# Omnibus Codes (for North Carolina Only)

**Policy Number**: CSNCT0535.06
**Effective Date**: April 1, 2024

Instructions for Use

**Table of Contents** **Page**



| Related Policies |
|---|
| None |

## Application

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

## Coverage Summary

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

| Code | Description | Conclusion |
|---|---|---|
| 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 |
| 0075T | Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; initial vessel | Unproven |
| 0076T | Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; each additional vessel (List separately in addition to code for primary procedure) | Unproven |
| 0100T | Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy | Unproven |
| 0163U | Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins [teratocarcinoma derived growth factor-1 (TDGF-1, Cripto-1), carcinoembryonic antigen (CEA), extracellular matrix protein (ECM)], with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas | Unproven |
| 0174T | Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed concurrent with primary interpretation (List separately in addition to code for primary procedure) | Unproven |

| Code | Description | Conclusion |
|---|---|---|
| 0175T | Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed remote from primary interpretation | Unproven |
| 0207T | Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral | Unproven |
| 0208T | Pure tone audiometry (threshold), automated; air only | Unproven |
| 0209T | Pure tone audiometry (threshold), automated; air and bone | Unproven |
| 0210T | Speech audiometry threshold, automated | Unproven |
| 0211T | Speech audiometry threshold, automated; with speech recognition | Unproven |
| 0212T | Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated | Unproven |
| 0234T | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery | Unproven |
| 0235T | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel | Unproven |
| 0236T | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta | Unproven |
| 0237T | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel | 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 | Unproven |

| Code | Description | Conclusion |
|---|---|---|
| | 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 | 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 |
| 0333T | Visual evoked potential, screening of visual acuity, automated, with report | Unproven |
| 0335T | Insertion of sinus tarsi implant | Unproven |
| 0338T | Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral | Unproven |
| 0339T | Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral | Unproven |
| 0347T | Placement of interstitial device(s) in bone for radiostereometric analysis (RSA) | Unproven |
| 0348T | Radiologic examination, radiostereometric analysis (RSA); spine, (includes cervical, thoracic and lumbosacral, when performed) | Unproven |
| 0349T | Radiologic examination, radiostereometric analysis (RSA); upper extremity(ies), (includes shoulder, elbow, and wrist, when performed) | Unproven |
| 0350T | Radiologic examination, radiostereometric analysis (RSA); lower extremity(ies), (includes hip, proximal femur, knee, and ankle, when performed) | 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 |

| Code | Description | Conclusion |
|---|---|---|
| 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 |
| 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 |

| Code | Description | Conclusion |
|---|---|---|
| 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 |
| 0485T | Optical coherence tomography (OCT) of middle ear, with interpretation and report; unilateral | Unproven |
| 0486T | Optical coherence tomography (OCT) of middle ear, with interpretation and report; bilateral | Unproven |
| 0506T | Macular pigment optical density measurement by heterochromatic flicker photometry, unilateral or bilateral, with interpretation and report | Unproven |
| 0507T | Near-infrared dual imaging (i.e., simultaneous reflective and trans-illuminated light) of meibomian glands, unilateral or bilateral, with interpretation and report | Unproven |
| 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; both components of pulse generator (battery and transmitter) only | Unproven |
| 0518T | Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; battery component only | Unproven |
| 0519T | Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; both components (battery and transmitter) | Unproven |
| 0520T | Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only | 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 | Unproven |

| Code | Description | Conclusion |
|---|---|---|
| | supervision and interpretation; complete system (electrode and implantable monitor) | |
| 0526T | Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; electrode only | Unproven |
| 0527T | Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; implantable monitor only | Unproven |
| 0528T | Programming device evaluation (in person) of intracardiac ischemia monitoring system with iterative adjustment of programmed values, with analysis, review, and report | Unproven |
| 0529T | Interrogation device evaluation (in person) of intracardiac ischemia monitoring system with analysis, review, and report | Unproven |
| 0530T | Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; complete system (electrode and implantable monitor) | Unproven |
| 0531T | Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; electrode only | Unproven |
| 0532T | Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; implantable monitor only | Unproven |
| 0559T | Anatomic model 3D-printed from image data set(s); first individually prepared and processed component of an anatomic structure | Unproven |
| 0560T | Anatomic model 3D-printed from image data set(s); each additional individually prepared and processed component of an anatomic structure (List separately in addition to code for primary procedure) | Unproven |
| 0561T | Anatomic guide 3D-printed and designed from image data set(s); first anatomic guide | Unproven |
| 0562T | Anatomic guide 3D-printed and designed from image data set(s); each additional anatomic guide (List separately in addition to code for primary procedure) | Unproven |
| 0563T | Evacuation of meibomian glands, using heat delivered through wearable, open-eye eyelid treatment devices and manual gland expression, bilateral | Unproven |
| 0567T | Permanent fallopian tube occlusion with degradable biopolymer implant, transcervical approach, including transvaginal ultrasound | Unproven |
| 0568T | Introduction of mixture of saline and air for sonosalpingography to confirm occlusion of fallopian tubes, transcervical approach, including transvaginal ultrasound and pelvic ultrasound | Unproven |
| 0571T | Insertion or replacement of implantable cardioverter-defibrillator system with substernal electrode(s), including all imaging guidance and electrophysiological evaluation (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters), when performed | Unproven |
| 0572T | Insertion of substernal implantable defibrillator electrode | Unproven |
| 0573T | Removal of substernal implantable defibrillator electrode | Unproven |
| 0574T | Repositioning of previously implanted substernal implantable defibrillator-pacing electrode | Unproven |

| Code | Description | Conclusion |
|---|---|---|
| 0575T | Programming device evaluation (in person) of implantable cardioverter-defibrillator system with substernal electrode, with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional | Unproven |
| 0576T | Interrogation device evaluation (in person) of implantable cardioverter-defibrillator system with substernal electrode, with analysis, review and report by a physician or other qualified health care professional, includes connection, recording and disconnection per patient encounter | Unproven |
| 0577T | Electrophysiologic evaluation of implantable cardioverter-defibrillator system with substernal electrode (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters) | Unproven |
| 0578T | Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter-defibrillator system with interim analysis, review(s) and report(s) by a physician or other qualified health care professional | Unproven |
| 0579T | Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter-defibrillator system, remote data acquisition(s), receipt of transmissions and technician review, technical support and distribution of results | Unproven |
| 0580T | Removal of substernal implantable defibrillator pulse generator only | 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 |
| 0594T | Osteotomy, humerus, with insertion of an externally controlled intramedullary lengthening device, including intraoperative imaging, initial and subsequent alignment assessments, computations of adjustment schedules, and management of the intramedullary lengthening device | Unproven |
| 0600T | Ablation, irreversible electroporation; 1 or more tumors per organ, including imaging guidance, when performed, percutaneous | Unproven |
| 0601T | Ablation, irreversible electroporation; 1 or more tumors, including fluoroscopic and ultrasound guidance, when performed, open | Unproven |
| 0607T | Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; set-up and patient education on use of equipment | Unproven |
| 0608T | Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; analysis of data received and transmission of reports to the physician or other qualified health care professional | Unproven |
| 0614T | Removal and replacement of substernal implantable defibrillator pulse generator | Unproven |
| 0615T | Eye-movement analysis without spatial calibration, with interpretation and report | Unproven |

| Code | Description | Conclusion |
|---|---|---|
| 0616T | Insertion of iris prosthesis, including suture fixation and repair or removal of iris, when performed, without removal of crystalline lens or intraocular lens, without insertion of intraocular lens | Unproven |
| 0617T | Insertion of iris prosthesis, including suture fixation and repair or removal of iris, when performed; with removal of crystalline lens and insertion of intraocular lens | Unproven |
| 0618T | Insertion of iris prosthesis, including suture fixation and repair or removal of iris, when performed; with secondary intraocular lens placement or intraocular lens exchange | 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 (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation), other than for screening for peripheral arterial disease, image acquisition, interpretation, and report; first anatomic site | 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 |
| 0659T | Transcatheter intracoronary infusion of supersaturated oxygen in conjunction with percutaneous coronary revascularization during acute myocardial infarction, including catheter placement, imaging guidance (e.g., fluoroscopy), angiography, and radiologic supervision and interpretation | Unproven |
| 0664T | Donor hysterectomy (including cold preservation); open, from cadaver donor | Unproven |
| 0665T | Donor hysterectomy (including cold preservation); open, from living donor | Unproven |
| 0666T | Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor | Unproven |
| 0667T | Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor | Unproven |
| 0668T | Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary | Unproven |
| 0669T | Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each | Unproven |
| 0670T | Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each | Unproven |
| 0672T | Endovaginal cryogen-cooled, monopolar radiofrequency remodeling of the tissues surrounding the female bladder neck and proximal urethra for urinary incontinence | Unproven |
| 0692T | Therapeutic ultrafiltration | Unproven |
| 0694T | 3-dimensional volumetric imaging and reconstruction of breast or axillary lymph node tissue, each excised specimen, 3-dimensional automatic specimen reorientation, interpretation and report, real-time intraoperative | Unproven |

| Code | Description | Conclusion |
|---|---|---|
| 0695T | Body surface-activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of implant or replacement | Unproven |
| 0696T | Body surface-activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of follow-up interrogation or programming device evaluation | Unproven |
| 0766T | Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, with identification and marking of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; first nerve | Unproven |
| 0767T | Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, with identification and marking of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; each additional nerve (List separately in addition to code for primary procedure) | Unproven |
| 0859T | Noncontact near-infrared spectroscopy (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation), other than for screening for peripheral arterial disease, image acquisition, interpretation, and report; each additional anatomic site (List separately in addition to code for primary procedure) | Unproven |
| 0861T | Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; both components (battery and transmitter) | Unproven |
| 0862T | Relocation of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only | Unproven |
| 0863T | Relocation of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; transmitter component only | Unproven |
| 19105 | Ablation, cryosurgical, of fibroadenoma, including ultrasound guidance, each fibroadenoma | Unproven |
| 31634 | Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, with assessment of air leak, with administration of occlusive substance (e.g., fibrin glue), if performed | Unproven |
| 33289 | Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision and interpretation, and pulmonary artery angiography, when performed | Unproven |
| 43206 | Esophagoscopy, flexible, transoral; with optical endomicroscopy | Unproven |
| 43252 | Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy | Unproven |
| 53451 | Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance | Unproven |
| 53452 | Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance | Unproven |
| 53453 | Periurethral transperineal adjustable balloon continence device; removal, each balloon | Unproven |

| Code | Description | Conclusion |
|---|---|---|
| 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 |
| 69705 | Nasopharyngoscopy, surgical, with dilation of eustachian tube (i.e., balloon dilation); unilateral | Unproven |
| 69706 | Nasopharyngoscopy, surgical, with dilation of eustachian tube (i.e., balloon dilation); bilateral | Unproven |
| 80145 | Adalimumab | Unproven |
| 80230 | Infliximab | Unproven |
| 80280 | Vedolizumab | Unproven |
| 81490 | Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score | Unproven |
| 81599 | Unlisted multianalyte assay with algorithmic analysis (when used to report PreTrm) | Unproven |
| 88375 | Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session | Unproven |
| 93264 | Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional | Covered in certain circumstances |
| 93702 | Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s) | Unproven |
| A4542 | Supplies and accessories for external upper limb tremor stimulator of the peripheral nerves of the wrist | Unproven |
| C1839 | Iris prosthesis | Unproven |
| C2624 | Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components | Unproven |
| E0734 | External upper limb tremor stimulator of the peripheral nerves of the wrist | Unproven |
| E2001 | 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 |
| K1030 | External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only | Unproven |
| L8608 | Miscellaneous external component, supply or accessory for use with the Argus II Retinal Prosthesis System | Unproven |
| L8699 | Prosthetic implant, not otherwise specified [when used to report an absorbable nasal cartilage support implant] [when used to report three-dimensional (3-D) printed cranial implants] | Unproven |
| 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 |

| Code | Description | Conclusion |
|---|---|---|
| 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 |
| S2117 | Arthroereisis, subtalar | Unproven |



# Coverage Rationale/Clinical Evidence

| 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.

An ECRI clinical evidence assessment (2022) states that the evidence for SFDI is inconclusive as there are too few data on outcomes. SFDI may eventually be used to estimate foot ulcer risk, but the available data are insufficient to determine its efficacy compared to other diagnostic methods.
Weinkauf et al. (2019) analyzed 47 patients (94 limbs) with and without diabetes. The SFDI Reflect RS machine was used to collect maps showing StO2 and hemoglobin content within the papillary dermis or microcirculation (HbT1) and reticular dermis or macro - circulation (HbT2) of the plantar aspects of each foot. The authors evaluated the SFDI hemoglobin maps, which identified the total hemoglobin present in the papillary and reticular dermis in addition to the pedal Doppler waveforms; these were used as standards for estimating lower extremity blood supply. After review and analysis of the data, the authors concluded that the SFDI technology is a noninvasive technology that can be a tool to manage patients with peripheral arterial disease; however, further studies will need to be designed to fully evaluate the applicability of this new technology. Limitations of the study included small sample size, the absence of a “gold standard” for non-invasive imaging of lower extremity perfusion, and a design that did not allow assessment of whether the use of SFDI improves patient care or patient outcomes.

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

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

(Accessed August 1, 2023)

For information on current clinical trials evaluating SFDI, go to www.clinicaltrials.gov. (Accessed August 1, 2023)

## Reference(s)

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Modulin. https://modulim.com/technology. Accessed March 14, 2022.

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

| Code | Description |
|---|---|
| 0075T | Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; initial vessel |
| 0076T | Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; each additional vessel (List separately in addition to code for primary procedure) |

**Transcatheter placement of extracranial vertebral artery stent(s) is considered unproven and not medically necessary due to insufficient evidence of efficacy.**

## Clinical Evidence

The European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease state:

- Open or endovascular interventions are not recommended for individuals with asymptomatic vertebral artery atherosclerotic lesions.
- Routine stenting is not recommended for individuals presenting with a vertebrobasilar territory transient ischemic attack or stroke and a 50-99% vertebral artery stenosis.
- Revascularization may be considered for individuals with recurrent vertebrobasilar territory symptoms (despite best medical therapy) and a 50-99% extracranial vertebral artery stenosis.
- Synchronous carotid and vertebral artery revascularization are not recommended for individuals with combined carotid and vertebral artery disease.
- For individuals undergoing vertebral artery stenting, drug-eluting stents should be considered in preference to bare metal stents.

Additionally, the clinical practice guidelines recommend that all those who have a stroke or TIA due to narrowing in their vertebral arteries will benefit from the same lifestyle advice, risk factor control, and medications (e.g., antiplatelet agents, medicines to lower blood pressure, statins to reduce cholesterol and careful management of diabetes) as described for individuals with symptoms due to carotid disease. Open operations are rarely performed for individuals symptomatic with narrowing in their vertebral arteries, and most are treated by medicines alone. The 2023 ESVS guidelines say that stenting of vertebral artery narrowing may be considered for individuals with recurrent TIA/stroke despite taking their medications (Naylor et al., 2023).

In 2022, Xu and associates assessed the safety and efficacy of percutaneous transluminal angioplasty, with or without stenting combined with medical treatment (MT), compared to MT alone, for individuals with episodes of cerebral ischemia due to vertebral artery stenosis. In the form of a systematic review, all randomized controlled trials that compared endovascular treatment (ET) with MT and MT alone were included. All types of ET modalities were included, and the MT included risk factor control, antiplatelet therapy, lipid-lowering therapy, and individualized management of those with hypertension or diabetes. The primary outcomes measured were death/stroke after 30 days of randomizations and fatal/non-fatal stroke after 30 days post-randomization to the completion of the follow-up. A total of 349 participants with symptomatic vertebral artery stenosis averaging 64.4 years were included. No significant difference in the 30-day post-randomization of deaths and strokes between the ET and MT and MT alone was seen [risk ratio (RR) 2.33, 95% confidence interval (CI) 0.77 to 7.07; 3 studies, 349 participants; low-certainty evidence]. There were no significant differences between ET plus MT and MT alone in fatal/non-fatal strokes in the territory of the treated vertebral artery stenosis after 30 days post-randomization to completion of follow-up (RR 0.51, 95% CI 0.26 to 1.01; 3 studies, 349 participants; moderate-certainty evidence), ischemic or hemorrhagic stroke during the entire follow-up period (RR 0.77, 95% CI 0.44 to 1.32; 3 studies, 349 participants; moderate-certainty evidence), death during the whole follow-up period (RR 0.78, 95% CI 0.37 to 1.62; 3 studies, 349 participants; low-certainty evidence), and stroke or

transient ischemic attack (TIA) during the entire follow-up period (RR 0.65, 95% CI 0.39 to 1.06; 2 studies, 234 participants; moderate-certainty evidence). The authors concluded through this Cochrane review that low-to moderate-certainty of evidence suggests that there are no significant differences in the short- or long-term risks of stroke, death, or TIA for individuals with symptomatic vertebral artery stenosis while treated with either ET plus MT or those treated with MT alone.

Through a prospective, randomized, open, parallel, blinded end-point clinical trial, Markus et al. (2019) sought to compare the risks and benefits of vertebral angioplasty and stenting with the best medical treatment (BMT) alone for recently symptomatic vertebral artery stenosis. The Vertebral Artery Ischaemia Stenting Trial (VIST) took place in 14 hospitals in the UK, where individuals were followed up for at least one year. Participants had to have symptomatic vertebral stenosis of at least 50% manifested from presumed atheromatous disease to be included in the trial. The participants were assigned randomly (1:1) to either vertebral angioplasty/stenting plus BMT (n = 91) or BMT alone (n = 88), for a total of 179 contributing to the follow-up data and outcomes measured. The outcomes measured were the occurrence of fatal or non-fatal stroke in any arterial territory during follow-up. The trial results showed a median follow-up was 3.5 (interquartile range 2.1-4.7) years. Of the 61 participants who were stented, 48 (78.7%) had extracranial stenosis, and 13 (21.3%) had intracranial stenosis. No perioperative complications occurred with extracranial stenting; two strokes occurred during intracranial stenting. The primary end-point occurred in five people (including one fatal stroke) in the stent group and 12 participants (including two fatal strokes) in the medical group (giving a hazard ratio of 0.40, 95% confidence interval 0.14 to 1.13; p = 0.08), with an absolute risk reduction of 25 strokes per 1000 person-years. The authors concluded that there was no difference in risk of the primary end-point between the two points. The post hoc analysis suggests that stenting could be associated with a decrease in recurrent stroke risk for symptomatic vertebral arteries. Further studies are necessary to confirm the findings, especially with extracranial vertebral artery stenosis, as the complication rates with stenting were meager. The trial was limited by its failure to reach the target recruitment and the high rate of non-confirmation of stenosis in the stented group of the trial.

## Reference(s)


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Naylor R, Rantner B, Ancetti S, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease. Eur J Vasc Endovasc Surg. 2023 Jan;65(1):7-111.

Xu R, Zhang X, Liu S, et al. Percutaneous transluminal angioplasty and stenting for vertebral artery stenosis. Cochrane Database Syst Rev. 2022 May 17;5(5):CD013692.


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

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

## Clinical Evidence

The Argus® II Retinal Prosthesis System (Second Sight Medical Products, Inc.) is a retinal implant that requires use of an external device to provide electrical stimulation to the retina to induce some visual perception in blind individuals with severe to profound retinitis pigmentosa (RP). On August 30, 2022, Second Sight Medical Products, Inc. announced the completion of its merger with Nano Precision Medical, Inc. and changed its name to Vivani Medical, Inc. Manufacturing of the Argus II Retinal Prosthesis System has ceased.

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

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

The device is intended for use in one eye—the worse-seeing eye. The HDE approval required the company to conduct 2 post-approval studies, including an extended (10-year) follow-up of patients receiving the implant and a 5-year, prospective, multicenter study of the visual function, device reliability, and adverse events (AEs) in patients receiving the implant. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H110002. (Accessed August 1, 2023)

Further information can be found at the FDA Post Approval Studies Database: Post-Approval Studies (PAS) Database (fda.gov). (Accessed February 20, 2023)

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, including control participants, are required to better outline the risks and benefits of this approach to addressing blindness secondary to severe-to-profound outer retinal degeneration.

Duncan et al. (2017) conducted single arm, prospective, unmasked clinical trial on thirty patients at ten centers in the United States and Europe. The authors reported on the change in quality of life (QOL) after implantation of the Argus II Epiretinal Prosthesis in patients with end stage retinitis pigmentosa (RP) in the United States or outer retinal degeneration in Europe. Comparisons were made between baseline and post-implant follow up measurements, or with the device turned off or on. All patients completed a minimum of three year follow-up. Vision-specific QoL was measured using the VisQoL multi-attribute utility instrument. This tool evaluates six domains that may be affected by visual impairment (injury, life, roles, assistance, activity and friendship), and is validated for a low-vision population (it has not been validated for patients with RP or severe loss of vision). The authors noted that a new vision-related QoL questionnaire was developed for patients with severe loss of vision, but was not available when this study began. Follow up visits were completed at 12, 18, 24 and 36 months, and device outcomes were considered stable at the 12 month point. The results showed that eighty percent of the participants reported moderate to severe difficulty in one or more VisQoL dimensions, and following implantation, three of the six VisQoL dimensions (injury, life and roles) showed significant and lasting improvement. The remaining dimensions, (assistance and activity) appeared to show an improvement, and finally, the VisQoL dimension, friendship was not reported as a deficit in baseline measurements. The authors commented on the fact that all patients presented with a wide variety of baseline scores (from 0.22 to 0.99), and this did not change significantly over time, despite reports of significant improvements in visual acuity with the Argus prosthesis. The authors concluded that for patients that report vision loss as having an impact on their QoL, the Argus II prosthesis can give significant and lasting improvement. The findings are however limited by lack of comparison group and unmasked study design.

