-up period.

A randomized controlled pilot trial was conducted by Page et al (2013). to compare the efficacy of a RTP in a person with chronic, moderate upper extremity impairment A total of 16 people was utilized (7 males; mean age 57.0 ± 11.02 years; mean time post stroke 75.0 ± 87.63 months; 5 left-sided strokes) all exhibiting chronic, stable, moderate upper extremity impairment. Each person was given an RTP in which they participated in valued, functional tasks using their paretic upper extremities. Both groups were supervised by a therapist and were administered therapies targeting their paretic upper extremities that were 30 minutes in duration, occurring 3 days/week for eight weeks. One group participated in RTPs entirely while wearing the portable robotic, while the other performed the same activity regimen manually. Upon completion of the study itself each group showed the same Fugl-Meyer score increases of ≈2.1 points; the group using robotics exhibited larger score changes on all but one of the Canadian Occupational Performance Measure and Stroke Impact Scale subscales, including a 12.5-point increase on the Stroke Impact Scale recovery subscale. It was noted that the finding suggest that therapist supervised task- specific practice with an integrated robotic device could be as efficacious as manual practice in some subjects with moderate upper extremity impairment. Additional studies are needed as there is still insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

The U.S. Food and Drug Administration (FDA) cleared the Myomo e100 for marketing through the 510(k) process in April 2007 (K062631). Myomo e100 is a Class II device with Product Code OAL. The indications for use are as follows:

- The Myomo e100 is indicated for use by stroke patients undergoing rehabilitation to facilitate the following:
  - Stroke rehabilitation by muscle re-education
  - Maintaining or increasing range of motion

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Code	Description
P2031	Hair analysis (excluding arsenic)

Hair analysis is unproven and not medically necessary for evaluating any disorder or condition due to insufficient evidence of safety and/or efficacy.

Clinical Evidence

Hair analysis has been proposed as an aid in the diagnosis of several conditions including 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).

Hardy et al. (2021) conducted a pilot cohort study to compare the information obtained from the analysis of urine versus hair for exposure to pesticides. In ninety-three pregnant women, one urine and one hair sample were collected simultaneously. Samples were analyzed using GC-MS/MS analytical methods allowing for the detection of both parent pesticides and metabolites and designed to be as similar as possible between urine and hair for reliable inter-matrix comparison. Fifty-two biomarkers of exposure were targeted, including parents and metabolites of organochlorines, organophosphates, pyrethroids, carbamates, phenylpyrazoles and other pesticides. The results showed the number of different compounds detected ranged from 16 to 27 (median = 22) in hair, and from 3 to 22 (median = 12) in urine. In hair, 24 compounds were found in > 40% of the individuals, whereas only 12 compounds presented the same frequency of detection in urine. Among the chemicals detected in > 80% of both hair and urine samples, only one (pentachlorophenol) showed a signification correlation between hair and urine concentrations. The authors concluded that these results highlight multiple exposures and suggest that hair provides more comprehensive information on pesticide exposure than urine analysis and supports the relevance of hair analysis in future epidemiological studies investigating association between exposure and adverse health effects.

In a 2019 systematic review and meta-analysis, Huang et al. sought to identify whether magnesium levels are lower in children with ADHD. A total of twelve studies were included. The results showed magnesium levels in the hair of children diagnosed with ADHD were significantly lower than those in controls (k = 4, Hedges' g = -0.713, 95% CI = -1.359 to -0.067, p = .031). In this meta-analysis, the authors found that children diagnosed with ADHD have lower serum and hair magnesium levels than children without ADHD. The authors concluded that further study is needed to investigate the behavioral influence on ADHD due to lower magnesium levels, the association between brain and serum magnesium levels, and the effects brought about by larger longitudinal cohort studies.

Khajuria et al. (2018) conducted a review designed to investigate the efficacy of chromatography for detection of drugs of abuse in hair. A comprehensive review of articles from last two decades on hair analyses via PubMed and similar resources was performed. The results showed a hair sample may be chosen over traditional biological samples such blood, urine, saliva or tissues due to its inimitable ability to provide a longer time frame for drug detection. Its collection is almost non-invasive, less cumbersome and does not involve any specialized training/expertise. Recent advances in analytical technology have resulted in better sensitivity, reproducibility and accuracy, thus providing a new arena of scientific understanding and test interpretation. The authors concluded that although recent studies have yielded insights into drug binding and drug incorporation in hair, the major challenge in hair analysis lies in the interpretation of results, which may be affected by external contamination and thus lead to false positives. Therefore, there is a need for more sensitive and selective analysis methods to be developed.

Mikulewicz et al. (2013) completed a systematic review to investigate the reference values of minerals in human hair. The five studies that met inclusion criteria reported reference ranges for the content of elements in hair: macro elements, microelements, toxic elements and other elements. Reference ranges were elaborated for different populations in the years 2000–2012. The analytical methodology differed, in particular sample preparation, digestion and analysis, as a result, the levels of hair minerals reported as reference values varied. The authors concluded standardization of procedures and detailed methodology are needed to validate hair mineral analysis. Only then it would be possible to provide meaningful reference ranges and take advantage of the potential that lies in Hair Mineral Analysis (HMA) as a medical diagnostic technique.

Wolowiec et al. (2013) conducted a systematic review on the relation between the mineral composition of hair and physical or mental disorders. Sixty-six studies were included in the review. Most of the studies reported that there exists a correlation between deficiency or excess of some elements in hair and occurrence of some diseases, such as: autism, cancer, hypertension, myocardial infarction, kidney disease and diabetes mellitus. However, not all results were consistent. The authors concluded that there is a need to standardize sample preparation procedures, in particular washing and mineralization methods.

A 2011 guideline for food allergy in children and young people from the National Institute for Health and Care Excellence (NICE) recommends against the use of hair analysis in the diagnosis of food allergy.

In their 2010 guidelines, the National Institute of Allergy and Infectious Diseases (NIAID) states that hair analysis for food allergies is non-standard and unproven. Additionally, the utility of these tests has not been validated for the diagnosis of FA and may result in false positive or false negative diagnoses.

In a 2014 joint practice parameter by the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), and the Joint Council of Allergy, Asthma & Immunology (JCAAI), hair analysis is listed as an unproven test for the evaluation of food allergies.

A practice parameter from the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society states that there is insufficient evidence to support the use of hair analysis for the diagnosis and evaluation of autism (Filipek et al., 2000. Reaffirmed August 2014).

In 2013, the American Society of Addiction Medicine (ASAM) published a document titled, Drug Testing: A White Paper of the American Society of Addiction Medicine. This document indicates that hair sample benefits include difficulty in falsifying sampling and a longer period of detection. However, the ASAM noted that recent exposures cannot be detected in hair samples, and hair coloring can cause modest degradation of drugs in the matrix. The ASAM notes that one distinct disadvantage to hair testing is that some drug classes (e.g., benzodiazepines) are poorly detected in hair.

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Policy History/Revision Information

Date	
04/01/2022	Coverage Rationale *Cardiac Contractility Modulation using an Implantable Device (CPT codes 0408T, 0409T, 0410T, 0412T, 0413T, 0414T, 0415T, 0416T, 0417T, 0418T, and K1030)* • Updated list of applicable HCPCS codes to reflect quarterly edits; added K1030 Supporting Information • Archived previous policy version 2022T0535_KK

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, please 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).

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