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

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

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

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

Geruschat et al. (2016) compared observer-rated tasks in patients implanted with the Argus II Retinal Prosthesis System, when the device is ON versus OFF. The Functional Low-Vision Observer Rated Assessment (FLORA) instrument was administered to 26 blind patients implanted with the Argus II Retinal Prosthesis System at a mean follow-up of 36 months. The tasks are

evaluated individually and organized into four discrete domains, including 'Visual orientation', 'Visual mobility', 'Daily life and 'Interaction with others. Twenty-six patients completed each of the 35 tasks. Overall, 24 out of 35 tasks (69 percent) were statistically significantly easier to achieve with the device ON versus OFF. This study is however limited by the lack of comparison group with a different treatment mode or no treatment that could provide data on quality of life (QOL) and real-life day-to-day function. These findings require confirmation in a larger study.

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

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Duncan JL, Richards TP, Arditi A, et al. Improvements in vision-related quality of life in blind patients implanted with the Argus II Epiretinal Prosthesis. Clin Exp Optom. 2017 Mar;100(2):144-150.

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Geruschat DR, Richards TP, Arditi A, et al. An analysis of observer-rated functional vision in patients implanted with the Argus II Retinal Prosthesis System at three years. Clin Exp Optum. 2016 May;99(3):227-32.

Health Quality Ontario. Retinal Prosthesis System for Advanced Retinitis Pigmentosa: A Health Technology Assessment Update. On Health Technol Assess Ser. 2017 Nov 6;17(13):1-62.

National Institute for Health and Care Excellence (NICE). Insertion of a subretinal prosthesis system for retinitis pigmentosa. 2015.

Schaffrath K, Schellhase H, Walter P, et al. One-year safety and performance assessment of the Argus II Retinal Prosthesis: A post approval study. JAMA Ophthalmol. 2019 Aug 1;137(8):896-902.


| 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™-CRC 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 colorectal cancer (CRC). BeScreened™-CRC is manufactured by Beacon Medical Inc. and partnered with Sonora Quest Laboratories is an ELISA-based multiplexed, CLIA laboratory developed 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.biospace.com/article/releases/bescreened-blood-based-colorectal-cancer-test-provides-affordable-early-detection-and-without-the-mess/. (Accessed February 15, 2023)

In a systematic review, Harlid et al. (2021) summarized the evidence from 53 studies (between 2011 and 2021) that used blood-based colorectal cancer biomarkers in pre-diagnostic, asymptomatic settings. The quality of the studies was mostly high, but very few possible biomarkers showed consistent results in more than one study. The most promising biomarkers was the anti-p53 antibodies which performed well with constant findings in one screening cohort and in the 3-4 years prior to diagnosis in two prospective cohort studies. Proteins were the most common type of biomarker assessed, particularly carcinoembryonic

antigen (CEA) and C-reactive protein (CRP), with uncertain results. Other possible promising biomarkers included proteins, such as AREG, MIC-1/GDF15, LRG1 and FGF-21, metabolites and/or metabolite profiles, non-coding RNAs and DNA methylation, as well as re-purposed routine lab tests, such as ferritin and the triglyceride-glucose index. Biomarker panels generally achieved higher discriminatory performance than single markers. There were study limitations which included: general search topic in a many different exposures, lack of define criteria to differentiate the etiology verses the biomarkers between the studies and relevant studies before 2011 were not included which could have missed other biomarkers. In conclusion, this systematic review highlighted anti-p53 antibodies as a promising blood-based biomarker for use in colorectal screening panels, together with other specific proteins. Additional research is needed to evaluate these promising biomarkers in independent pre-diagnostic settings.

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

Bhardwaj et, al. (2020) used a two-stage design to measure 275 protein markers by proximity extension assay (PEA), first in plasma samples of a discovery set consisting of 98 newly diagnosed CRC cases and 100 age- and gender-matched controls free of neoplasm at screening colonoscopy. An algorithm predicting the presence of early- or late-stage CRC was derived by least absolute shrinkage and selection operator regression with .632 + bootstrap method, and the algorithms were then validated using PEA again in an independent validation set consisting of participants of screening colonoscopy with and without CRC (n = 56 and 102, respectively). Three different signatures for all-, early-, and late-stage CRC consisting of 9, 12, and 11 protein markers were obtained in the discovery set with areas under the curves (AUCs) after .632 + bootstrap adjustment of 0.92, 0.91, and 0.96, respectively. External validation among participants of screening colonoscopy yielded AUCs of 0.76 [95% confidence interval (95% CI), 0.67-0.84], 0.75 (95% CI, 0.62-0.87), and 0.80 (95% CI, 0.68-0.89) for all-, early-, and late-stage CRC, respectively. The authors concluded that although the identified protein markers are not competitive with the best available stool tests, the combination of identified protein markers with other informative blood-based markers could contribute to the development of a promising blood-based test for CRC screening. Additionally, this study is based on more biomarkers and a different algorithm from BeScreened™-CRC.

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

Hayes (2019) For use of liquid biopsy tests for colorectal cancer (CRC) screening to reduce CRC morbidity and mortality. Evidence from 3 studies suggests that CRC screening-eligible adults, especially those who reject a colonoscopy screen, prefer a blood-based test for mSEPTIN9 to a standard stool-based test. However, evidence comparing new versus established

screening test performance in an unselected, prospective screening population is insufficient to support conclusions. Similarly, evidence for other types of liquid biopsy CRC screening tests is lacking.

## Reference(s)


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Hayes Liquid Biopsy Tests for Colorectal Cancer Screening 2019.

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


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

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

## Clinical Evidence

Computer aided detection (CAD) systems are adjunctive tools used in assessing chest radiographs. CAD uses a computer algorithm to analyze features of a lesion to determine the level of suspicion and is intended to enhance the reader's diagnostic performance. CAD is thought to improve the accuracy and consistency of radiological diagnosis by reducing the time it takes to interpret images.

The published literature regarding CAD for chest radiographs consists primarily of the technical capabilities of CAD systems. There is presently inadequate evidence in the medical literature that population-based mass screening with CAD for chest radiographs will contribute substantially to the detection of smaller cancers, or decreases mortality. High-quality, randomized trials examining the effect of CAD systems for chest radiographs are necessary to determine the true impact of this technology on health outcomes.

In a systematic review, Haber et al. (2020) aimed to identify whether there was an advantage to using Computer Aided Detection (CAD) to support CXR interpretation of pulmonary nodules; our findings were inconclusive. From the 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 treat melbornian gland dysfunction (MGD). These devices are intended to treat individuals with dry eye disease and other conditions that cause MDG.

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).

Novo-Diez et al. (2022) conducted a prospective, single-center, open-label study to assess the prophylactic effect of LipiFlow treatment in MGD. There were two aims of the study: the first was to assess the efficacy of a single LipiFlow treatment in MGD patients over a 12-month period under normal environmental conditions and the second was to evaluate the prophylactic benefits of LipiFlow in patients with MGD undergoing an adverse environmental humidity exposure. patients with MGD were exposed to normal (23 °C; 50% relative humidity; 30 min) and adverse (23 °C; 10% relative humidity; 2 h) controlled environments consecutively during baseline and follow-up visits (3, 6, and 12 months) after a single LipiFlow treatment. Ocular Surface Disease Index (OSDI), lipid layer thickness (LLT), fluorescein tear break-up time (TBUT), corneal and conjunctival staining, change in dry eye symptoms questionnaire (CDES-Q), and meibomian gland yielding liquid secretion (MGYLS), were assessed. Linear mixed-effects and cumulative logit mixed models were fitted to assess the effect of the LipiFlow treatment over time and within the controlled environments. Seventeen females and 4 males (59.6 ±9.4 years) completed the study. LLT and TBUT did not vary significantly ($p > 0.05$) after LipiFlow treatment. OSDI, corneal and conjunctival staining, and MGYLS scores were improved ($p \leq 0.01$) 12 months after treatment. After the adverse exposure, corneal staining increased at all visits ($p = 0.01$), and there was no significant improvement in CDES-Q scores after LipiFlow treatment ($p \geq 0.07$). One LipiFlow treatment improved objective and subjective outcomes in MGD disease for at least one year. Further studies are needed to support that LipiFlow might also help as an adjuvant to avoid acute flares against an adverse environmental humidity. The study is limited by lack of a contemporary comparison group undergoing a different treatment.

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

Tauber (2020) conducted a single-center, 6-week, prospective, randomized, single-masked study of adults with inflammatory 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 RCTs that compared the efficacy of vectored thermal pulsation treatment (VTPT) and warm compress treatment (WCT) in treating dry eye disease (DED). The primary outcome was the gland function. The analysis consisted of 4 trials with 385 patients. Significantly greater improvement was observed in meibomian gland function, tear breakup time, and Standard Patient Evaluation for Eye Dryness at 2 to 4 weeks in the VTPT group than in the WCT group. A significantly greater decrease in Ocular Surface Disease Index was observed at 2 to 4 weeks and 3 months in the VTPT group than in the WCT group. The authors concluded that a single 12-minute VTPT was more efficacious than traditional WCT in treating DED either in objective or subjective measurements. There were several study limitations. All four included trials were considered at high risk of overall bias. All participants belonged to an age group (45-65 years) therefore the results may not apply to the younger population. The authors also notes that it was not known if the WCT group was treated per the protocol. Lastly the included trials were limited to three-months follow-up. These findings require confirmation in RCTs 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 VTP treatment in contact lens wearers with (MGD) and dry eye symptoms. The trial included 55 soft contact lens (SCL) wearers with MGD and evaporative dry eye. Subjects were randomized to the single VTP treatment group or an untreated control. The controls received a crossover VTP treatment at 3 months (crossover treatment group). Primary effectiveness measures were meibomian gland secretion (MGS) score and Standard Patient Evaluation of Eye Dryness (SPEED) that were evaluated at baseline, at 1 and 3 months post-VTP treatment, and at 1-month post-VTP treatment in the crossover treatment group. Exploratory variables included fluorescein tear break-up time (TBUT), lid wiper epitheliopathy (LWE), lid parallel conjunctival folds (LIPCOF), ocular surface staining, frequency of over-the-counter (OTC) drop use, and hours of comfortable contact lens wear. At 3 months, the treatment group showed significantly greater mean change from baseline in MGS, SPEED and significantly greater improvement in exploratory variables (TBUT, LWE, and frequency of OTC drop use) relative to the controls. Mean comfortable contact lens wearing time increased by 4.0 ±3.9 hours at 1 month. This was sustained for 3 months with no change in the control group. The crossover treatment group demonstrated similar results to the treatment group at 1-month post-VTP. The authors concluded that in SCL wearers with MGD, a single VTP treatment significantly improved mean meibomian gland function and significantly reduced dry eye signs and symptoms compared to an untreated control. This was a small study intended to assess the value of performing a larger clinical study in contact lens wearing patients with MGD. The authors indicated that they cannot rule out investigator bias or the placebo effect, especially in the context of an open-label trial. Furthermore, this study was funded by the manufacturer of Lipiflow (TearScience, Inc) and lack comparison to established treatments.

In a prospective, randomized, parallel-group, single-masked study, Hagen et al. (2018) compared the efficacy of a single bilateral 12-minute VTP procedure versus daily oral doxycycline for 3 months for moderate-to-severe (MGD). This study included 28 subjects who received either a single-dose VTP with the LipiFlow System (TearScience, Inc) or 3 months of doxycycline treatment. At baseline and 3 months post treatment, all subjects were evaluated for the following: dry eye symptoms with a standard dry eye questionnaire [the Standard Patient Evaluation for Eye Dryness (SPEED)], meibomian gland (MG) function by counting the number of glands yielding liquid secretion with the MG evaluator (MGE), tear breakup time (TBUT) and corneal and conjunctival staining. In the VTP group, at 3 months, there was a significant improvement in MG function, SPEED score, TBUT, corneal staining and conjunctival staining. In the doxycycline group, there was a significant improvement in MG function, SPEED score and conjunctival staining, but the improvement in TBUT and corneal staining was not statistically significant. At 3 months, SPEED score was significantly better in the VTP group; other parameters were comparable between the two groups. The authors concluded that a single 12-minute bilateral VTP procedure was significantly more effective than the 3-month daily course of oral doxycycline at improving the dry eye symptoms secondary to MGD and that a single 12-minute VTP treatment was at least as effective as a dose of doxycycline for 3 months, in improving MG function

and all measured signs of MGD. According to the authors, given the minimal risk profile of the single VTP procedure over long-term doxycycline use, a single VTP presents a favorable alternative to long-term antibiotic use. According to the authors, this is a small study that can serve as a pilot study for additional investigations. It was disclosed that 2 of the authors are either a consultant or employee of TearScience, Inc. Furthermore, the study may have been too small to detect clinically significant differences between groups.

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

## Clinical Practice Guidelines

### *Tear Film and Ocular Surface Society (TFOS)*

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

### *American Academy of Ophthalmology*

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

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

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

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

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

Gupta et al., (2022) in a masked RCT evaluated the safety and effectiveness of a single TearCare procedure compared with a single LipiFlow procedure in the treatment of dry eye disease associated with MGD. 135 subjects received a single TearCare (TC) treatment (n = 67) or a single LipiFlow (LF) treatment (n = 68) at baseline and were followed up for 1 month posttreatment. Tear film breakup time, meibomian gland function, and corneal and conjunctival staining scores were assessed as dry eye signs at baseline, 2 weeks, and 1 month; dry eye symptoms were assessed using the Ocular Surface Disease Index, Symptom Assessment in Dry Eye, and eye dryness questionnaires at baseline and 1 month. At 1 month posttreatment, both groups demonstrated significant improvements ($p < 0.0001$) in mean tear film breakup time and meibomian gland secretion score to 3.0 ±4.4 and 11.2 ±11.1 in the TC group and 2.6 ±3.3 and 11.0 ±10.4 in the LF group, respectively. The mean eye dryness,

Symptom Assessment in Dry Eye, and Ocular Surface Disease Index scores were significantly reduced ($p < 0.0001$) by 35.4 ±34.1, 38.2 ±31.0, and 27.9 ±20.5 in the TC group and 34.9 ±26.9, 38.0 ±25.9, and 23.4 ±17.7 in the LF group, respectively. The groups showed no statistically significant differences for any one result. The TC group demonstrated numerically greater improvements consistently in all signs and symptoms. Device-related ocular adverse events were reported in 3 patients in the TC group (superficial punctate keratitis, chalazion, and blepharitis) and 4 patients in the LF group (blepharitis, 2 cases of foreign body sensation, and severe eye dryness). Study limitations included outcomes were subjective, interpretation of results from the examiner even though masked and lack of long-term follow-up. The authors concluded that a single TearCare treatment alleviates the signs and symptoms of dry eye disease in patients with MGD and is equivalent in its safety and effectiveness profile to LipiFlow treatment as shown in this 1-month follow-up study. Due to study limitations, further well-controlled studies that includes long-term efficacy are needed.

Karpecki et al. (2020) conducted a prospective exploratory single-arm interventional study to evaluate the safety and effectiveness of the TearCare® System to treat adults with signs and symptoms of dry eye disease (DED). A total of fifty-eight eyes (29 subjects) received a single TearCare procedure and were assessed at baseline, post-procedure 1-week and 1-month. Effectiveness was assessed as mean change from baseline in tear break-up time (TBUT), Ocular Surface Disease Index (OSDI), total Meibomian Gland Secretion Score (MGSS), and corneal/conjunctival staining. Adverse events (AE) and changes in visual acuity were used to assess safety. The baseline TBUT of 3.7 ±1.1 seconds was improved by 2.6 ±1.6 (70%) seconds at 1-week and by 3.1 ±2.2 (84%) seconds at 1-month ($p < 0.0001$). Mean baseline OSDI of 54.9 ±20.2 improved by 17.9 ±20.9 at 1-week and 25.8 ±24.3 at 1-month ($p < 0.001$). A clinically meaningful improvement was seen in 83% of subjects as per the Miller-Plugfelder definition and 66% of subjects improved by at least 1 OSDI category. The baseline MGSS of 5.6 ±4.0 improved by 9.3 ±4.0 at 1-week and 8.8 ±5.8 at 1-month ($p < 0.0001$). Corneal and conjunctival staining improved by 1.4 ±2.8 and 1.2 ±2.9 from a mean baseline of 4.8 ±2.5 and 5.9 ±3.2, respectively. Similar lines of improvement were also observed for subgroups of subjects ranked by severity. Subjects with more severe gland obstruction at baseline had greater improvements in TBUT and staining compared to the less severe subgroup. No device-related adverse events or significant changes in visual acuity were observed. Study limitations included the possibility of subjective grading of endpoints by investigators even though they underwent thorough training in an attempt to adhere to standardization. Another limitation is the sample size did not allow for hypothesis testing and statistical analysis. Significant improvements were seen in all subjects (100%) in all signs and symptoms of DED within 1-week of treatment and 83% of subjects experienced symptom relief. In addition, TearCare seems to be effective in treating DED associated with all levels of meibomian gland obstruction. Authors indicate that these promising preliminary results related to safety and effectiveness will support future robust RCTs. The findings of this study are limited by lack of comparison group.

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

Badawi (2018) evaluated the safety and effectiveness of the TearCare System in adult patients with clinically significant DED in a prospective, single-center, randomized, parallel-group, clinical trial. Subjects with DED were randomized to either a single TearCare treatment conducted at the clinic or 4 weeks of daily warm compress (WC) therapy. The TearCare procedure consisted of 12 minutes of thermal eyelid treatment immediately followed by manual expression of the meibomian glands. WC therapy consisted of once daily application of the compresses to the eyelids for 5 minutes. Subjects were followed until 6 months post-treatment. The primary effectiveness end point was defined as change from baseline to 4 weeks for TBUT. Twenty-four subjects were enrolled, and all subjects completed 6 months follow-up. At the 1-month follow-up, TearCare subjects

demonstrated an improvement from baseline in mean (±SD) TBUT of 11.7 ±2.6 seconds compared with an average worsening of -0.3 ±1.1 seconds for subjects in the WC group. Significantly greater improvements in the change from baseline in meibomian gland scores, as well as corneal and conjunctival staining scores, were observed in the TearCare group. Subjects in the TearCare group also showed significantly greater improvement in dry eye symptoms as measured by 3 questionnaires. Both treatments were well-tolerated. The investigator concluded that the findings of this pilot study suggest that the TearCare System is an effective treatment option for patients with DED, with the effects on the signs and symptoms of DED persisting for at least 6 months. This study was limited by lack of masking to the intervention. A larger number of subjects enrolled at different centers is needed to enhance the evidence base for this technology.

## Clinical Practice Guidelines

### *American Academy of Ophthalmology*

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

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| Code | Description |
|---|---|
| 0208T | Pure tone audiometry (threshold), automated; air only |
| 0209T | Pure tone audiometry (threshold), automated; air and bone |
| 0210T | Speech audiometry threshold, automated; |

| Code | Description |
|---|---|
| 0211T | Speech audiometry threshold, automated; with speech recognition |
| 0212T | Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated |

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

## Clinical Evidence

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

Wasman et al. (2022) conducted a systematic review of the current status of automation and machine learning approaches in hearing assessment using validated pure-tone audiometry with possible indicators of accuracy, reliability, and efficiency of these approaches. These automated methods are being developed for self-administered digital hearing assessments without the direct administration by professionals. This review is an extension of a 2013 systematic review (Mahomed, 2013). Fifty-six reports from 2012 to June 2021 were included. There were 27 select automated approaches that were identified. The authors noted the following. Machine learning approaches require fewer trials than conventional threshold-seeking approaches, and personal digital devices make assessments more accessible. Validity can be improved using digital technologies for quality surveillance, including noise monitoring and detecting inconclusive results. In the past 10 years, an increasing number of automated approaches have reported similar accuracy, reliability, and time efficiency as manual hearing assessments. Limitations included commercialized automated approaches may have been developed without peer-reviewed reports, no gold standard for reporting audiometry validation studies, which confines a consistent comparison among methods and early users could lead to more optimistic findings. New developments, including machine learning approaches, offer features and versatility beyond manual audiometry. Additional peer-reviewed studies are needed to support their use in the future while taking the limitations into consideration (Colsman, 2020 and Mahomed, 2013 are included below).

Chen et al. (2021) conducted a systematic review and meta-analysis to summarize the factors that influence the diagnostic accuracy of smartphone-based hearing assessments for hearing loss. Their aim was to provide more standard evidence of the benefit of smartphone audiometry in clinical application in the future**.** Pure tone audiometry (PTA) is the gold standard for hearing assessment, but it is often not available in many settings due to a lack of qualified testing individuals. Smartphone-based audiometry may be equally effective and can improve access to adequate hearing evaluations. A total of 4470 patients from twenty-five studies were included in the meta-analysis. The overall sensitivity, specificity, and area under the receiver operating characteristic curve for smartphone-based audiometry were 89% (95% CI 83%-93%), 93% (95% CI 87%-97%), and 0.96 (95% CI 0.93-0.97), respectively; the corresponding values for the smartphone-based speech recognition test were 91% (95% CI 86%-94%), 88% (95% CI 75%-94%), and 0.93 (95% CI 0.90-0.95), respectively. Meta-regression analysis revealed that patient age (accuracy was lower in elderly and children), equipment used, and the presence of soundproof booths were significantly related to diagnostic accuracy. Limitations included a different threshold among the studies leading to a threshold effect and heterogeneity regarding the study designs, test protocols, and reference PTA thresholds which may have biased the results when combining them into the meta-analyses. The author's indicated that smartphone-based audiometry could be equal to that of the standard PTA for assessing hearing loss where there are limited resources available. Future studies should focus on adjusting the potential factors that may affect smartphone-based audiometry diagnostic accuracy. (Saliba 2017 included below).

Colsman et al. (2020) examined the accuracy and reliability of a calibrated application (app) for pure-tone screening audiometry by self-assessment on a tablet computer: The Audimatch app installed on Apple iPad 4 in combination with Sennheiser HDA-280 headphones. In a repeated measures design audiometric thresholds collected by the app were compared to those obtained by standardized automated audiometry administered by a trained professional and additionally test-retest reliability was evaluated. A total of 68 subjects aged 19 to 65 years with normal hearing were tested in a sound-attenuating booth. A similar test revealed comparable hearing thresholds for the app compared with standardized automated audiometry. A test-retest reliability analysis within each method showed a high correlation coefficient for the app (Spearman rank correlation: rho = 0.829) and for the automated audiometer (rho = 0.792). The authors concluded that the results indicated that the self-assessment of audiometric thresholds via a calibrated mobile device represents a valid and reliable alternative for stationary

assessment of hearing loss thresholds, supporting the potential use within the area of occupational health care. Study limitations includes the following: the sessions were performed in a sound-insulated booth and therefore the findings may not be generalizable to other environments where self-administered audiometry could be performed; the participant can self-administer the test, yet calibration with the app is required; special headphones are required; the sample was not completely a random selection and only participants with normal hearing were included; and the authors were involved in the development of the app, which could have introduced a bias in the interpretation of the findings. Future studies are needed to explore the validity of this app.

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

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

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

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

automated audiometry using KUDOwave, however variations in study design were significant and future research is recommended.

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

## Reference(s)


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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.

Pereira O, Pasko LE, Supinski J, et al. Is there a clinical application for tablet-based automated audiometry in children? Int J Pediatr Otorhinolaryngol. 2018; 110:87-92.

Saliba J, Al-Reefi M, Carriere JS, Verma N et al. Accuracy of mobile-based audiometry in the evaluation of hearing loss in quiet and noisy environments. Otolaryngol Head Neck Surg. 2017.

Wasmann JW, Pragt L, Eikelboom R, et al. Digital approaches to automated and machine learning assessments of hearing: Scoping Review. J Med Internet Res. 2022 Feb 2;24(2):e32581.


| Code | Description |
|---|---|
| 0234T | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery |
| 0235T | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel |
| 0236T | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta |
| 0237T | Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel |

**Transluminal peripheral atherectomy of visceral, renal, abdominal, or brachiocephalic arteries is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy**.

## Clinical Evidence

Atherectomy is the endovascular removal of atheromatous plaque by cutting drilling, shaving, pulverizing, lasing, or sanding. The result is improved compliance of the vessel wall and enlargement of the treated lumen. Atherectomy devices are categorized by their mode of action and include directional, rotational, orbital intravascular lithotripsy, excimer laser and a peripheral chronic total occlusion (CTO) recanalization system the Crosser™ (Bard Peripheral Vascular, Inc.) (Chowdhury et al., 2022).

The published evidence on the safety and efficacy of atherectomy of the visceral, renal, abdominal and brachiocephalic arteries is limited to case reports, and the effectiveness and safety of these procedures cannot be established (Chowdhury et al., 2022; Diaz et al., 2020; Genet et al., 2019; Naganuma et al., 2018; Richard et al., 2016; Manunga et al., 2012). There are multiple ongoing clinical trials investigating different devices for different arteries. For more information refer to the following website: https://www.clinicaltrials.gov/. (Accessed May 2, 2023)

## Reference(s)


Chowdhury M, Secemsky EA. Atherectomy vs other modalities for treatment during peripheral vascular intervention. Curr Cardiol Rep. 2022 Jul;24(7):869-877.

Diaz MA, Patton M, Benincasa M, et al. Laser atherectomy to treat severe in stent restenosis of the superior Mesenteric Artery. J Cardiol Cases. 2020 Feb 6;21(5):176-178.

Genet MD, Hohlastos ES, Resnick SA. Orbital atherectomy in severely calcified visceral artery lesions. J Vasc Interv Radiol. 2019 Oct;30(10):1689-1691.

Manunga JM, Oderich GS. Orbital atherectomy as an adjunct to debulk difficult calcified lesions prior to mesenteric artery stenting. J Endovasc Ther. 2012 Aug;19(4):489-94.

Naganuma T, Kawamoto H, Onishi H, et al. Successful rotational atherectomy for abdominal aortic stenosis with severe calcification in a patient treated with transfemoral transcatheter aortic valve implantation. Kardiol Pol. 2018;76(4):809.

Richard M, Krol E, Dietzek A. Successful use of orbital atherectomy as an adjunct in treating extensively calcified mesenteric artery lesions. Ann Vasc Surg. 2016 Oct;36:296.e5-296.e8.


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

## Clinical Evidence

PreTRM it is a blood test to predict spontaneous preterm birth (sPTB) risk by measuring two proteins, insulin-like growth factor-binding protein 4 and sex hormone-binding globulins (IBP4 and SHGB) that are relatively over- or under-expressed and are predictive of premature birth (or delivery) (Sera Prognostics website). There is insufficient evidence to support the use of serum-based proteomic testing to predict the risk of preterm delivery in asymptomatic pregnant women.

A Hayes precision medicine research brief concluded that there are insufficient peer reviewed studies to perform a full technology assessment or provide evidence for the impact of the PreTRM test on outcomes (Hayes, 2022).

Burchard et al. (2021) replicated a second independent study to validate the findings of the Multicenter Assessment of a spontaneous Preterm Birth Risk Predictor (TREETOP) (Markenson et al.) and the Proteomic Assessment of Preterm Risk (PAPR) (Saade, et al.) studies mentioned below which assessed the ability of the ratio of IBP4 to SHBG to risk stratify preterm delivery and associated adverse outcomes. The authors assessed an actionable threshold learned in one study and applied to the second in a critical and rigorous manner to show that not only the likelihood of spontaneous preterm delivery is similarly significantly predicted, but also the associated and clinically adverse end points are well predicted and similarly elevated at or above the threshold. Both studies of the IBP4/SHBG proteomic biomarker showed the ratio's potential to predict the majority of preterm birth based on tested populations in excess of 1000 subjects, and for predicting associated newborn complications of prematurity as well. The primary objective of this research was to demonstrate that statistically significant thresholds of prediction of adverse pregnancy outcomes in PAPR are also significant in the independent TREETOP population. The authors indicated that an additional strength of this comparison of the PAPR and TREETOP studies is that while the subpopulations analyzed are both the same in the intended use population for the proteomic biomarker, they are notably different on several demographic and baseline characteristics (maternal age, BMI, education, race, prior sPTB, etc.). Also, the eligible PAPR and TREETOP subjects for this study were enrolled at 10 and 14 clinical sites, respectively. All of these factors would provide further

confidence that despite these demographic differences and diversity in site enrollment, the same proteomic biomarker threshold identified pregnancies of increased risk of sPTB and associated adverse outcomes. The authors concluded that this comparison demonstrated consistency and accordance of the proteomic biomarker in two large studies for predicting preterm delivery in a large diverse segment of low-risk pregnant women tested at a time in the second trimester when most women are seen for their anatomic ultrasound. The authors noted that this provides confidence that pregnancies can be robustly risk-stratified by the proteomic biomarker.

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

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

Saade et al. (2016) conducted the prospective Proteomic Assessment of Preterm Risk study to discover, verify and validate biomarkers for preterm birth. A total of 5,500 pregnant women between 17-28 weeks gestation were followed from 2011-2014 at 11 clinical sites in the United States. Of those, 5,235 remained in the study until their delivery and 4,825 were analyzed (410 were excluded due to being on progesterone therapy for preventing preterm birth). Of those 4,825 women, 4,292 carried their babies to term while 248 experienced spontaneous preterm birth (285 had medically indicated preterm births and were excluded.) Of these 248 sPTB subjects, 31 were excluded for pre -analytic reasons, leaving 217, 86 of which were used in discovery, 50 in verification, and 81 in validation. The discovery and verification process identified 2 serum proteins, insulin-like growth factor binding protein 4 (IBP4) and sex hormone-binding globulin (SHBG), as predictors of spontaneous preterm delivery. The study found that the test was able to predict whether a woman would deliver before 37 weeks with 75 percent sensitivity and 74 percent specificity, and an area under the receiver operating curve of .75. It was able to predict delivery before 35 weeks with 100 percent sensitivity and 83 percent specificity and an AUC of .93. These biomarkers may predict risk for preterm sPTB. However, the study had several limitations including small sample size and had insufficient number of women with prior preterm delivery, and less than one-third of participants had transvaginal ultrasound cervical length performed. Further studies are needed to determine the clinical application of this test and how it relates to the current techniques used to identify high risk for preterm labor.

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

## Reference(s)

American College of Obstetricians and Gynecologists (ACOG). ACOG Committee on Practice Bulletins – Obstetric. ACOG Practice Bulletin No. 234: Prediction and Prevention of Spontaneous Preterm Birth. Obstet Gynecol. Vol. 138, No. 2, August 2021.

Burchard J, Polpitiya AD, Fox AC, et al. Clinical validation of a proteomic biomarker threshold for increased risk of spontaneous preterm birth and associated clinical outcomes: A replication study. J Clin Med. 2021 Oct 29;10(21):5088.

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Markenson GR, Saade GR, Laurent LC, et al. Performance of a proteomic preterm delivery predictor in a large independent prospective cohort. Am J Obstet Gynecol MFM. 2020 Aug;2(3):100140.

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-the-pretrm-test/. Accessed March 30, 2023.

| 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 May 2, 2023)

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 May 2, 2023)

Coverage for revision or removal of carotid sinus baroreflex activation devices may be addressed in the complication section of the benefit document. Refer to federal, state or contractual requirements for coverage.

## Clinical Evidence

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

## *Hypertension*

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

Wallbach et al. (2023) conducted a prospective single-arm observational study to evaluate if programming of an intensified nighttime stimulation interval improved the dipping profile in long-term baroreflex activation therapy (BAT) treated individuals. Individuals with resistant hypertension do not show nighttime dipping which is thought to be associated with an increased cardiovascular risk and organ damage. This study included non-dippers treated with BAT for at least 6 months. BAT programming was modified in a two-step intensification of nighttime stimulation at baseline and week 6. Twenty-four hours ambulatory BP (ABP) was measured at inclusion and after 3 months. A number of 24 patients with non- or inverted dipping pattern, treated with BAT for a median of 44 months (IQR 25-52) were included. At baseline of the study, patients were 66 ±9 years old, had a BMI of 33 ±6 kg/m$^2$, showed an office BP of 135 ±22/72 ±10 mmHg, and took a median number of antihypertensives of 6 (IQR 4-9). Nighttime stimulation of BAT was adapted by an intensification of pulse width from 237 ±161 to 267 ±170 μs (p = .003) while frequency (p = .10) and amplitude (p = .95) remained unchanged. Up titration of BAT programming resulted in an increase of systolic dipping from 2 ±6 to 6 ±8% (p = .03) accompanied with a significant improvement of dipping pattern (p = .02). Twenty-four hours ABP, day- and nighttime ABP remained unchanged. Programming of an intensified nighttime BAT interval improved dipping profile in individuals treated with BAT, while the overall 24 h ABP did not change. Whether the improved dipping response contributes to a reduction of cardiovascular risk beyond the BP-lowering effects of BAT was not determined. There are a number of study limitations that includes, very small sample size, lack of comparison group or randomization, addressing the adherence of antihypertensive medications and also the lack of indicators to measure sympathetic activity such as urinary catecholamines. Larger randomized trials that includes more parameters are needed to confirm these results.

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

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

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

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

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

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

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

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

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

Recruiting has been completed for the interventional, multicenter 100-patient Nordic BAT study, a randomized, double-blind, parallel-design clinical trial to examine the effect of baroreflex activation therapy (BAT) compared to continuous pharmacotherapy on blood pressure, as well as arterial and cardiac function and structure using non-invasive high technology

methodology. This study has a primary completion date of November 2022, with a final completion date of April 2028. For more information, go to (NCT02572024) www.clinicaltrials.gov. (Accessed May 2, 2023)

Recruiting has been completed for the 300-patient Calm-2 trial, a prospective, multi-center randomized, sham-controlled, double-blinded study using the MobiusHD device in patients with drug-resistant hypertension. This study has a primary completion date of May 2025 with a final completion date of May 2025. For more information, go to (NCT03179800) www.clinicaltrials.gov. (Accessed May 2, 2023)

### *Heart Failure*

Coats et al. (2022) conducted an individual patient data analysis (IPD) from patients that were enrolled in two multicenter controlled trials (Abraham 2015 and Zile 2020 included below), that included (heart failure with reduced ejection fraction) HFrEF patients to baroreflex activation therapy (BAT) + guideline-directed medical therapy (GDMT) or GDMT alone (open label). Their main attempt was to evaluate the effect of baroreflex activation therapy (BAT) on heart failure symptoms, QoL and N-terminal pro-brain natriuretic peptide (NT-proBNP) in HFrEF. Several other subsets were also evaluated in this larger patient population. Endpoints included 6-month changes in 6-min hall walk (6MHW) distance, Minnesota Living With Heart Failure (MLWHF) QoL score, NT-proBNP, and New York Heart Association (NYHA) class in all patients and three subgroups. A total of 554 randomized patients were included. In all patients, BAT provided significant improvement in 6MHW distance of 49 m [95% confidence interval (CI) 33, 64], MLWHF QoL of -13 points (95% CI -17, -10), and 3.4 higher odds of improving at least one NYHA class (95% CI 2.3, 4.9) when comparing from baseline to 6 months. These improvements were similar, or better, in patients who had baseline NT-proBNP <1600 pg/ml, regardless of the cardiac resynchronization therapy indication status. Limitations included a small sample size since the meta-analysis only included two randomized trials and both with a limited number of patients restricting the ability to see minor differences in responses between patient cohorts of interest and lack of systematic review to include all available evidence. In addition, both trials were open-label, which may result in bias in having more subjective endpoints. Yet, the results are encouraging as the authors wait for more long-term clinical results from the second post-market phase of the BeAT-HF trial. The author's note that of all the therapies with autonomically targeted devices, meta-analysis suggests that BAT improves exercise capacity, NYHA class, and QoL in HFrEF patients receiving GDMT. BAT was also associated with an improvement in NT-proBNP in subjects with a lower baseline NT-proBNP. These clinically positive findings were consistent across the range of patient's studies.

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

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

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

Zile et al. (2020) evaluated the safety and effectiveness of BAT in patients with heart failure with reduced ejection fraction (HFrEF) in the Baroreflex Activation Therapy for Heart Failure (BeAT-HF) clinical trial. This prospective, multi-center RCT involved 408 participants with HFrEF randomized into two study arms, one receiving BAT with optimal medical management or

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

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

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

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

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

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

Two clinical trials are currently recruiting to study Barostim Therapy in Heart Failure. Recruiting is currently underway for the CVRx Barostim Therapy in Heart Failure with Reduced Ejection Fraction (HFrEF) Registry. The registry will include individuals who were recently implanted with the Barostim System for heart failure. Enrollment is expected to be up to 5,000 patients, from whom evaluations will be taken prior to device implant, at implant, and every six months after implant, up to 36 months. The

purpose of the registry is to develop valid scientific evidence of the safety and efficacy of Barostim in this patient population. This study has an estimated completion date of June 2028 (NCT04502316).

Recruiting is also currently underway for a study of Barostim Therapy In Heart Failure With Preserved Ejection Fraction (HFpEF). This registry will include individuals who were recently implanted with the Barostim System for heart failure. Enrollment is estimated to be 70 patients with resistant hypertension that also have evidence of heart failure with preserved ejection fraction (HFpEF). Data will be obtained from standard of care measurements taken prior to implant, at enrollment/baseline, and at 3 and 6 months after the device. The purpose of the study is to evaluate the Barostim Neo System in this population. The study has an estimated completion date of July 2024 (NCT02876042).

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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.

Singh et al. (2022) assessed the repeatability, reproducibility, and agreement between three diagnostic imaging platforms for tear film evaluation. The study included fifteen consecutive subjects (n = 30 eyes), with a mean age of 43 years, diagnosed with dry eye disease (DED) at a single site. The study also included thirty subjects (n = 60 eyes), with a mean age of 31 years, without DED as a control group. The study evaluated the LipiView® II Ocular Surface Interferometer, the IDRA Ocular Surface Analyzer (IDRA-OSA), and the Oculus® keratograph 5 M (K5M). Two investigators operated the diagnostic imaging platforms, and a single measurement was performed when determined acceptable by the instrument. One investigator repeated the measurements in all subjects. No two readings on the same subject were separated by more than a week. The lipid layer thickness (LLT) measurements with the IDRA-OSA and Lipiview did not show significant intraobserver differences between the control and DED groups. The coefficient of variation (CoV) was more in the DED group when compared to the control group. However, both groups demonstrated low repeatability. The IDRA-OSA showed better repeatability compared to the Lipiview. A Bland-Altman analysis also showed poor reproducibility and limits of agreement between two devices. The mean tear meniscus height (TMH) measured with the IDRA-OSA and K5M revealed high CoV in both the control and DED groups. While statistically insignificant for the K5M, the repeatability was poor for both diagnostic imaging platforms. A Bland-Altman analysis showed good reproducibility of both the IDRA-OSA and K5M. However, there was poor agreement between IDRA-OSA and K5M. The average non-invasive tear break-up time (NIBUT) values obtained using IDRA-OSA and K5M had lesser CoV in the control group when compared to the DED group. The intraobserver values did not show a significant difference. A Bland-Altman analysis showed good reproducibility of both the IDRA-OSA and K5M, but poor agreement between them. Between the three diagnostic imaging platforms, LLT, TMH, and NIBUT were significantly different for same observer. Limitations of this study include the number of eyes examined, uneven number of subjects between groups, and the different proportions of gender and age between groups. The study authors concluded the IDRA-OSA, K5M, and Lipiview cannot be used interchangeably; and tear film imaging should be interpreted considering the variability of these diagnostic imaging platforms and the variability in tear film irrespective of the device used.

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 does not assess diagnostic performance or clinical utility of tear film imaging.

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

The American Academy of Ophthalmology Summary Benchmarks on cornea/external disease (2022) recommend slit-lamp biomicroscopy to monitor or assess blepharitis and dry eye syndrome.

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

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

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

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

## Clinical Evidence

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

Tamaki et al. (2022) analyzed patients who were enrolled in an ongoing, single-center, prospective cohort study, the Osaka Prefectural Trial: Acute Heart Failure Syndrome Registry (OPAR). The study included 407 consecutive patients who were admitted for acute decompensated heart failure (ADHF) and who survived to discharge. The study authors sought to validate a recently developed 2-year cardiac mortality risk model and to compare its prognostic value with that of the Acute Decompensated Heart Failure National Registry (ADHERE) and Get With The Guidelines-Heart Failure (GWTG-HF) risk scores. The 2-year cardiac mortality risk model was calculated using four parameters: age, left ventricular ejection fraction, New York Heart Association functional class, and cardiac iodine-123 meta-iodobenzylguanidine (MIBG) heart-to-mediastinum ratio. ADHERE and GWTG-HF risk scores were calculated on admission. Cardiac MIBG imaging and echocardiography were performed just before discharge, after stabilization of HF symptoms. Patients were stratified into three groups based on their 2-year cardiac mortality risk: low-risk, intermediate-risk, or high-risk. The primary endpoint was cardiac death, including pump failure death, sudden cardiac death, and death due to acute myocardial infarction. The secondary endpoints were all-cause death, unplanned hospitalization for worsening HF (WHF), a composite of cardiac death and WHF, and a composite of all-cause mortality and WHF. Over a median follow-up period of 1,039 days, 135 patients died. Of those patients, 61 died from cardiac causes and 74 died from non-cardiac causes. WHF occurred in 120 patients. The median 2-year cardiac mortality rates estimated by the MIBG-based risk model were almost the same as those actually observed in each risk group: 3% versus 4% for the low-risk group, 7% versus 9% for the intermediate-risk group, and 20% versus 23% for the high-risk group. A receiver operating characteristic curve analysis of the 2-year follow-up period revealed that the 2-year MIBG-based risk model had higher predictive values, not only for cardiac death but also for all secondary endpoints, than the ADHERE and GWTG-HF risk scores. The authors concluded the 2-year MIBG-based cardiac mortality risk model was useful for predicting post-discharge clinical outcomes in patients with ADHF, but larger multicenter studies were needed to further evaluate its usefulness. The authors identified several limitations of the single-center study including the small sample size and that the ADHERE and GWTG-HF risk scores were developed for patients admitted with ADHF to predict in-hospital mortality, but not long-term prognosis.

Seo et al. (2022) also utilized the data from Osaka Prefectural Trial: Acute Heart Failure Syndrome Registry (OPAR); a prospective, single-center, observational prospective cohort to study 148 individuals admitted with acute decompensated heart failure (ADHF) and nonischemic preserved left ventricular ejection fraction (HFpEF) who underwent cardiac iodine-123 labeled metaiodobenzylguanidine ($^{123}$I-MIBG) imaging at discharge. The author's goal was to uncover the prognostic value of cardiac sympathetic nerve dysfunction using $^{123}$I-MIBG single-photon emission computed tomography (SPECT) imaging in those individuals with HFpEF. Methods utilized for the study include the cardiac $^{123}$I-MIBG heart to mediastinum ratio (H/M), which calculated the delayed planar image (late H/M), and SPECT analysis of the delayed image conducted, with the tracer uptake in all 17 regions on the polar map, scored with a 5-point scale. Calculating the total defect score (TDS) was accomplished by adding the score of each of the 17 segments, with the primary endpoint being the association between TDS and cardiac events. The authors concluded that from a mean follow-up period of 2.4 +/- 1.6 years, 61 individuals suffered cardiac events. TDS and cardiac events were significantly associated following the multivariate Cox adjustment ($p < 0.0001$). Those individuals with high

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

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

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

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

Jacobson et al. (2010) conducted a large prospective study evaluating global I-MIBG uptake and clinical outcomes. The study was known as the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure study (ADMIRE-HF). In this study, planar

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

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| Code | Description |
|---|---|
| 0333T | Visual evoked potential, screening of visual acuity, automated, with report |

**The use of automated visual evoked potentials (VEPs) for visual acuity screening is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy.**

## Clinical Evidence

Hutchinson, et al. (2022) published an American Academy of Ophthalmology's (ACOG).

Pediatric Eye Evaluations Preferred Practice Pattern. While this guideline addresses instrument-based screening techniques, such as photoscreening and autorefraction, as being useful for assessing amblyopia and reduced-vision risk factors for children ages 1 to 5 years, and instrument-based screening as useful for older children who are unable to participate in optotype-based screening, there is no mention of using visual evoked potential screening in this preferred practice pattern guideline for either population.

In their 2022 vision screening recommendations, The American Association for Pediatric Ophthalmology (AAPOS) and Strabismus does not specifically mention the use of automated visual evoked potentials.

Data from 55 infants with severe cerebral visual impairment (CVI) were retrospectively reviewed by Howes et al. (2022) to see if pattern reversal visual evoked potentials (PRVEPs) would predict visual acuity. Behavioral visual acuity and visual evoked potentials (VEPs) were compared from the infants' initial ophthalmology visit at median age of 14 months, to their final visit at late preschool/early school age (an approximate four-year follow-up). Median age was 14 months at T1 (range: 6-44mo) and 63 months at T2 (range: 29-150mo). The presence of a PRVEP produced by a check width of 50' (minutes of arc) or smaller (T1) predicted ($p = 0.05$) the presence of measurable preferential looking acuity at T2. The presence of PRVEP to check widths of 25' or smaller (T1) predicted ($p = 0.02$) better preferential looking acuity (logMAR-equivalent) scores at T2. The latter association was independent of presenting acuity at T1. The authors concluded that VEPs may have prognostic value regarding future visual acuity in young children with CVI. This study is limited by small sample size. Additionally, the severity of CVI in the study's participants does not allow generalizing these results to the entire CVI population and the implication of these findings for routine screening are unclear.

In this systematic review, Hamilton et al. (2021) attempted to collate descriptions of the visual evoked potential (VEP) limit in humans, and to look at the accuracy and preciseness of VEP spatial frequency (SF) limits on visual acuity. A total of 155 studies were included in this retrospective review. The difference between VEP SF limit and behavioral acuity is variable and strongly dependent on the VEP stimulus and choice of acuity test. VEP SF limits mature rapidly, from 1.5 to 9 cpd by the end of the first month of life to 12–20 cpd by 8–12 months, with slower improvement to 20–40 cpd by 3–5 years. VEP SF limits are much better than behavioral thresholds in the youngest, typically developing infants. This difference lessens with age and reaches equivalence between 1 and 2 years; from around 3–5 years, behavioral acuity is better than the VEP SF limit, as for adults. Healthy, artificially blurred adults had slightly better behavioral acuity than VEP SF limits across a wide range of acuities, while adults with heterogeneous ophthalmic or neurological pathologies causing reduced acuity showed a much wider and less consistent relationship. For refractive error, ocular media opacity or pathology primarily affecting the retina, VEP SF limits and behavioral acuity had a fairly consistent relationship across a wide range of acuity. This relationship was much less consistent or close for primarily macular, optic nerve or neurological conditions such as amblyopia. VEP SF limits were almost always normal in patients with non-organic visual acuity loss. Especially in pre-verbal children, or patients with motor or learning impairments, the authors concluded that the VEPSF limit has great use as an objective acuity estimator. The authors further state that VEPSF diagnostic power depends heavily on adequate, age-stratified, reference data, age-stratified empirical calibration with behavioral acuity, and interpretation in the light of other electrophysiological and clinical findings. Future developments could encompass faster, more objective and robust techniques such as real-time, adaptive control.

In their recommendation statement for vision screening in children ages 6 months to 5 years, the U.S. Preventive Services Task Force (USPSTF, 2017), has not recommended vision screening for infants and young children. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of vision screening for children less than 3 years of age. There is no mention of screening with automated visual evoked potentials in this recommendation.

In this comparison study, Kurtenbach et al. (2013) reviewed visual acuities estimated by three methods of visual evoked potential recordings to those obtained by two subjective measures ETDRS and FrACT (Freiburg acuity test), in ten healthy subjects (mean age 43.5 years). “Best-corrected acuity determined by the ETDRS was between 0.03 and -0.3 logMAR (mean -0.06). Sweep VEPs (sweepVEP), pattern appearance VEPs (pappVEP) and steady-state VEPs (ssVEP) were recorded with two electrode placements (10-20 and Laplace) with best optical correction and with artificially degraded vision using five Bangerter occlusion foils, reducing acuity to about 0.1, 0.22, 0.52, 0.7 and 1.0 logMAR (0.8, 0.6, 0.3, 0.2 and 0.1 decimal scale). Two runs were performed. ETDRS and FrACT acuities showed good agreement, even though ETDRS seemed to underestimate acuity compared with FrACT at higher acuities. Laplace derivation did not improve any of the VEP-estimated acuities over the 10-20. SweepVEP tended to overestimate lower FrACT acuities, but showed good repeatability. PappVEP placed FrACT acuities into correct or neighboring categories in 87% of cases. Average ssVEP acuity showed little difference to those of FrACT but variance was larger. ROC analysis for typical clinical application showed good performance for all three methods. The authors concluded that the two subjective measurements of acuities are well correlated. Under the conditions of this experiment, sweepVEP results were less variable and had a better repeatability than ssVEP acuities, whose analysis, in contrast to sweepVEP, can be automated. PappVEP estimates, however, offer a viable alternative, that is, quicker but lower performance regarding the detection of low acuity thresholds. The authors additionally stated that if an average of two runs is used, all of the methods employed had good performance related to minimum acuity detection. A limitation of this study is small sample size.

A study to assess visual acuity (VA) in 190 children, by determining the value of pattern visual evoked potentials (PVEP) to five consecutive check size patterns was undertaken by Gundogan et al. (2010). Eventually, eighty-five children in the study group and 74 children in the control group who cooperated well with PVEP testing were included. Results of this study showed normal values for latency, amplitude, and normalized interocular amplitude/latency difference in each check size were defined in the control group. PVEP-estimated VA (PVEP-VA) in the amblyopic eye was defined by the normal PVEP responses to the smallest check size associated with normal interocular difference from the non-amblyopic eye, and was considered predictive if it is within +/-1 Snellen line (1 decimal) discrepancy with BCVA in that eye. Mean age was 9.7 +/- 1.9 and 9.9 +/- 2.2 years in the study and the control groups, respectively. LogMAR (logarithm of minimum angle of resolution) Snellen acuity was well correlated with the logMAR PVEP-VA ($r = 0.525$, $p < 0.001$) in the study group. The Snellen line discrepancy between BCVA and PVEP-VA was within +/-1 Snellen line in 57.6% of the eyes. The authors concluded that PVEP to five consecutive check sizes may predict objective VA in amblyopic children.

Simon et al. (2004) studied a new child-friendly VEP system for use in vision screening. Visual evoked potentials were compared to standard ophthalmology examination in one hundred and twenty-two children, ages six months to five years, with the test being completed by 94% of the study group. A statistical program analyzed VEP differences between fellow eyes to

determine a "pass" or "fail" for each child. For verbal patients, clinical amblyopia was defined as an interocular difference of two or more lines in best-corrected visual acuity. For preverbal patients, clinical amblyopia was defined by the clinician's decision to treat with occlusion or atropine penalization. Preverbal children with significant refractive errors or structural eye pathology were also considered clinically abnormal. The authors concluded that this test shows promise as a screening tool to detect amblyopia and other visual deficits in young children, as this new system overcame technical difficulties associated with older VEP techniques due to its easy electrode placement and rapid attractive stimulus.

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

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

## Clinical Evidence

Flexible flatfoot (Flexible Pes Planovalgus, Pes Planus) is the result of the loss of the medial logitudinal arch, abduction of the forefoot and subtalar aversion. It is common in children, and in adults may be due to trauma, overuse and inflammatory disorders. It may be asymptomatic or become painful and require intervention. Non-surgical interventions include rest, physical therapy, orthotics and anti-inflammatory medications. Surgery may be indicated when conservative treatment is not successful.

Subtalar arthroereisis (SA) is a surgical procedure designed to correct the excessive movement of the joint by placing an implant in the sinus tarsi, or adjacent to it. The implants are commonly made of titanium or a resorbable poly-L-lactic acid (PLLA).

Garcia Bistolfi et al. (2022) conducted a retrospective cross sectional study to evaluate the clinical/functional and radiographic outcomes of percutaneous subtalar arthroereisis in pediatric patients with painful and disabling Flexible Flat Foot (FFF) for a minimum period of 6 months, and refractory to conservative treatment. Fourteen patients (19 feet) aged 8-14 and followed for at least 24 months met the inclusion criteria. The results showed that all radiographic angles measured improved significantly, and only the talar declination angle and Kite’s angle reached normal values. No signs of subtalar osteoarthritis were found in any of the patients with follow-up longer than 5 years, and no implants were removed due to breakage, migration or pain. The American Orthopedic Foot and Ankle Scale (AOFAS) score showed significant improvement in all patients. These results however should be interpreted with caution, as this score has not been validated for pediatric patients, and answers given by children may be influenced by parents or interviewer. The authors concluded that subtalar arthroereisis is effective for improving clinical-functional and radiographic parameters in painful moderate pediatric FFF in children aged 8-14 as patients

under 8 may undergo spontaneous resolution of their flat feet, and those over 14 have little remaining growth and, therefore, limited remodeling capacity. This study is limited by its small number of participants, retrospective design and lack of a control group.

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

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

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

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

In a 2020 evidence- based consensus statement on the appropriate clinical management of adult acquired flatfoot deformity, the American College of Foot and Ankle Surgeons stated that subtalar arthroereisis should not be considered as a single corrective procedure for stage IIB AAFD. The rationale for this is that the use of a subtalar implant alone to address pronation of the foot has limited literature demonstrating its use in the flexible deformity without advanced disease of surrounding soft tissues including tendon and ligament. The subtalar implant is designed to be performed with tensioning of the soft tissue structures to allow for their protected healing (Piraino et al., 2020).

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

A 2020 Hayes health technology assessment (updated in 2023) regarding subtalar arthroereisis for the treatment of pediatric flatfoot (FF) focused on this treatment for children with symptomatic flatfoot deformity that does not respond to conservative measures and negatively impacts daily activities of living (ADLs). 13 studies were included and 11 of those included children with idiopathic flexible flatfoot (FFF) and 2 included children with spastic FF associated with cerebral palsy (CP). An overall low-quality body of evidence suggests that SA is relatively safe and efficacious for treating idiopathic FFF in children with pain, decreased function, and other symptoms that are refractory to standard medical therapies. However, the majority of studies are retrospective, there are few comparative studies, and no well-designed controlled studies to draw firm conclusions regarding its efficacy and safety. For children with spastic FF, there is a paucity of evidence and the overall quality of the body of evidence is very low. Indications were consistent in studies of idiopathic or spastic FF, but overall substantial heterogeneity exists in surgical approaches, implant devices, and concomitant procedures. Clinical outcome measures varied from validated questionnaires and scales to patient-reported, subjective results (e.g., patient satisfaction with SA). There is a need for additional well-designed clinical studies to develop patient selection criteria and evaluate the long-term efficacy and safety.

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

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

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

Despite the good clinical results of subtalar arthroereisis for the management of flexible flatfoot in children, it is mostly performed using a metallic screw which typically requires removal after 2-3 years. Giannini et al. (2017), included in Smolle

study above, conducted a retrospective cohort study of a consecutive series of 44 patients treated with a bioabsorbable calcaneal screw. The surgical technique was simple, and no intraoperative complications were reported. The mean follow-up duration was 56 months, with more than 95% of the patients reporting excellent or good clinical results. The authors concluded that the using the absorbable screw was an effective solution for flexible flatfoot in pediatric patients, simple, reliable and minimally invasive, with a high patient satisfaction level by eliminating a second surgical procedure for implant removal.

National Institute for Health and Care Excellence (2009) guidance concluded that current evidence on the safety and efficacy of sinus tarsi implant insertion for mobile flatfoot was inadequate in quality and quantity and should only be used with special arrangements for clinical governance, consent and audit or research.

Numerous implant systems have received FDA approval through the 510(k) process. Refer to the following website for more information (use product code HWC): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed March 9, 2023)

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

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

## Clinical Evidence

The 2023 NICE Interventional Procedure guidance recommended that percutaneous transluminal renal sympathetic denervation (RSD) for resistant hypertension should only be used with unique clinical governance, consent, and audit or research arrangements. It states that the evidence suggests that there are no major safety concerns in the short term, and complications are well recognized such as renal artery damage. The evidence shows that it reduces blood pressure in the short and medium term. Overall, there are uncertainties about how well it works in the long term and whether there are long-term complications. So, it should only be used with special arrangements.

A clinical consensus by the European Society of Cardiology (ESC) Council on Hypertension and the European Association and Percutaneous Cardiovascular Interventions (EAPCI) proposes that renal denervation (RDN) is an adjunct treatment option in uncontrolled resistant hypertension, confirmed by ambulatory BP measurements, despite best efforts at lifestyle and pharmacological interventions and that RDN may also be used in patients who are unable to tolerate antihypertensive medications in the long term. A shared decision-making process is a key feature and preferably includes a patient who is well informed on the benefits and limitations of the procedure. Multidisciplinary hypertension teams encompassing hypertension specialists and interventionalists should gauge the indication and allow/disallow the RDN procedure. Centers executing these procedures require the skills and sources to deal with possible complications. Future research is needed to address open questions and research the influence of BP-lowering with RDN on clinical outcomes and prospective clinical indications outside hypertension (Barbato et al., 2023).

In an effort to evaluate the safety and efficacy of endovascular ultrasound RDN for individuals with resistant hypertension, Azizi et al. (2021) conducted a randomized, single-blind international sham-controlled clinical trial that took place at 28 facilities in the United States and 25 facilities in Europe (RADIANCE-HTN). Individuals aged 18-75 with office-measured BP of at least 140/90 despite the use of at least 3 antihypertensives (including diuretics) were included. Of 989 total originally enrolled, 136 participants met all inclusion criteria and were randomly assigned to either RDN (n = 69) or sham (n = 67) procedure. Both the participants and those making assessments were masked to randomization. Participating individuals were switched to a daily, fixed-dose, single-pill, including an angiotensin receptor blocker, a calcium channel blocker, and a thiazide diuretic, which continued for 4 weeks. Change in daytime ambulatory systolic BP at 2 months in the intention-to-treat group was the primary endpoint of the study, along with safety. With measured adherence to combination medication similar in both groups (82% in the RDN group vs 82% in the sham group), the RDN group showed a reduced ambulatory systolic BP compared to the sham procedure. The median between-group difference was -4.5 mm Hg, and among participants with complete ambulatory BP data, the difference was -5.8 mm Hg. No difference in safety outcomes was noted between the two groups. The authors concluded that ultrasound RDN resulted in reduced BP after 2 months in participants with resistant hypertension compared to the sham procedure. They suggest that if studies continue to demonstrate the safety and BP-lowering effects of RDN, it may become an option (potentially as an alternative to the addition of further antihypertensive medication) for treating individuals with resistant hypertension.

Azizi et al. (2022) conducted a prespecified evaluation after the RADIANCE-HTN TRIO randomized clinical trial. At six months post randomization a smaller quantity of drugs was added in the uRDN group [n = 64, mean (SD), 0.7 (1.0) medications] vs sham [n = 65, mean (SD), 1.1 (1.1) medications; p = .045], and fewer participants in the uRDN group took aldosterone antagonists at six months [26 of 65 (40.0%) vs. 39 of 64 (60.9%); p = .02]. Even though less intensive standardized stepped-care antihypertensive treatment, mean (SD) daytime ambulatory BP at six months was 138.3 (15.1) mm Hg with uRDN vs. 139.0 (14.3) mm Hg with sham, while home systolic BP was reduced to a greater degree with uRDN by 4.3 mm Hg (95% CI, 0.5-8.1 mm Hg; p = .03) in a mixed model adjusting for baseline and number of medications. The authors concluded that for individuals with resistant hypertension originally randomly assigned to uRDN or a sham procedure and who had a persistent rise of BP two months after the procedure, a protocolized increase of antihypertensive medications resulted in a comparable BP decrease at six months in both groups, with less added drugs, particularly aldosterone antagonists, in the uRDN group. Limitations to the study are the short duration of follow-up to evaluate the longer-term durability of the BP-lowering outcome of uRDN and its safety.

In 2022, Kario et al. conducted an RCT (REQUIRE trial) to explore the BP -lowering efficacy of RDN for treating individuals with resistant hypertension. The prime endpoint was the difference in baseline systolic BP at three months. The study included 143 individuals, with 72 assigned to the RDN group and 71 to sham control. The outcomes showed that reduction from baseline in

24-hour ambulatory systolic BP at three months was not meaningfully different among the RDN (-6.6 mmHg) and sham control (-6.5 mmHg) groups (difference: -0.1, 95% confidence interval -5.5, 5.3; p = 0.971). Decreases from baseline in home and office systolic BP (differences: -1.8 mmHg [p = 0.488] and -2.0 mmHg [p = 0.511], respectively), and medication load, did not differ significantly between the two groups. The procedure-device-related major adverse events were not seen. Though BP decrease after renal denervation was comparable to other sham-controlled studies, the sham group in this study established a much more substantial reduction. Limitations to the study include an absence of standardization of antihypertensive medications or objective measurement of medication adherence, absence of double-blinding, marked seasonal variations in the temperature and BP, and relatively short duration of follow-up. Clinical Trial Registration: NCT02918305.

Bhatt, et al conducted a 36-month follow-up results from the single-blind, multicenter, sham-controlled, randomized trial SYMPLICITY HTN-3 trial (2022). The study aimed showed safety but not efficacy of the Simplicity system at 6 months post randomization. A total of 88 centers were included, and adults with treatment-resistant hypertension on stable, maximally tolerated doses of three or more medications, including a diuretic, with a systolic BP of 160mmHg or more (seated) and a 24h ambulatory systolic BP of 135 mmHg or more were randomized in a 2:1 ratio to renal artery denervation using the single electrode (Flex) catheter or sham control. The participants were unmasked at the 6-month point, where the eligible participants in the sham control group meeting inclusion criteria were given the option to cross over to the treatment group. The changes in systolic BP were then followed up to 36 months and analyzed by comparing groups. Of 1442 participants, 364 received active treatment, and 171 received sham control; 219 individuals were available for 36-month follow-up, 63 in the crossover group, and 33 in the non-crossover group. The results showed that the change in 24 h ambulatory systolic BP at 36 months was -15·6 mm Hg (SD 20·8) in the renal artery denervation group and -0·3 mm Hg (15·1) in the sham control group (adjusted treatment difference -16·5 mm Hg [95% CI -20·5 to -12·5]; p ≤ 0·0001). Without imputation, the renal artery denervation group spent a significantly longer time in the therapeutic BP range (i.e., better BP control) than participants in the sham control group (18% [SD 25·0] for the renal artery denervation group vs. 9% [SD 18·8] for the sham control group; p ≤ 0·0001) despite a similar medication burden, with consistent and significant results with imputation. Rates of adverse events were similar across treatment groups, with no evidence of late-emerging complications from renal artery denervation. The rate of the composite safety endpoint to 48 months, including all-cause death, new-onset end-stage renal disease, a significant embolic event resulting in end-organ damage, vascular complication, renal artery re-intervention, and hypertensive emergency was 15% (54 of 352 individuals) for the renal artery denervation group, 14% (13 of 96 individuals) for the crossover group, and 14% (10 of 69 individuals) for the non-crossover group. The authors concluded that this final report of the SYMPLICITY HTN-3 trial adds to the evidence supporting renal artery denervation's safety 36 months after the procedure. From 12 months to 36 months after the procedure, those who were originally randomly assigned to receive renal artery denervation had more significant reductions in BP and better BP control than participants who received sham control. The findings are however limited by lack of randomization after six months.

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

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

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

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

Silverwatch et al. (2021) published a systematic review and network meta-analysis (NMA) of RCT comparing the efficacy and safety of existing RDN interventions for uncontrolled hypertension and resistant hypertension to determine their effects on several intermediate and clinical outcomes. Twenty RCTs were included, with 2,152 participants (mean ages 48-64 years old) with resistant hypertension and/or uncontrolled hypertension and follow-up time ranging from two to six months. NMA and frequentist framework were used to evaluate RDN interventions such as radiofrequency in the main renal artery (MRA) and branches, radiofrequency in MRA, radiofrequency in MRA plus antihypertensive therapy (AHT), ultrasound (US) in MRA, sham, and AHT. The data findings were that radiofrequency in MRA, and branches were the best intervention to reduce 24-h ambulatory, daytime, and nighttime SBP and DBP compared to other interventions; only 24-h ambulatory SBP and DBP were significantly reduced in comparison. Radiofrequency in MRA plus AHT was the best intervention to lower office SBP and DBP compared to other interventions, but neither was significant. The leading RDN interventions were similar after analysis in six-month follow-up and resistant hypertension only trials. The authors concluded that scarce data and uncommonly described outcomes in the existing trials led to no significant difference in RDN on clinical outcomes. Therefore, more clinical outcome data is needed for future trials to further the safety and efficacy of RDN interventions. The studies by Desch et al. (2015), and Bhatt et al. (2014), included in the previous versions of this policy, are included in this systematic review and are no longer discussed in detail below. In addition, this systematic review is included in the 2021 Hayes Evolving Evidence Review above.

A systematic review and meta-analysis regarding the state of RSD for managing individuals with hypertension was published by Syed et al. in 2021. Eight studies, with a total of 1363 individuals, were included. The mean age was 56 years of age ±2.6 years, and 29% of participants included were women. Data was pooled from RCT, and a comparison of RSD in managing hypertension to sham procedures was performed. The median maximum follow-up was 6-month range (3-12 months). Data showed a 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 the management of hypertension demonstrated reduced ambulatory and office BP compared to sham procedure(s); however, additional high-quality RCTs of RSD are needed to assess the impact on clinical outcomes and confirm safety and reproducibility. The studies by Desch et al. (2015), Bhatt et al. (2014), Esler et al. (2012), included in the previous versions of this policy, are included in this systematic review and are no longer discussed in detail below.

Lambert et al. (2012) evaluated the effects of RDN 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 RDN for individuals with uncontrolled BP. For baseline comparisons, matched data were extracted from the Australian Diabetes, Obesity, and Lifestyle database. Before RDN, individuals 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 with the change in QOL. RDN did not have a detrimental effect on any elements of the 36-Item Short-Form Health Survey. These results indicate that individuals 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 RDN; however, this was not directly associated with the magnitude of BP reduction. Study limitations included a lack of a comparison group.

Brandt et al. (2012) investigated the effect of catheter-based RSD on left ventricular hypertrophy (LVH) and systolic and diastolic function in a cohort study of individuals with resistant hypertension. Forty-six people underwent bilateral RDN, and 18 served as controls. Transthoracic echocardiography was performed at baseline and after 1 month and 6 months. Besides the reduction of systolic and diastolic BP (-22.5/-7.2 mm Hg at 1 month and -27.8/-8.8 mm Hg at 6 months, p < 0.001 at each time point), RDN 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 RDN 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 a reduction of LV filling pressures. No significant changes were observed in control group. Study authors suggest that RDN significantly reduces LV mass and improves diastolic function, which might have important prognostic implications for individuals with resistant hypertension at high cardiovascular risk.

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| Code | Description |
|---|---|
| 0347T | Placement of interstitial device(s) in bone for radiostereometric analysis (RSA) |
| 0348T | Radiologic examination, radiostereometric analysis (RSA); spine, (includes cervical, thoracic and lumbosacral, when performed) |
| 0349T | Radiologic examination, radiostereometric analysis (RSA); upper extremity(ies), (includes shoulder, elbow, and wrist, when performed) |
| 0350T | Radiologic examination, radiostereometric analysis (RSA); lower extremity(ies), (includes hip, proximal femur, knee, and ankle, when performed) |

**Radiostereometric analysis (RSA) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.**

## Clinical Evidence

Radiostereometric analysis (RSA) is a technique used to predict the stability of joint implants by assessing early movement. At the time of surgery, small tantalum markers are embedded into the bone, and then postoperative biplanar x-rays are taken through a calibration cage, which has known reference points. These images are analyzed with an RSA software package that calculates micromotion between the implant and bone in 3D. These measurements are then converted into the maximal total point motion. By repeating the x-ray analysis at 6-month intervals, the maximal total point motions can be compared (Aspinall and Dunbar, 2009).

RSA is widely utilized in clinical research to evaluate devices and materials. However, there is inadequate evidence of its effectiveness in impacting clinical outcomes. Larger scale randomized controlled trials comparing outcomes with standard imaging technologies are needed to demonstrate efficacy.

### *Orthopedic Implants*

Pijls et al. (2018) conducted a systematic review and meta-analysis to evaluate the early and long-term migration patterns of tibial components of total knee replacement (TKR) of all known RSA studies. The inclusion criteria were primary TKR, and maximal total point motion (MTPM). Fifty three studies comprised of 111 study groups and 2,470 knees were included. Prostheses were classified according to prosthesis, fixation and insert (PFI) methodology, and a study group was defined as a group of patients in a study with the same PFI. Migration pattern was defined as at least 2 postoperative follow-up moments within the first 2 years of follow-up. One year follow up was the most frequently reported and used for the meta-analysis. The results showed that the pooled increase in migration between 6 months and 1 year in MTPM was 0.04 mm (CI 0.02–0.07) based on 70 study groups, and between 1 and 2 years was 0.04 mm (CI 0.02–0.06) based on 105 study groups. 8 study groups reported MTPM migration results up to 10 years' follow-up and the majority of TKR stabilized during follow-up, although 2

uncemented types of TKR continued to migrate. The majority of early migration occurs in the first 6 postoperative months followed by a period of no or very little migration within the bone. The authors concluded that RSA has a place in the monitoring of new TKR migration and should be part of all phased introduction of new implants. This SR is limited by the lack of standardized reporting of outcomes in the included studies, making an accurate assessment on clinical efficacy not possible.

In a 2017 systematic review, Ten Brinke et al. evaluated 23 studies to investigate the accuracy and precision of RSA to analyse early migration of prostheses of the upper limb (shoulder (14), elbow (4), wrist, and 5 involving the trapeziometacarpal (TMC) joint). Due to the small number of studies on RSA for the upper limb, all types of study design were included. Accuracy data were collected from studies that compared RSA with another method that calculates migration and has a substantially better resolution. The precision of translation and rotation values was assessed by all results from double examinations. The standard deviations (SDs) of the migration calculated using double examination was used to determine precision, defined as 1.96 × SD. Precision was calculated separately for the shoulder, elbow, and TMC joint. If prosthesis components were analyzed separately, precision was calculated for each component. If precision was given for all 3 axes (the x-, y-, and z-axis), the lowest precision was used to calculate the mean precision. For accuracy, there were no studies that reported accuracy data from marker and model based RSA despite ISO standards calling for both measurements as part of clinical studies. For precision, the values of translation measurements were comparable for those seen with RSA of total hip and knee arthroplasty, with values for the shoulder in the 0.06-0.88 mm, 0.05-10.7° range, elbow 0.05-0.34 mm and 0.16–0.76° range, and 0.16–1.83 mm and 11–124° range for the trapeziometacarpal joint. The authors concluded that RSA is a highly precise technique for detecting early migration of upper limb implants. This review is limited by the small number of studies analyzed and the lack of the studies adherence to ISO guidelines for precision. Further research is needed in assessing the value of RSA for upper limb arthroplasty.

### *Bone Fracture Healing*

Lee and Copp (2022) conducted a review of the published literature on the use of new and emerging technologies to assess fracture healing. RSA was included in this review and the results have shown to be accurate, precise and safe in evaluating various aspects of fracture care including the early detection of nonunion. However, challenges remain, including implantation difficulty in some areas, as well as difficulty in inducible micromotion at various stages in healing. The authors concluded that RSA is a potentially powerful tool in fracture care, and more research with larger patient populations is needed to validate these findings

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

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

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

## Clinical Evidence

Optical coherence tomography (OCT) is a high-speed, high resolution microscopic imaging modality. OCT is the optical equivalent of ultrasound, relying on the echo of near-infrared light instead of sound to produce micron-scale resolution through 1–2 mm in biological tissue. In contrast to high-energy X-rays and gamma rays, OCT relies on low-energy near-infrared light, which is nondestructive to tissue and can resolve microscopic structures that cannot be seen with X-rays or computed tomography (CT) and does not require contrast injection (Mojahed et al. 2019). By enabling surgeons to rapidly visualize tissue morphology beneath the surface and over large surface areas while preserving tissue structure, OCT has the potential to become an invaluable intraoperative tool for assessing margin status.

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

Heidkamp et al. (2021) conducted a systematic review and meta-analysis on 134 studies evaluating the use of novel imaging techniques for intraoperative margin assessment in human subjects, with histopathology as the reference standard. This overview of 16 techniques, which included optical coherence tomography (OCT), assessed technical properties, feasibility in clinical practice and diagnostic accuracy. Most studies (73% n = 66) were in the early stages of research and development. The majority (n = 100; 75%) of techniques were applied in open surgical procedures and most techniques (n = 108) assessed margins on the specimen resected. Only one fourth of all studies (n = 33) reported diagnostic accuracy on margin assessment with sensitivities ranging from 21% to 100% and specificities from 37% to 100%. Per the authors, the field of novel techniques (including OCT) for intraoperative margin assessment is highly evolving and in early developmental stages; the results suggested that none of the techniques studied were superior nor had high feasibility or diagnostic accuracy. The researchers concluded that this review does not support the recommendation of any of these techniques as showing promise for clinical practice. A comparison of all techniques within one framework could assist in the selection of imaging techniques for intraoperative margin assessment that meet specific needs and may subsequently guide research and development of promising techniques.

Zysk et al. (2015) assessed forty-six patients with early-stage breast cancer undergoing BCS at two study sites, During BCS, cavity-shaved margins were obtained, and the final margins were examined ex vivo in the operating room with a probe incorporating optical coherence tomography (OCT) hardware and interferometric synthetic aperture microscopy (ISAM) image processing. Images were interpreted after BCS by three physicians blinded to final pathology-reported margin status. Individual and combined interpretations were assessed. Results were compared to conventional postoperative histopathology. Out of eight patients (17%) with positive margins (0 mm), the device identified all positive margins in five (63%) of them where reoperation could potentially have been avoided. Among patients with pathologically negative margins (> 0 mm), an estimated mean additional tissue volume of 10.7 ml (approximately 1% of overall breast volume) would have been unnecessarily removed due to false positives. The authors concluded that intraoperative optical imaging of specimen margins with a handheld probe may potentially eliminate many reoperations. However, this study is limited by the small study population.

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.

## Reference(s)

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

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

## Clinical Evidence

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

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

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

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

In 2019, the American Society for Parenteral and Enteral Nutrition (ASPEN) conducted a systematic review to use the best available evidence to develop guidelines on the validity of different body composition methods. Regarding BIA, no recommendations can be made due to limited data, or the proprietary nature of specific devices.

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

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

Brantlov et al. (2017) conducted a systematic review to study the degree to which BIA publications conducted in healthy pediatric populations (aged 0-17 years) were standardized. Internationally recognized electronic databases and hand searching of the reference lists was conducted to identify relevant papers. The review was limited to lead-type BIA devices for whole-body, segmental- and focal impedance measurements. In total, 71 papers published between 1988 and 2016 were included. To evaluate the degree of standardization of the papers, a recently published review detailing critical factors that may impact on BIA measurements in children was used as a model for structuring and extracting data. The results showed a general lack of BIA standardization, or its reporting, which hinders comparison of data between studies and could potentially lead to erroneous measurements. The authors concluded that if the BIA technique is accepted clinically for routine use in pediatric populations, but that there is a need for an increased focus on the importance of improved standardization and its reporting in future studies.

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

Johnstone et al. (2014) conducted a study utilizing three groups of six obese men to evaluate the accuracy of bioelectrical impedance spectroscopy (BIS) in measuring the following: FM, 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 very low calorie diet (VLCD) (2.5 MJ/day for 3 weeks); or (iii) a low calorie diet (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 BIA. The purpose of the study was to measure the TBW and percent body fat before and 12 months after bariatric surgery. The findings showed that the T0 to T12 median (IQR) change in deuterium TBW and 3C% fat was -6.4 L (6.4 L) and -14.8% (13.4%), respectively. There were no statistically significant differences between deuterium and BIA determined TBW [median (IQR) difference: T0 -0.1 L (7.1 L), p = 0.75; T12 0.2 L (5.7 L), p = 0.35; ∆ 0.35 L

(6.3 L), p = 1.0]. Compared with 3C, BIA underestimated %fat at T0 and T12 [T0 -3.3 (5.6), p < 0.001; T12 -1.7 (5.2), p = 0.04] but not change [0.7 (8.2), p = 0.38]. Except for %fat change, Bland-Altman plots indicated no proportional bias. However, 95% limits of agreement were wide (TBW 15-22 L, %fat 19-20%). According to the authors, BIA may be appropriate for evaluating group level response among severely obese adults. The authors state that clinically meaningful differences in the accuracy of BIA between individuals exist.

## Reference(s)


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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

Traditional brachytherapy refers to the placement of radioactive sources on or inside the cancer tissues. Based on the type of sources, brachytherapy can be classified as radionuclide and electronic brachytherapy. Electronic brachytherapy is a new form of radiotherapy that delivers a very high dose of radiation inside or very close to the cancer tissues. These devices utilize a miniaturized X-ray source to deliver radiation at relatively high dose rates to the target volume. Electronic brachytherapy eliminates some of the accidents related to radionuclide brachytherapy such as loss of sources, radiation leakage in off state, transportation accidents and radioactive waste. It finds wide applications in the treatment of cancers including skin, breast, endometrium, cervix and spinal metastasis. Electronic brachytherapy is a promising technology of the future and could potentially replace radionuclide brachytherapy (Ramachandran 2017).

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 (ABS 2019).

## *Breast Cancer*

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer do not specifically address electronic brachytherapy (NCCN, 2023).

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, 2019).

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).

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, 2023a; 2023b).

An American Brachytherapy Society consensus statement for skin cancer brachytherapy states that **s**tudies of electronic brachytherapy for keratinocyte carcinoma (previously nonmelanoma skin cancer) (KC) are promising and the current recommendation is that it be used in prospective registries or clinical trials (ABS 2020).

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

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 (AAD 2018c).

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 routine 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 (AAD 2018a, b).

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 for BBC and SCC (2016 revised 2021) presents the following guiding principles:

- 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 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.

### *Other Indications*

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

A 2021 ECRI clinical evidence assessment regarding the Axxent Electronic Brachytherapy System (iCAD, Inc.), focused on its safety and effectiveness in treating gynecological cancers and how it compares with conventional brachytherapy. Seven case series were assessed, all of which were at high risk of bias, due to 2 or more of the following: small study size, retrospective design, single-center focus, and lack of parallel controls. Additionally, some studies enrolled patients with various types and stages of gynecologic cancers or used external beam radiation therapy (EBRT) in addition to electronic brachytherapy (EBT), or 192Ir high-dose rate (HDR) brachytherapy before EBT treatment, both of which limits evidence interpretation. One study enrolled patients both with and without previous chemotherapy, further confounding results. Furthermore, two studies may have had patient overlap, but reported on different outcomes of interest. It was concluded that the evidence is inconclusive and

does not demonstrate that electronic brachytherapy with the Axxent system improves outcomes in women with gynecological cancers better than conventional brachytherapy and large trials that assess its effectiveness in each type of cancer are needed.

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 (ABS 2019).

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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 |

| Code | Description |
|---|---|
| 43252 | Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy |
| 88375 | Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session |

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

## Clinical Evidence

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

Vithayathil et al (2022) conducted a randomized crossover trial with the primary aim to evaluate the diagnostic accuracy for dysplasia of autofluorescence imaging (AFI)-guided probe-based confocal laser endomicroscopy (pCLE) compared with high-resolution white-light endoscopy (HRWLE) and Seattle protocol biopsies in patients with BE and no endoscopically visible lesions. The secondary aim was to evaluate the added diagnostic value of molecular biomarkers, the time to perform standard and experimental procedures, and the acceptability by patients of optical dysplasia diagnosis. A total of 154 patients were recruited, of whom eight were excluded based on presence of clear macroscopic lesions consistent with BE-related neoplasia upon first endoscopy. A total of 134 patients completed both arms of the study, with crossover occurring after a 6-to-12-week interval. Endoscopists were blinded to the endoscopy and histology results of the pretrial endoscopy and other study arm. In the per-lesion analysis, optical diagnosis by CLE had a sensitivity and specificity for high-grade dysplasia (HGD)/intramucosal cancer (IMC) of 69.2% and 73.2%, respectively. In the per-patient analysis, there was no difference in the sensitivity of CLE for dysplasia compared with Seattle protocol for HGD/IMC (76.5% for both; p = 1.00) or all grades of dysplasia (74.3% vs. 80.0%, respectively; p = .48). The specificity of CLE was 60.7% for HGD and 66.7% for all grades of dysplasia. Use of a 3-biomarker panel consisting of one or more of optical dysplasia on CLE, aberrant p53 on immunohistochemistry, and/or aneuploidy on flow cytometry was associated with a per-patient sensitivity and specificity of 94.1% and 49.6% for HGD and 91.4% and56.6% for all grades of dysplasia, respectively. Study limitations included the following; the referral histology within the prior 12 months was only available in 64.2% of cases, secondly based on the crossover study design, it could not be excluded that prior biopsy sites may have appeared as irregularities on second endoscopy, variations in endoscopists indicated that two had a low sensitivity for detecting dysplasia, and lastly, the results may not be generalized across the general public sense the study was only performed at two high volume tertiary referral centers . The authors concluded that CLE has similar diagnostic accuracy for dysplasia compared with standard Seattle protocol endoscopy. In addition, the trial provides a methodological model for future studies investigating the endoscopic diagnosis of flat dysplasia. The addition of the use of molecular biomarkers could improve diagnostic accuracy.

Park et al. (2019) conducted a randomized controlled trial assessing probe confocal laser endomicroscopy (pCLE) and if this 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, may demonstrate a limitation. Other limitations included different biopsy samples were used for histopathological examination of tumor markers. There may be a learning curve for the pCLE examination and lack of data on

patients' outcomes limiting the conclusions that can be drawn on the clinical utility of this technology. Results will need to be validated with further studies on this new emerging technique.

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

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

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

In a small prospective study evaluating lesions of the larynx (30 lesions in 19 patients), Vollger et al. concluded that when used in conjunction with optical coherence tomography, CLE seems helpful for discrimination of noninvasive lesions, although it tends to overrate the severity of the changes (2016).

In a systematic review and meta-analysis, Su et al. (2013) assessed the effectiveness of CLE for discriminating colorectal neoplasms from non-neoplasms. The secondary aim of the review was to compare the efficacy of endomicroscopy and chromoendoscopy for diagnosing colorectal neoplasms. Pooled sensitivity and specificity were compared using univariate regression analysis according to prespecified subgroups. Pooled relative risk was computed to compare the accuracy of endomicroscopy and chromoendoscopy. Fifteen studies (published between 2000 and 2012) involving 719 patients and 2290 specimens were included in the analysis. The pooled sensitivity of all studies was 0.94, and pooled specificity was 0.95. Real-time CLE yielded higher sensitivity and specificity than blinded CLE. For real-time CLE, endoscopy-based systems had better sensitivity and specificity than probe-based systems. CLE yielded equivalent accuracy compared with magnifying virtual chromoendoscopy and magnifying pigment chromoendoscopy. The authors concluded that CLE is comparable to colonoscopic histopathology in diagnosing colorectal neoplasms, and that CLE is better when used in conjunction with conventional endoscopy. According to the authors, this review was limited by the relatively high heterogeneity presented across the 15 enrolled studies. The authors stated that there is a need for prospective randomized studies to obtain unbiased results

on the effectiveness of CLE along with standardization of the procedure and a comparison between this strategy and conventional colonoscopy.

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

## Clinical Practice Guidelines

### *American College of Gastroenterology (ACG)*

The ACG updated 2022 clinical guideline on Diagnosis and Management of Barrett's Esophagus offers recommendations for the diagnosis, screening, surveillance, and endoscopic and medical therapy of Barrett's Esophagus. A variety of advanced imaging techniques have been developed in an effort to improve the detection of dysplasia and esophageal adenocarcinoma (EAC) and thereby improve on the Seattle protocol in combination with high-definition white light endoscopy. Confocal laser endomicroscopy uses blue laser light to illuminate the esophageal tissue after intravenous injection of fluorescein. This allows for real-time in vivo imaging at high magnification to take optical targeted biopsies. To date, two systems have been developed; endoscope and probe based, with only the second still being commercially available. The most recent systematic review and meta-analysis of 7 studies of 473 patients who combined both probe-based and endoscope-based systems found a pooled sensitivity for per patient analysis when compared with histopathology of 89% (95% CI 0.82–0.94; $I^2$ = 31.6%) and specificity of 83% (95% CI 0.78–0.86; $I^2$ = 90.1%). While results are promising, there are multiple limitations, including the need for intravenous fluorescein, training in image interpretation, and time to complete the examination. Given that many of these studies were performed in centers with a high prevalence of dysplasia/neoplasia, the relevance of these data to a general observation population is unknown. Despite the limitations, in centers with a high prevalence of neoplasia or dysplasia, confocal endomicroscopy may be helpful in targeting biopsies and guiding therapy, although the value above that of high-definition white light and electronic chromoendoscopy is unclear.

### *American Gastroenterological Association (AGA)*

The AGA in a 2022 Clinical Practice Update on advances and innovation regarding the screening and surveillance of Barrett's esophagus provided the best practice advice indicating that advanced imaging technologies may be used as adjunctive imaging techniques to identify dysplasia. The panel was supportive of the need to have improved imaging technologies to better identify areas of dysplasia and early cancer. Technologies considered for this discussion included confocal (CLE) or volumetric laser endomicroscopy. A meta-analysis of 14 studies of 789 patients with 4047 lesions found CLE had a per-lesion analysis pooled sensitivity and specificity of 77% (95% confidence interval [CI], 0.73–0.81) and 89% (95% CI, 0.87–0.90), respectively. A separate meta-analysis of 5 studies involving 251 patients assessing within-patient comparisons of narrow band imaging and CLE found the pooled additional detection rate of CLE for per-lesion detection of neoplasia in patients with BE was 19.3% (95% CI, 0.05–0.33), but a comparable per-patient pooled sensitivity and specificity. Volumetric laser endomicroscopy, though not currently available commercially, has introduced several new advances with regards to imaging in BE, including laser marking and the interpretation of imaging using artificial intelligence. The panelists felt strongly this was an important area where further improvement is needed, but that the use of these techniques was not required for a high-quality exam and the data to date did not support its routine use. Nevertheless, the panel felt these technologies were promising and supported potential benefits in certain cases while being performed at expert centers.

### *American Society for Gastrointestinal Endoscopy (ASGE)*

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

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Xiong YQ, Ma SJ, Hu HY, et al. Comparison of narrow-band imaging and confocal laser endomicroscopy for the detection of neoplasia in Barrett's esophagus: A meta-analysis. Clin Res Hepatol Gastroenterol. 2018;42(1):31-39.


| 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

(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 individuals with essential tremor (ET) who have not responded to medication. Additional information is available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-mri-guided-focused-ultrasound-device-treat-essential-tremor. (Accessed: April 20, 2023)

The FDA approved an expansion of the indication of ExAblate Neuro to include the treatment for individuals 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 populations may benefit from this therapy.

## *Essential Tremor*

In 2022, Cosgrove and colleagues evaluated MRgFUS thalamotomy for ET at 4- and five years posttreatment and the long-term safety and efficacy in a prospective, controlled, multicenter clinical trial. At four years, 40 individuals completed follow-ups, and 45 completed the follow-ups at five years. Improvements were seen in the Clinical Rating Scale for Tremor (CRST) by 73.3% and 73.1% from baseline at 48 and 60 months after treatment, in that order. Improvements were also seen in the combined hand tremor/motor scores demonstrating 49.5% and 40.4% at 48 and 60 months, respectively. Improvements of the functional disability and Quality of Life in Essential Tremor (QUEST) scores. The authors concluded that unilateral MRgFUS thalamotomy demonstrated sustained, significant improvement overall at the five-year follow-up. The loss of follow-up and the small sample size are limiting factors in this trial. Investigation of bilateral staged MRgFUS thalamotomy for ET is necessary for future conclusions on this approach's safety, efficacy, and feasibility.

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

Giordano et al. (2020) performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement to compare unilateral MRgFUS thalamotomy to unilateral and bilateral DBS for treating ET in terms of tremor severity and quality of life improvement. Forty-five eligible articles, published between 1990 and 2019, were retrieved. 1202 participants 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 individuals with medication refractory ET. Overall, the 3-year attrition from the treated cohort was 31%, with a loss of 23 participants. 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 $p < 0.0001$). The 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. Individuals 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 analysis differed from the cohorts present in the original RCT and the two-year follow-up. This study provides Class IV evidence that for individuals with severe ET, unilateral tcMRgFUS thalamotomy provides durable benefit after 3 years.

Altinel et al. (2019) conducted a systematic review and meta-analysis evaluating RCTs of DBS and lesion surgery (LS) in the treatment of tremor. PubMed, Embase, and the Cochrane database were searched to include RCTs with either LS, deep brain stimulation, or controls. The outcomes were the change in tremor score, quality of life, cognitive function, and neuropsychiatric function. Fifteen trials, including 1508 participants, met eligibility criteria. No significant difference in change of tremor scale (SMD -0.07, 95% 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 70 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 treating individuals 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 ET. A systematic review of current pharmacological and surgical treatments for ET 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 ET and overcome the limitation of small sample sizes, cross-over studies, short-term follow-up studies, and use of non - validated clinical scales (Ferreira et al., 2019).

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

A systematic literature review was conducted by Langford et al. (2018) to identify and analyze evidence supporting the use of the emerging MRgFUS compared to alternative stimulatory and ablative interventions (ablative interventions included radiofrequency thalamotomy, unilateral DBS, and stereotactic radiosurgery) for treating medication-refractory ET. 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 CRST Total) and health-related quality of life (measured by CRST 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 CRST maximum achievable scores in the literature meant comparisons were only possible for two interventions (MRgFUS and DBS) and two outcomes (CRST Total and Part C scores). Data availability allowed analyses only at the 1-, 3-, 6-, and 12-month time points, meaning conclusions on efficacy were limited to the short-term effect of these interventions. Further analyses are required to determine the comparative efficacy between these two interventions on a long-term basis with direct comparison. The study is limited by indirect comparison.

Mohammed et al. (2018) conducted a meta-analysis to analyze the overall outcomes and complications of MRgFUS in the treatment of ET. The change in the CRST score after treatment was analyzed. The improvement in disability was assessed with the QUEST Questionnaire score. Nine studies with 160 people 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 in 25.1% of the participants. 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 for individuals 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 population. According to the authors, randomized trials comparing DBS (the current standard surgical treatment for medication-refractory ET) to MRgFUS are the needed. Authors Elias et al., 2016; Kim et al., 2017; and Huss et al., 2015 are included in this meta-analysis.

The National Institute for Health and Care Excellence (NICE) evidence-based guideline for unilateral MRgFUS thalamotomy concluded that MRgFUS thalamotomy for treatment-resistant ET raises no major safety concerns, but evidence of efficacy was limited in quantity. NICE recommends that this procedure should not be used unless there are special arrangements for oversight. NICE suggests that future research include the identification of patient selection criteria and long-term follow-up data (NICE, 2018).

Elias et al. (2016) conducted a double-blind, sham-controlled randomized trial to evaluate the efficacy of MRgFUS thalamotomy for treating ET. Trial selection criteria included individuals with moderate or severe postural or intention tremor of the hand (≥ 2 on the CRST) and refractory to at least two trials of medical therapy, including at least one first-line agent (propranolol or primidone). A total of 74 participants 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% 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 the participants and paresthesia or numbness in 38%; these adverse events persisted at 12 months in 9% and 14% of individuals, respectively. The investigators concluded that MRI-guided focused ultrasound thalamotomy reduced hand tremor for individuals with ET. 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 syndrome. This guideline does not mention the use of magnetic resonance guided focused ultrasound therapy as a treatment option (Zesiewicz et al., 2011, reaffirmed on July 16, 2022).

### *Parkinson Disease*

In 2022, the European Academy of Neurology/Movement Disorder Society- European Section guideline on treating PD focused on the invasive therapies for those who suffer from the illness. The society created a clinical consensus statement stating, “No sufficient RCTs available for uni- or bilateral MRgFUS of the thalamus for medically resistant tremor in PD. Despite promising preliminary data, this treatment should only be applied within clinical studies or registries (16 voters, 100%).” The society also said: “Consider using unilateral MRgFUS of the STN in people with distinctly unilateral PD only within clinical studies or registries due to the limited data on this new treatment (16 voters, 100%).” Research and use of MRgFUS are currently rapidly developing, but essential questions are still open (Deuschl et al. 2022).

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

Lennon & Hasson (2021) completed a systematic review utilizing data bases PubMed, CINAHL, PsycINFO, and Cochrane Library from January 2016 to January 2020. The authors reviewed clinical trials comprehensively assessing pre- and post-

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

Lin et al. (2021) compared the efficacy of DBS and MRI-guided focused ultrasound (MRIgFUS) in parkinsonian tremor. The literature was searched for articles published between January 1990 and October 2020 using three databases: PubMed, Embase and Cochrane Library (The Cochrane Database of Systematic Reviews). A total of 24 studies were included in the analysis, comprising data from 784 participants. The findings revealed similar efficacy of DBS and MRIgFUS in parkinsonian tremor suppression. Compared with internal globus pallidus (GPi)-MRIgFUS, GPi-DBS -1.84 (-6.44, 2.86), pedunculopontine nucleus (PPN)_DBS -3.28 (-9.28, 2.78), PPN and caudal zona incerta (cZI)-DBS 0.40 (-6.16, 6.87), subthalamic nucleus (STN)_DBS 0.89 (-3.48, 5.30), STN and cZI-DBS 1.99 (-4.74, 8.65), ventral intermediate nucleus (VIM)_DBS 1.75 (-2.87, 6.48), VIM_FUS 0.72 (-5.27, 6.43), cZI-DBS 0.27 (-4.75, 5.36) there was no significant 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) there also was no significant 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's symptoms to ensure that the appropriate intervention and therapeutic approach are applied.

Xu et al. (2021) conducted a systematic review to investigate the safety and efficacy of MRgFUS for PD by systematically reviewing related literature. Eleven studies containing 80 participants 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 individuals. 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.

Martínez-Fernández et al. (2020) conducted a randomized trial on focused ultrasound subthalamotomy for PD by randomly assigning individuals in a 2:1 ratio. Individuals with markedly asymmetric PD whose motor signs were uncontrolled by medication or those disqualified for deep-brain stimulation surgery received the focused ultrasound subthalamotomy on the opposite side of main motor sign or received a sham procedure. The characteristics of the participants were similar in the two groups at baseline. Efficacy and principal safety results were measured at 4 months. Efficacy outcomes in the between-group variances from baseline to 4 months was assessed with the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) for the affected side in the off-medication state. The trial consisted of 40 individuals, 27 assigned to focused ultrasound subthalamotomy and 13 in the sham procedure. The average MDS-UPDRS III score for the most affected

side indicated improvement from 19.9 at baseline to 9.9 at 4 months in the active-treatment group. The control group resulted in MDS-UPDRS score of 17.1 from 18.7 at 4 months ensuing a between-group difference of 8.1 points. Adverse events in the non-medicated, active-treatment individuals were recorded with results as follows: Dyskinesia was noted in 6 individuals; with symptoms persisting at 3 months follow-up, and dyskinesia found in 6 individuals who were on medication; with persistent symptoms at 1 month follow-up. Weakness was recorded in 5 individuals on the treated side and continued in 2 individuals at 4 months follow up. Speech disturbances were documented in 15 individuals and continued in 3 individuals at 4 months. Facial weakness was logged in 3 individuals and persisted in 1 individual at 4 months. Gait disturbance was noted in 13 individuals which persisted in 2 individuals at 4 months. In the active-treatment group, 6 individuals were recorded to have the same deficits present at 12 months follow up. Limitations include small sample size. The authors conclude focused ultrasound subthalamotomy in one hemisphere improved motor features of PD in selected individuals with asymmetric signs. However, adverse events included speech and gait disturbances, weakness on the treated side, and dyskinesia. Longer-term and larger trials are needed to determine the role of focused ultrasound subthalamotomy in the management of Parkinson disease and its effects compared with other available treatments.

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

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| Code | Description |
|---|---|
| 0408T | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes |
| 0409T | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only |
| 0410T | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only |
| 0411T | Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only |
| 0412T | Removal of permanent cardiac contractility modulation system; pulse generator only |
| 0413T | Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular) |
| 0414T | Removal and replacement of permanent cardiac contractility modulation system pulse generator only |
| 0415T | Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead) |
| 0416T | Relocation of skin pocket for implanted cardiac contractility modulation pulse generator |
| 0417T | Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, implantable cardiac contractility modulation system |
| 0418T | Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system |
| K1030 | External recharging system for battery (internal) for use with implanted cardiac contractility modulation generator, replacement only |

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

## Clinical Evidence

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

The Optimizer™ implantable CCM system received FDA premarket approval (P180036) on March 21, 2019. Based on this FDA approval, the device is indicated to improve 6-minute hall walk distance, quality of life, and functional status of New York Heart Association (NYHA) Class III HF 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 (LVEF) ranging from 25% to 45%. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180036. (Accessed March 3, 2023)

The AHA/ACC/HFSA developed a guideline for the management of HF intended to provide patient-centric recommendations for clinicians to prevent, diagnose, and manage patients with HF. The guideline text states that CCM has been associated with augmentation of left ventricular contractile performance. Cardiac contractility modulation is FDA-approved for patients with NYHA class III with LVEF of 25% to 45% who are not candidates for CRT. Four RCTs have shown benefits in exercise capacity and quality of life but, as of yet, no benefits in death or hospitalizations. Most patients in these trials had class III congestive heart failure. The guideline, however, does not provide any specific recommendation for the use of CCM but lists CCM as one of the technologies that should be further studied in the evidence gap section of the guideline (Heidenreich et al. 2022).

Linde et al. (2022) conducted a prospective, multicenter, single-arm, pilot study of CCM in patients with heart failure with preserved ejection fraction (HFpEF). The study included 47 patients with HFpEF and NYHA class II or III who were followed for 24 weeks after CCM device implantation. Patients returned for follow-up visits at two, twelve, and twenty-four weeks. The primary efficacy endpoint (mean change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score) improved by18.0 ±16.6 points ($p < 0.001$) and there was an event-free rate of 93.6% for the primary safety endpoint (device- and procedure-related complications). The authors noted no obvious impact on safety and significant improvement in observed health status. The authors suggest CCM use may be promising and benefit patients with HFpEF, although future RCTs with a longer follow-up time are recommended. Study limitations include small sample size and the single-arm design with lack of control group.

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

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

Giallauria et al. (2020) conducted an individual data meta-analysis of all prospective RCTs of CCM versus control that measured functional capacity and/or quality of life questionnaires in patients with HF plus data from one single arm study. Peak oxygen

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

An ECRI clinical evidence assessment 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 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 risk of bias in two of the studies which had a single-center focus and/or lack of randomization and blinding. Longer term follow up comparing Optimizer with OMT with a focus on mortality and HF-related hospitalization is recommended (ECRI, 2019; updated 2021).

A Hayes 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 HF. 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 (Hayes 2019; Updated 2021).

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

Kloppe et al. (2016) conducted a single center pilot evaluation study involving 19 medically refractory symptomatic patients with HF 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 MLWHFQ, maximal oxygen consumption in the cardio-pulmonary stress test (peak VO2), NYHA classification, 6-min walk distance (6MWD), and ejection fraction. At the end of 24 weeks, clinical improvement was observed in the entire cohort in all efficacy measures. There were no significant differences, either clinically or statistically, between the groups receiving CCM for 5 h/day versus 12 h/day. Given the small sample size, further studies are warranted. Additionally, the design of the study does not allow comparison of CCM to other approaches.

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

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

## Clinical Evidence

In a clinical evidence assessment, ECRI (2023) concluded that the evidence for Iovera System (Pacira Biosciences, Inc.) for treating knee osteoarthritis pain is unclear addressing clinical utility. The evidence identified by ECRI suggests that whether Iovera reduces postoperative pain and opioid use and improves functionality and quality of life compared with standard care in patients who underwent total knee arthroplasty (TKA) is unclear because available studies (two RCTS and 3 non-randomized controlled studies), all at high risk of bias, report conflicting results. Limitations include comparison groups, follow-up time, and outcome reporting varied widely across studies, which precludes generalizing study results.

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

rigorous clinical trials including a larger population, comparator group(s) and better characterization of participants at baseline to establish efficacy and safety.

In a 2021 Evolving Evidence Review, Hayes reported on the state of the evidence regarding the FDA-approved iovera system for treatment of chronic knee pain due to osteoarthritis (OA). One fair quality randomized sham-controlled clinical trial and one systematic review was identified. Although no serious treatment-related adverse events were reported, the randomized sham-controlled trial suggested short-term improvement in pain and function; by 6 months post-treatment advantages diminished. The systematic review included only one study addressing the use of iovera for knee pain due to OA (the randomized sham-controlled trial mentioned above). Other studies included addressed iovera as an adjunct to total knee arthroplasty. No clinical practice guidelines or position statements provided recommendations or support for the iovera system for treatment of knee pain due to OA. Hayes indicates that further high-quality studies are required to compare iovera with standard care or potential alternatives for treating knee pain from OA and evaluate clinical benefit from repeat iovera treatments. In Hayes (2022) Evolving Evidence Review, there is no change to the current recommendation.

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

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

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

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

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

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

## Clinical Evidence

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

Rubião et al. (2021) conducted a phase II controlled study of individuals with primary open-angle glaucoma (POAG) and ocular hypertension (OH), comparing the safety and efficacy of bimatoprost ocular inserts to bimatoprost eye drops. Thirteen OH patients, and sixteen POAG patients with Intraocular pressure (IOP) greater than 21 and less than or equal to 30mmHg, and a control group of five normal patients with IOP less than or equal to 14 mmHg were included in the study. Participants were between the ages of 40 and 75 years of age. For all participants, a chitosan-based insert of bimatoprost was placed in the upper conjunctival fornix of the right eye. In the left eye, every night for three weeks, one drop of Lumigan TM eye drops was used. “IOP reduction was similar during three weeks of follow-up (19.5 ±2.2 mmHg and 16.9 ±3.1 mmHg), insert, and eye drop, respectively; p = 0.165). The percentage of IOP reduction in the third week was 30% for insert and 35% for eye drops (p = 0.165). No intolerance or discomfort with the insert was reported. Among the research participants, 58% preferred the use of the insert while 25% preferred eye drops, and 17% reported no preference.” The authors concluded that both methods showed similar efficacy during follow-up, which might suggest a possible change in the daily therapeutic regimen for treatment of these two conditions. A limitation of this study is small sample size, which may not have been large enough to detect clinically significant differences (type 2 error), and short follow-up period.

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

months with a bimatoprost ocular insert and seems to be safe and well tolerated. According to the authors, longer-term studies of a high-risk (low-adherence) population will be required to demonstrate the full usefulness of this ocular drug-delivery system in preserving visual fields.

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

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

## Reference(s)


American Academy of Ophthalmology. Primary open-angle glaucoma preferred practice pattern. March 14, 2022. Available at: AAO Primary Open-Angle Glaucoma Preferred Practice Pattern Guideline Summary (guidelinecentral.com) Accessed April 5, 2023.

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| 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

There is currently insufficient evidence to support the use of retinal birefringence scanning; well-designed studies with larger sample sizes including the general population are needed to ascertain its clinical value.

Retinal polarization scanning, also known as retinal birefringence scanning (RBS), is a method for detecting the central fixation of the eye. RBS can be used in pediatric ophthalmology screening. By simultaneously measuring the central fixation of both eyes, small- and large angle strabismus can be detected. The method is non-invasive and requires little cooperation by the patient, allowing it to be used for detecting strabismus in young children. The method is aimed at trying to provide a reliable detection of strabismus and has also been used for detecting certain kinds of amblyopia.

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

Bosque et al. (2021) reported results of a prospective test validation study evaluating the accuracy of the blinq pediatric vision scanner for the detection of amblyopia and strabismus. Testing was performed by individuals masked to the diagnosis. Following testing, pediatric ophthalmologists performed complete examinations and were masked to the screening result. The study included 193 subjects, (53 previously treated, 140 treatment-naïve subjects), “including 65 (46%) with amblyopia or strabismus, 11 (8%) with risk factors/suspected binocular vision deficit without amblyopia/strabismus, and 64 (46%) controls. Sensitivity was 100%, with all 66 patients with referral-warranted ocular disease referred. Five patients with intermittent

strabismus receiving pass results were deemed "acceptable pass" when considering patient risk factors and amblyogenic potential. Specificity was 91%, with 7 incorrect referrals. Subanalysis of children aged 2-8 years (n = 92) provided similar results (sensitivity 100%; specificity 89%).**"** The authors concluded that very high sensitivity and specificity for detecting referral-warranted unilateral amblyopia and strabismus was detected with the blinq scanner. The authors further stated that "Implementation of the device in vision screening programs could lead to improved rates of disease detection and reduction in false referrals. The study is limited by the use of non-standard calculations of adjusted sensitivity and specificity.

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

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

Loudon, et al. (2011) performed a prospective study to investigate whether the PVS could detect anisometropic amblyopia as well as strabismus. The authors also followed patients during treatment to determine whether the improvements gained from treatment would be reflected in improved vision test results. A total of 154 patients and 48 controls between the ages of 2 and 18 years participated in the study with 21 children followed longitudinally to detect changes in their binocularity (BIN) scores. The control group consisted of subjects with no strabismus, amblyopia, or anisometropia. The authors concluded that PVS identified children with amblyopia or strabismus with high sensitivity and specificity, while successful treatment restored normal BIN scores in amblyopic patients without strabismus. Study limitations again include small size, single center, and engagement of patients with known risk factors; it was also noted in this study that there was a lack of racial diversity with 74% of the participants identified as Caucasian.

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

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

## Reference(s)


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

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

## Clinical Evidence

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

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

Monroy et al. (2018) conducted a prospective case series study to assess otitis media-(OM) associated biofilm structures affixed to the mucosal surface of the TM, both in vivo and in surgically recovered in vitro samples. Forty pediatric patients that were scheduled for tympanostomy tube placement surgery were imaged intraoperatively under general anesthesia. Following myringotomy, a portable OCT imaging system was used to assess for the presence of any biofilm affixed to the mucosal surface of the TM. OCT was achieved for 38 patients. Samples of suspected microbial infection-related structures were

collected through the myringotomy incision. The sampled site was reimaged with OCT to confirm collection from the original image site. In vitro analysis was done based on confocal laser scanning microscope (CLSM) images of fluorescence in situ hybridization-tagged samples, and polymerase chain reaction (PCR) provided microbiological characterization and verification of biofilm activity. Thirty-four samples were collected from 38 subjects. CLSM images provided evidence of clustered bacteria in 32 of 33 samples. PCR detected the presence of active bacterial DNA signatures in 20 of 31 samples. The results showed that PCR and CLSM analysis of fluorescence in situ hybridization-stained samples validates the presence of active bacteria that have formed into a middle ear biofilm that extends across the mucosal layer of the TM. The authors concluded that OCT can rapidly and noninvasively identify middle ear biofilms in subjects with severe and persistent cases of OM. This study is limited by a small number of participants, no control group, and a high risk of bias. The clinical utility of this method to diagnose OM has not been established, and large well-designed studies are required to validate these findings.

Park et al. (2018) conducted a prospective study to examine the tympanic membranes (TMs) of 120 patients with middle ear conditions using a handheld optical coherence tomography-based otoscope (860 nm central wavelength, 15 μm axial resolution, 15 μm lateral resolution, and 7 mm scanning range using relay lens). Both OCT and oto-endoscope images were compared according to the clinical characteristics such as perforation, retraction, and postoperative healing process. The objective grade about the thickness of perforation margins and the accurate information about the extent of TM retraction that was not distinguishable by oto-endoscopic exam could be identified using this system. The postoperative healing process of TMs could also be followed using the OCT device. The authors concluded that their findings suggest that the handheld OCT device would be another useful application.

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

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

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

Nguyen et al. (2013) investigated the acoustic effects of bacterial biofilms, confirmed using OCT in adult ears. Biofilms have been linked to chronic OM and OM with effusion in the middle ear. Non-invasive OCT images were collected to visualize the 2D cross-sectional structure of the middle ear, verifying the presence of a biofilm behind the TM of five 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.

Five clinical trials were found regarding optical coherence tomography for the middle ear. Two trials are not yet recruiting (NCT05445388, NCT05497934), two are in the process of recruiting (NCT05085379, NCT05353569) and one is active, not recruiting (NCT03890107).

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

## Reference(s)


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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. 2018 Apr;138(4):367-374.

Preciado D, Nolan RM, Joshi R, et al. Otitis media middle ear effusion identification and characterization using an optical coherence tomography otoscope. Otolaryngol Head Neck Surg. 2020 Mar;162(3):367-374.


| 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

Hong et al. (2020) in a retrospective study evaluated the association of macular pigment optical density (MPOD) with age in the Korean population using a device (MPSII®) that measures MPOD based on heterochromatic flicker photometry (HFP). Macular pigment (MP) is studied mainly because of the proposed link between low levels of macular pigment optical density (MPOD) and an increased risk of developing age-related macular degeneration (AMD). There were 126 eyes that were retrospectively reviewed. In the simple regression analysis, a statistically significant linear regression model was observed, and the estimated values of MPOD decreased by 0.005 as age increased by 1 year. Aged (> 50 years) showed lower MPOD than younger (30-49 years) subjects. But, in the healthy population, the estimated MPOD values exhibited a decreasing trend with age; there were no significant differences according to age, after excluding patients with AMD. MPOD was significantly lower in patients with AMD than in aged healthy controls. Furthermore, hypertension, dyslipidemia, and smoking were identified as risk factors for AMD. Study limitations included the following: the study sample was small, and further research with a larger sample is needed. Second, because the emphasis was exclusively on AMD, the relationship of this technique to other diseases remains unclear. Third, measurements of the relationship between serum or dietary carotenoid levels and MPOD were not performed. Lastly, the results did not show a significant correlation between MPOD reduction and the occurrence of AMD. Nevertheless, the author's note this was the first study to demonstrate the changes in MPOD according to age and difference in MPOD with and without

AMD. The estimated values using MPSII® were measurable in all ages, especially older patients who might have dry AMD. The results of this study may lead to an increased use of MPSII® in practice and to identify the need for dietary supplementation in patients with lower MPOD. Additional studies are needed to assess the effect of MPOD on the pathologic process of AMD and MPOD levels in other diseases.

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)

Hong IH, Jung WH, Lee JH, et al. Macular pigment optical density in the Korean population: a cross sectional study. J Korean Med Sci. 2020 Feb 10;35(5):e30.

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

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

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

## Clinical Evidence

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

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

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

Finis et al. (2015) conducted an evaluation of meibomian gland dysfunction (MGD) and local distribution of meibomian gland atrophy by non-contact infrared meibography. A retrospective analysis of 128 patients (92 women and 36 men, 57 ±17 years) from a dry eye clinic was performed. Infrared meibography was performed using the Keratograph 5 M (Oculus, Wetzlar, Germany) and evaluated with a scoring system introduced by Arita et al. The results showed a significant inverse correlation between Meibomian gland atrophy measured by meibography and expressible Meibomian glands ($r = -0.197$, $p = 0.003$) as well as between meiboscore and TBUT ($r = -0.1615$, $p = 0.012$). There also was a significant correlation between the total meiboscore and the age ($r = 0.33$, $p < 0.0001$). The authors found a strong and highly significant correlation between the total meiboscore and the individual meiboscore of the upper eyelid ($r = 0.905$, $p < 0.0001$) and the lower eyelid ($r = 0.892$, $p < 0.0001$). There was no significant difference of Meibomian gland atrophy between the individual thirds of the upper eyelid, but for the lower eyelid, a higher degree of Meibomian gland atrophy was found in the nasal third compared with the middle and

the temporal third (Dunn's post hoc test, $p < 0.0001$). The authors concluded that meibomian gland atrophy seems to be not constant over the tarsal plate, but the examination of the lower tarsus might be sufficient in most of the cases. The correlation of the meiboscore with functional dry eye parameters suggest that in patients with detectable Meibomian gland atrophy there is also an impaired Meibomian gland function. However, meibography seems not to be sufficient as a single test for the diagnosis of MGD. Larger, prospective studies are needed to confirm these results and further evaluate the potential of meibography in the diagnosis of MGD.

## Reference(s)

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.ca/products/lipiscan-dynamic-meibomian-imager. Accessed April 24, 2023.

| Code | Description |
|---|---|
| 0515T | Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; complete system [includes electrode and generator (transmitter and battery)] |
| 0516T | Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only |
| 0517T | Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; both components of pulse generator (battery and transmitter) only |
| 0518T | Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; battery component only |
| 0519T | Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; both components (battery and transmitter) |
| 0520T | Removal and replacement of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only |
| 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 |
| 0861T | Removal of pulse generator for wireless cardiac stimulator for left ventricular pacing; both components (battery and transmitter) |
| 0862T | Relocation of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; battery component only |
| 0863T | Relocation of pulse generator for wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming; transmitter component only |

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

## Clinical Evidence

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

The WiSE (Wireless Stimulation Endocardially) CRT System (EBR Systems, Inc., Sunnyvale, CA) (formerly the WiCS-LV) is currently undergoing clinical trials. The WiSE CRT System is a wireless LV pacing system that works with a conventional

pacemaker and/or defibrillator for patients in whom CRT is indicated. The WiSE CRT system is comprised of an ultrasonic transmitter attached to a battery unit and a tiny wireless receiver which acts as a pacing electrode. The WiSE system allows for biventricular pacing while eliminating the need for a LV pacing wire in the coronary sinus. The system allows the provider to customize electrode placement to the optimal location for pacing, which varies among patients; this differs significantly from conventional LV pacing leads, which are limited by coronary sinus anatomy. The FDA granted WiSE-CRT system Breakthrough Device Designation status for the treatment of HF (Hayes, 2019; updated 2023).

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

Okabe et al. (2022) prospectively collected data from 19 centers where WiSE-CRT systems were implanted during the roll-in phase of the SOLVE-CRT trial. The study aimed to evaluate short-term outcomes in centers with no prior WiSE-CRT system implanting experience. Participants were assessed at one, three, and six months, with a transthoracic echo included in the six-month evaluation. Implantation was successful in all thirty-one attempted cases and thirty of thirty-one patients completed the six-month follow-up. One patient underwent heart transplantation one month after implantation and was excluded. Fourteen (46.7%) patients demonstrated ≥ 1 New York Heart Association (NYHA) class improvement. Transthoracic echocardiogram data were available in 29 patients. LV ejection fraction, LV end-systolic volume, and LV end-diastolic volume improved from 28.3% ±6.7% to 33.5% ±6.9% ($p < .001$), 134.9 ±51.3 mL to 111.1 ±40.3 mL ($p = .0004$), and 185.4 ±58.8 mL to 164.9 ±50.6 mL ($p = .0017$), respectively. There were three (9.7%) device-related type 1 complications: one insufficient LV pacing, one embolization of an unanchored LV electrode, and one skin infection. The authors concluded that the success rate of LV endocardial electrode placement in centers with no prior implanting experience was high. Additionally, positive clinical responses in HF symptoms and significant LV reverse remodeling were noted. Limitations include small sample size, short-term follow-up, and lack of comparison group.

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.

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

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

A Hayes emerging technology report found no published RCTs evaluating the WiSE system for CRT in patients with HF. Published evidence is limited to reports from nonrandomized single-arm trials and registry data. These reports suggest that

endocardial CRT with the WiSE system may be a treatment option for patients with HF who do not respond to conventional CRT or who have contraindications to LV lead implantation. Further evidence is needed to better characterize the safety and efficacy of the device (Hayes, 2019; updated 2021).

## Reference(s)


Auricchio A, Delnoy PP, Butter C, et al. Feasibility, safety, and short-term outcome of leadless ultrasound-based endocardial left ventricular resynchronization in heart failure patients: results of the wireless stimulation endocardially for CRT (WiSE-CRT) study. Europace. 2014;16(5):681-688.

Cang J, Liu Y, Zhu D, et al. WiSE CRT Is beneficial for heart failure patients as a rescue therapy: evidence from a meta-analysis. Front Cardiovasc Med. 2022 Mar 15;9:823797.

EBR Systems, Inc. website. Available at: https://ebrsystemsinc.com/. Accessed April 4, 2023.

Hayes, nc. Emerging Technology Report. WiSE Cardiac Resynchronization Therapy System. Lansdale, PA: Hayes, Inc. May 2019. Updated January 30, 2023.

Okabe T, Hummel JD, Bank AJ, et al. Leadless left ventricular stimulation with WiSE-CRT System - Initial experience and results from phase I of SOLVE-CRT Study (nonrandomized, roll-in phase). Heart Rhythm. 2022 Jan;19(1):22-29.

Reddy VY, Miller MA, Neuzil P, et al. Cardiac resynchronization therapy with wireless left ventricular endocardial pacing: The SELECT-LV study. J Am Coll Cardiol. 2017;69(17):2119-2129.

Sidhu BS, Porter B, Gould J, et al. Leadless left ventricular endocardial pacing in nonresponders to conventional cardiac resynchronization therapy. Pacing Clin Electrophysiol. 2020 Sep;43(9):966-973.

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

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

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

## Clinical Evidence

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

The AngelMed Guardian System received U.S. Food and Drug Administration (FDA) premarket approval (P150009) on April 9, 2018. The AngelMed Guardian System is indicated for use in patients who have had prior ACS events and who remain at high risk for recurrent ACS events. The AngelMed Guardian System is indicated as an adjunct to patient recognized symptoms. The system detects potential ongoing ACS events, characterized by sustained ST segment changes, and alerts the patient to seek medical attention for those potential ACS events. Additional FDA information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P150009. (Accessed April 5, 2023)

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

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

Gibson et al. (2019) reported the results of the ALERTS (AngelMed for Early Recognition and Treatment of STEMI; NCT00781118) trial. The ALERTS trial was a multicenter, randomized trial of an implantable cardiac monitor that alerts patients with rapidly progressive ST-segment deviation. Subjects at high-risk of ACS (n = 907) were randomized to a control (alarms deactivated) or treatment group for six 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 seven 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 two 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), four patients had ST-segment changes of ≥ 3 SDs of their normal daily range, in the absence of an elevated heart rate. This in combination with immediate hospital monitoring led to angiogram and/or intravascular ultrasonography, which confirmed thrombotic coronary occlusion/ruptured plaque. The median alarm-to-door time was 19.5 min (6, 18, 21, and 60 min, respectively). Alerting for demand-related ischemia at elevated heart rates, reflective of flow-limiting coronary obstructions, occurred in four patients. There were two false-positive ischemia alarms related to arrhythmias, and 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. AngelMed Guardian System (Angel Medical Systems, Inc.) for monitoring patients at high risk of acute coronary syndrome. Plymouth meeting (PA): ECRI; 2020 Jan. (Clinical Evidence Assessment). Updated February 23, 2022.

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

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

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

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

| Code | Description |
|---|---|
| 0559T | Anatomic model 3D-printed from image data set(s); first individually prepared and processed component of an anatomic structure |
| 0560T | Anatomic model 3D-printed from image data set(s); each additional individually prepared and processed component of an anatomic structure (List separately in addition to code for primary procedure) |
| 0561T | Anatomic guide 3D-printed and designed from image data set(s); first anatomic guide |
| 0562T | Anatomic guide 3D-printed and designed from image data set(s); each additional anatomic guide (List separately in addition to code for primary procedure) |

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

- Surgical planning
- Manufacturing of customized devices

## Clinical Evidence

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

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

A 2021 ECRI clinical evidence assessment was conducted on the use of 3D printed anatomic models for orthopedic surgical planning focusing on outcomes from the use of 3D printing in orthopedic surgery compared with those of conventional orthopedic surgical procedures. The evidence search dates were from January 2016 to June 2021 with a review of 2 systematic reviews, 5 clinical studies, 2 systematic review abstracts, 2 clinical studies, for a total of 2,212 patients reported on. The studies utilized reported on patients with different conditions necessitating orthopedic surgery. The studies show utilizing 3D patient-specific anatomic models for procedure planning reduces operative time, though is not a benefit over conventional surgical approaches regarding functional status, complication rates, and other patient-oriented outcomes. The limitations of the evidence consist of low-quality evidence, the need for large-sample, multicenter Randomized Controlled Trials (RCT's) which would address the evidence gap and establish 3D printing's efficacy in a clinical setting. Other limitations consist of variation in

outcomes reported, surgical procedure limits comparison in studies, high risk of bias, lack of follow up, and the studies conducted were outside the United States, thus results may not be generalized to the United States healthcare system. The 3D anatomic models may benefit surgical approach in planning for complex anatomy orthopedic surgeries, but there is a lack in high-quality RCTs to define benefits in orthopedic surgery (ECRI 2021).

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

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

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 October 2022).

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

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

Hasan et al. (2020) compared the migration of cementless, 3D-printed total knee arthroplasty (TKA) to cemented TKA of a similar design up to two years of follow-up using radio stereometric analysis (RSA) known for its ability to predict aseptic loosening. A total of 72 patients were randomized to either cementless 3D-printed or a cemented cruciate retaining TKA. RSA and clinical scores were evaluated at baseline and postoperatively at three, 12, and 24 months. A mixed model was used to analyze the repeated measurements. The mean maximum total point motion (MTPM) at three, 12, and 24 months was 0.33 mm (95% confidence interval (CI) 0.25 to 0.42), 0.42 mm (95% CI 0.33 to 0.51), and 0.47 mm (95% CI 0.38 to 0.57) respectively in the cemented group, versus 0.52 mm (95% CI 0.43 to 0.63), 0.62 mm (95% CI 0.52 to 0.73), and 0.64 mm (95% CI 0.53 to 0.75) in the cementless group ($p = 0.003$). However, using three months as baseline, no difference in mean migration between groups was found ($p = 0.497$). Three implants in the cemented group showed a > 0.2 mm increase in MTPM between one and two years of follow-up. In the cementless group, one implant was revised due to pain and progressive migration, and one

patient had a liner-exchange due to a deep infection. The authors concluded that the cementless TKA migrated more than the cemented TKA in the first two-year period. This difference was mainly due to a higher initial migration of the cementless TKA in the first three postoperative months after which stabilization was observed in all but one maligned and early revised TKA. The authors indicated that a longer follow-up is needed to determine whether the biological fixation of the cementless implants will result in an increased long-term survivorship.

Moralidou et al. (2020) conducted a systematic review of the existing literature for the use of 3D pre-operative planning in primary total hip arthroplasty (THA). The review focused on (1) the accuracy of implant sizing, restoration of hip biomechanics and component orientation; (2) the benefits and barriers of this tool; and (3) current gaps in literature and clinical practice. A total of 43 full scientific articles were reviewed. Clinical studies have highlighted the accuracy of 3D pre-operative planning in predicting the optimal component size and orientation in primary THAs. Component size planning accuracy ranged between 34-100% and 41-100% for the stem and cup, respectively. The absolute, average difference between planned and achieved values of leg length, offset, center of rotation, stem version, cup version, inclination and abduction were 1 mm, 1 mm, 2 mm, 4°, 7°, 0.5° and 4° respectively. The benefits of 3D pre-operative planning include 3D representation of the human anatomy for precise sizing and surgical execution. The Barriers of 3D pre-operative planning include increased radiation dose and learning curve. According to the authors, the long-term evidence investigating this technology is limited. Emphasis should be placed on understanding the health economics of an optimized implant inventory as well as long-term clinical outcomes.

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

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

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

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

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

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

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

## Reference(s)


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Omari A, Frendø M, Sørensen MS, et al. The cutting edge of customized surgery: 3D-printed models for patient-specific interventions in otology and auricular management-a systematic review. Eur Arch Otorhinolaryngol. 2022 Feb 15.

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, FemBloc has FDA Investigational Device Exemption, and Phase III PMA clinical trials are underway to assess the safety and efficacy. Further information can be found at the following website: https://www.clinicaltrials.gov/. (Accessed March 30, 2023)

## Reference(s)

Femasys® Inc. website. Available at: http://www.femasys.com/. Accessed March 30, 2023.

| Code | Description |
|---|---|
| 0568T | Introduction of mixture of saline and air for sonosalpingography to confirm occlusion of fallopian tubes, transcervical approach, including transvaginal ultrasound and pelvic ultrasound |

**Sonosalpingography, when used with a mixture of saline and air to confirm fallopian tube occlusion, is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.**

## Clinical Evidence

The FemVue® Saline-Air Device instills a consistent alternating pattern of saline and air as a continuous stream of contrast medium into the uterus and fallopian tubes to be used in conjunction with an intrauterine catheter for performance of sono-hysterosalpingogram (Femasys® website).

FemVue® received FDA premarket approval on April 28, 2011 (product code LKF). Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed June 7, 2023)

Beverly et al. (2018) conducted a prospective study to assess the performance of office-based hysterosalpingo-contrast sonography (HyCoSy) using the FemVue air-saline device as compared to traditional fluoroscopic hysterosalpingogram (HSG)

for evaluating tubal patency in women presenting with infertility. Tubal patency was evaluated in 20 patients aged 21–43 years. Primary outcome was the assessment of right and left fallopian tube patency. Uterine cavity assessment, presence of hydrosalpinx, and patient discomfort during each procedure were assessed as secondary outcomes. The authors findings stated tubal patency was confirmed in 32/39 (82%) fallopian tubes via HyCoSy and in 34/39 (87%) fallopian tubes via HSG, with a 77% concordance rate between HyCoSy and HSG techniques. Uterine cavity filling defect was detected in 5 patients. Only 1 of those 5 defects was detected on both HyCoSy and HSG, for a concordance rate of 16/20 (80%). The authors concluded tubal patency with HyCoSy using the FemVue device is comparable to HSG and is a convenient, well-tolerated method which may be performed easily in the office as part of the infertility evaluation.

## Reference(s)

Beverley R, Malik S, Collins R, et al. Evaluation of tubal patency with a saline-air device. J Reprod Med. 2018; 63(3):120-126.

| Code | Description |
|---|---|
| 0571T | Insertion or replacement of implantable cardioverter-defibrillator system with substernal electrode(s), including all imaging guidance and electrophysiological evaluation (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters), when performed |
| 0572T | Insertion of substernal implantable defibrillator electrode |
| 0573T | Removal of substernal implantable defibrillator electrode |
| 0574T | Repositioning of previously implanted substernal implantable defibrillator-pacing electrode |
| 0575T | Programming device evaluation (in person) of implantable cardioverter-defibrillator system with substernal electrode, with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional |
| 0576T | Interrogation device evaluation (in person) of implantable cardioverter-defibrillator system with substernal electrode, with analysis, review and report by a physician or other qualified health care professional, includes connection, recording and disconnection per patient encounter |
| 0577T | Electrophysiologic evaluation of implantable cardioverter-defibrillator system with substernal electrode (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters) |
| 0578T | Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter-defibrillator system with interim analysis, review(s) and report(s) by a physician or other qualified health care professional |
| 0579T | Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter-defibrillator system, remote data acquisition(s), receipt of transmissions and technician review, technical support and distribution of results |
| 0580T | Removal of substernal implantable defibrillator pulse generator only |
| 0614T | Removal and replacement of substernal implantable defibrillator pulse generator |

**Insertion, repositioning, programming, interrogation, and evaluation of implantable cardioverter-defibrillator system with a substernal (extravascular) electrode are considered unproven and not medically necessary due to insufficient evidence of efficacy.**

## Clinical Evidence

The Extravascular Implantable Cardioverter Defibrillator (EV ICD) system is a device in which a lead is placed outside of the heart and veins to deliver lifesaving defibrillation and anti-tachycardia pacing therapy in one system. The device is the same size as traditional, transvenous ICDs (Medtronic, 2019).

In 2022, Friedman et al. conducted a prospective, single-group, nonrandomized, premarket global clinical study for individuals with class I or IIa indication for implantable cardioverter defibrillator (ICD) and included all who received an ICD. The primary

efficacy endpoint was effective defibrillation at implantation. The efficacy goal would be met if the lower boundary of the one-sided 97.5% confidence interval (CI) for the percentage of those with effective defibrillation was greater than 88%. At six months, the primary safety endpoint was independence from the major system- or procedure-related complications. The safety aim would be met if the lower margin of the one-sided 97.5% CI for the percentage of individuals free from such complications was more substantial than 79%. The study resulted in the enrollment of 356 participants; 316 had an implantation attempt. Amongst the 302 individuals in whom ventricular arrhythmia could be induced and who accomplished the defibrillation testing protocol, the percentage of those with effective defibrillation was 98.7% (lower boundary of the one-sided 97.5% CI, 96.6%; $p < 0.001$ for the comparison with the performance goal of 88%); 299 of 316 participants (94.6%) were discharged with an operational ICD system. The Kaplan-Meier estimate of the percentage of those without major system- or procedure-related complications at six months was 92.6% (lower boundary of the one-sided 97.5% CI, 89.0%; $p < 0.001$ for the comparison with the performance goal of 79%). No major intraprocedural complications were reported. At six months, twenty-five major complications were observed in 23 of 316 individuals (7.3%). The success rate of anti-tachycardia pacing, as calculated with general estimating equations, was 50.8% (95% CI, 23.3 to 77.8). A total of twenty-nine participants received 118 incorrect shocks for eighty-one arrhythmic episodes. Eight systems were explanted without extravascular implantable cardioverter defibrillator (EV-ICD) replacement over the 10.6-month mean follow-up period. The authors concluded EV-ICDs were implanted safely and could identify and stop induced ventricular arrhythmias at implantation. The study is limited by lack of comparison to a standard therapeutic approach.

In 2022, Boersma et al. created a position paper by the European Heart Rhythm Association/Heart Rhythm Society/Latin American Heart Rhythm Society/Asia Pacific Heart Rhythm Society (EHRA/HRS/LAHRS/APHRS) on practical consideration, indications, and future perspectives on leadless and EV-ICD cardiac implantable electronic devices. The European Society of Cardiology (ESC) concludes that the current EV-ICD is a first-generation tool with limited published data and is not yet commercially accessible. The EV-ICD is structured to be Magnetic Resonance Imaging (MRI) conditional, with remote care capacity and durability similar to current transvenous implantable cardioverter defibrillator (TV-ICD) platforms. A large clinical trial for Conformité Européenne (CE) and Food and Drug Administration (FDA) approval has completed enrollment. Centered on presently accessible information, it can be implanted safely and identify and defibrillate induced ventricular fibrillation during testing.

In 2021, Swerdlow et al. studied the sensing and arrhythmia detection performance of an EV-ICD in a first-in-human single-arm pilot study. To conduct the study, electrograms were post-processed from induced ventricular fibrillation (VF) at implant to uncover virtual detection times for each programmable sensitivity and the least-sensitive safe sensitivity setting. For ambulatory individuals, programmed sensitivity supplied at least a double safety margin for identifying induced VF. Noise discrimination was stress evaluated, and source, posture, and lead maturation influences were governed by electrogram amplitude. Telemetry Holter monitors were used to measure under-sensing and over-sensing. The study's results showed that for twenty individuals at implant, the least-sensitive safe sensitivity for VF recognition varied from 0.1 to 0.6 mV. Seventeen participants were followed up for a total of 16.6 patient-years. Electrogram amplitudes were even over time, but there were substantial variations between postures and sensing vectors. For the primary sensing vector, the weighted over-sensing and under-sensing rates were 1.03% and 0.40%, correspondingly, on a beat-to-beat basis. Oversensing did not trigger improper therapy for individuals with in-situ leads. Oversensing discriminators suppressed VF recognition in four out of five spontaneous, continuous over-sensed episodes. Supraventricular Tachycardia-Ventricular Tachycardia (SVT-VT) discriminators appropriately categorized 93% of 128 sustained Supraventricular Tachycardia (SVT)s in monitor zones. The authors concluded that over-sensing in the EV-ICD pilot study did not cause incorrect therapy during ambulatory follow-up of stable leads.

In the first-in-human prospective nonrandomized pilot single-arm trial, Crozier et al., 2020 aimed to assess the safety and performance of an EV-ICD. The study was conducted at four centers in Australia and New Zealand. Participants were twenty-one people denoted for ICD implantation. Participants received EV-ICD systems. Data collection involved major systemic and procedural adverse events, defibrillation testing at implantation, and sensing and pacing thresholds. The study's results showed that between 20 individuals who underwent effective implantation, the median defibrillation threshold was 15 J, and 90% passed defibrillation testing with a ≥ 10-J safety margin. The mean R-wave amplitude was 3.4 ±2.0 mV, the mean ventricular fibrillation amplitude was 2.8 ±1.7 mV, and the pacing was victorious in 95% at ≤ 10 V. There were no intraprocedural complications. Two individuals have undergone elective chronic system extraction since hospital discharge. In the fifteen participants implanted, the systems were steady in long-term follow-up. The authors concluded that there is the practicability of substernal lead placement, defibrillation, and pacing with a chronically implanted system. There were no major acute complications and pacing, defibrillation, and sensing performance at implantation were adequate in most people.

In 2019, Boersma et al. published results from a ASD2 (Acute Extravascular Defibrillation, Pacing, and Electrogram) study evaluating the ability to adequately sense, pace, and defibrillate persons with a novel ICD lead implanted in the substernal space. This ASD2 study was the first reported human clinical study of pacing, sensing, and defibrillation from a lead designed specifically for the substernal space. In their single-arm study, the substernal lead was implanted in 79 individuals, with a median implantation time of 12.0 ±9.0 min. Ventricular pacing was successful in at least one vector in 76 of 78 participants (97.4%), and 72 of 78 (92.3%) participants had capture in ≥ 1 vector with no extracardiac stimulation. A 30-J shock successfully terminated 104 of 128 episodes (81.3%) of ventricular fibrillation in sixty-nine individuals. There were 7 adverse events for six individuals causally (n = 5) or possibly (n = 2) related to the ASD2 procedure. The authors concluded that the ASD2 study demonstrated the ability to pace, sense, and defibrillate using a lead designed specifically for the substernal space. The proximity of the lead to the pericardium resulted in R-wave amplitudes amenable to ICD sensing, a high rate of pacing capture, and a low degree of extracardiac stimulation during pacing and defibrillation efficacy was > 80% with a single 30-J shock. The authors concluded that further investigation for individuals who are ambulatory is needed, but taken together, these results demonstrated the feasibility of a novel extravascular approach to ICD therapy delivery.

In the Substernal Pacing Acute Clinical Evaluation (SPACE) study, Sholevar et al. (2018) evaluated the feasibility of pacing from an extravascular substernal location. This primary purpose of this prospective, nonrandomized, multicenter, feasibility single-arm study was characterization of pacing from the substernal space. Evaluation of extracardiac stimulation and recording electrograms were secondary goals. A commercially available electrophysiology catheter was implanted in the substernal space via minimally invasive subxiphoid access. Eligible participants were those undergoing cardiac surgery with midline sternotomy, primary ICD system implantation, or epicardial ventricular tachycardia ablation. Catheter placement was successful in all twenty-six participants who underwent the procedure. Mean placement time was 11.7 ±10.1 minutes. Eighteen individuals (69%) had successful ventricular capture in ≥ 1 tested vector. The mean pacing threshold at a pulse width of 10 ms was 7.3 ±4.2 mA across all vectors (5.8 ±4.4 V). The mean R-wave amplitude ranged from 2.98 to 4.11 mV in the unipolar configuration and from 0.83 to 3.95 mV in the bipolar configuration. One participant with a low level of extracardiac stimulation was identified. Suboptimal catheter placement or presumed air ingression was associated with failed capture. The author's concluded pacing is feasible from the extravascular substernal location. Limitations include the small population size, and the individuals were not typical those who would receive a defibrillator. Future studies would ideally avoid the use of paralytic medications to allow the investigation of extracardiac stimulation and will need to evaluate chronic substernal therapy delivery in for individuals with indications for a permanent ICD.

In 2017, Chan et al. prospective, nonrandomized feasibility study assessed the defibrillation efficacy of the substernal-lateral electrode configuration. The study was conducted in subjects scheduled for midline sternotomy or implant of an ICD. Using a percutaneous subxiphoid method, a blunted end tunneling tool was used to insert a defibrillation lead backside of the sternum. A skin patch electrode was placed on the left mid-axillary line at the fourth to fifth intercostal space. After ventricular fibrillation induction, a single 35-J shock was delivered between the lead and skin patch. The study's results showed that of sixteen subjects (12 males, four females; mean age: 61.6 ±11.8 years) enrolled, the mean lead placement time was 11.1 ±6.6 min. Of the fourteen subjects with effectively induced ventricular fibrillation episodes, 13 (92.9%) had thriving defibrillation. The one failure was linked to high and lateral shock coil placement. The average ventricular fibrillation duration was 18.4 ±5.6 s with a shock impedance of 98.1 ±19.3 ohms. Of the 11 subjects with coil-patch electrograms, the mean R-wave amplitude during sinus rhythm was 3.0 ±1.4 mV. The authors concluded that the initial data shows that substernal defibrillation is feasible and effective defibrillation can be accomplished with the shock energy offered in current TV-ICDs. This may open new alternatives to EV-ICD therapy.

In 2012, the Food and Drug Administration (FDA) approved the Cameron Health Subcutaneous Implantable Defibrillator S-ICD® System. According to the FDA's summary of safety and effectiveness data (SSED) the S-ICD® System is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias for those who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing. Additional information can be found at: https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110042B.pdf.

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

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

## Clinical Evidence

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

Van de Voort et al. (2021) performed a systematic review and meta-analysis of 37 articles which included 1266 patients that underwent a variety of ablation to treat small breast cancers and whether the intervention was an effective method to treat early-stage breast cancer with tumors ≤ 2 cm. Analysis included comparison of the five different ablation therapies and complication rates. Twenty four articles were reviewed by intervention. These included 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.

Cui et al. (2021) conducted a prospective study, registered in ClinicalTrials.gov under the identifier number NCT-02860104, to evaluate the efficacy of microwave ablation (MWA) for benign breast lesions (BBLs) and explore probable factors associated with the volume reduction rate (VRR) of ablated lesions. From November 2013 to December 2017, a total of 80 patients with 104 biopsies proven BBLs larger than 2 cm in size underwent MWA. After the procedure, patients were followed up via physical and imaging examination consisting of contrast-enhanced ultrasound (CEUS) and magnetic resonance imaging (MRI). Possible factors associated with 12-month volume reduction rate (VRR) were assessed, including basic patient characteristics, index lesions and parameters of ablation technique. The mean tumor size was 2.6 ±0.6 cm (ranging 2.0-6.3 cm). Of the 104 lesions, 70 were fibroadenomas, 27 adenosis and 7 fibrocystic changes. Post-procedure CEUS or contrast-enhanced MRI showed that all lesions were completely ablated. No immediate or delayed complications were observed. All patients were followed up for more than 12 months (median follow-up 12.5 months). After MWA, the ablated lesion volume decreased by 12 months ($p < 0.001$), with a mean volume reduction of 80.2 ±13.1%. Multiple linear regression analysis showed that location adjacent to areola ($\beta = 7.5$, 95%CI: 1.0-13.9, $p = 0.025$) and location adjacent to skin ($\beta = -7.4$, 95%CI: -12.7 to -13.9, $p = 0.007$) were independent factors respectively associated with the increased and decreased 12-month VRR. The authors concluded for BBLs larger than 2 cm, US-guided MWA is a favorable treatment modality, with BBLs adjacent to the areola being associated with more 12-month VRR after MWA. Limitations of this study include the small number of individuals with BBLs larger than 3 cm. In addition, the association between VRR and vascular supply of the ablated BBLs and the influence of MWA treatment on lactation were not analyzed. Further research is needed to determine the clinical relevance of these findings.

Liu et al. (2021) conducted a prospective study to investigate the safety, efficacy, and follow-up outcomes of microwave ablation (MWA) in patients with breast fibroadenoma from October 2017 to March 2019. A total of 171 individuals with 271 lesions were enrolled. The mean lesion diameter was 1.35 ±0.47 cm. The results revealed differential lesion states, including stability, enlargement, reduction, and complete regression, at 1-6, 6-12, and > 12 months of follow-up. The size was reduced in 22.14% (31/140), 26.36% (29/110), and 36.36% (16/44) of the lesions at 1-6, 6-12, and > 12 months of follow up, respectively. The proportion of lesions with complete regression was 24.29% (34/140) at 1-6 months, 45.45% (50/110) at 6-12 months, and 40.91% (18/44) at > 12 months of follow up. There was no relationship between the curative effect and age, lesion location, and blood flow in patients with breast fibroadenoma after MWA ($p > .05$), but there was statistical relationship with lesion diameter (categorized as < 1.5 cm and 1.5 cm) ($p < .05$). The authors concluded that the current evidence indicates that MWA is a safe and effective method for treating breast fibroadenoma. However, further large-scale prospective trials and well-designed future studies are warranted to validate their findings. This study has limitations. At the period of > 12 months after MWA, only 10 of the 44 lesions were maintained at a stable state (7 showing enlargement and 3 showing stability), and only 18 of 44 lesions (40.91%) completely regressed. The largest diameter of the lesions included was 30 mm; thus, the feasibility and efficacy of ultrasound guided MWA should be further investigated for larger lesions. In addition, a small sample size and short duration of follow-up makes it difficult to decide whether these conclusions can be generalized to a larger population.

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.

### *Clinical Practice Guidelines*

#### American Society of Breast Surgeons (ASBrS)

The ASBrS Consensus Statement developed and approved on October 16, 2018, on the Use of Transcutaneous and Percutaneous Ablation for the Treatment of Benign and Malignant Tumors of the Breast states: “Cryoablation is currently approved for treatment of benign and malignant soft tissue tumors by the FDA. Currently, there are no specific technologies that have FDA approval for breast tumors. Participation in registries and clinical trials evaluating the use of these technologies with and without surgical excision of a breast malignancy is advised as early data emerges on their efficacy.”

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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.

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

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

## Clinical Evidence

The Tubes Under Local Anesthesia (Tula) System is intended to insert ear tubes (tympanostomy tubes) into the eardrum in children and adults, using local anesthesia in a physician's office, to treat repeated ear infections (recurrent acute otitis media) or fluid in the ear (otitis media with effusion). The Tula® System consists of the Tula Iontophoresis System and the Tula Tube Delivery System. The Tula Iontophoresis System, which includes individually fitted disposable ear plugs and ear sets, delivers a local anesthetic solution, TYMBION™, to the eardrum resulting in numbness of the eardrum. The Tula Tube Delivery System is then used to place the ear tube in the eardrum, The Tula system received FDA premarket approval (P190016) on November 25, 2019. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P190016. (Accessed April 21, 2023)

Cohen et al. (2022) conducted a study to evaluate behavioral strategies to minimize in-office procedural distress associated with tympanostomy tube placement for children without general anesthesia, sedation, or papoose-board restraints. One hundred and twenty children, six months to four years old, and 102 children, 5-12 years old, were treated at 16 different practices. The in-office tube placement procedure included local anesthesia via lidocaine/epinephrine iontophoresis and tube placement using an integrated and automated myringotomy and tube delivery system. Behavioral strategies were utilized to decrease procedural distress; no anxiolytics, sedation, or papoose board were used. Pain was measured via the faces pain scale-revised (FPS-R) self-reported by the children ages five through 12 years. Independent coders supervised by a psychologist completed the face, legs, activity, cry, consolability (FLACC) behavior observational rating scale to quantify children's distress. Mean FPS-R score for tube placement was 3.30, in the "mild' pain range, and decreased to 1.69 at 5-min post-procedure. Mean tube placement FLACC score was 4.0 (out of a maximum score of ten) for children ages six months to four years and was 0.4 for children ages five to 12 years. Mean FLACC score 3-min post-tube placement was 1.3 for children ages six months to four years and was 0.2 for children ages five to 12 years. FLACC scores were inversely correlated with age, with older children displaying lower distress. The authors concluded the Tula System and behavioral program allow pediatric patients to receive in-office tympanostomy tube placement without general anesthesia, sedation, or mechanical restraints with minimal distress. Limitations included lack of a control group and two of the authors were funded for work on the project, which may introduce investigator bias. The authors recommend further studies to match intervention components and strategies to individuals.

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

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

Lustig et al. (2020, included in the 2022 Hayes Evidence Analysis Research Brief) published the results of a prospective multi-center case series evaluating the safety, technical success, and tolerability of tympanostomy tube placement under local anesthesia in an office setting (OTTER study). A total of 337 children across 18 different sites, ages six 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 five to 12 years old using the FPS-R tool, which is used to rate pain from zero (no pain) to 10 (very much pain). Bilateral tubes were placed successfully in 85.8% of children less than five years of age and 89.2% of children five 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 tympanostomy tube placement. 91.8% of implant tubes were still present at the six 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 Waldman et al. (2023), participants were followed for two years or until tube extrusion, and evaluated for tube retention, patency, and safety. In this follow-up group, tubes were placed in-office for 269 patients (449 ears) and in the operating room for 68 patients (131 ears). The median and mean times to tube extrusion for the combined operating room and In-Office cohorts were 15.82 and 16.79 months, respectively. Outcomes included ongoing perforation for 1.9% of ears (11/580) and medial tube displacement for 0.2% (1/580) observed at 18 months. Over a mean follow-up of 14.3 months, 30.3% (176/580) of ears had otorrhea and 14.3% (83/580) had occluded tubes. The authors concluded the in-office tympanostomy using lidocaine/epinephrine iontophoresis and Tula® System resulted in tube retention similar to grommet-type tubes and the complications were consistent with operating room tube placement. Limitations include lack of a control group and the study was industry sponsored.

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

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

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

Cohen et al. (2015) indicated that two complementary technologies have recently been developed comprising an iontophoresis system (IPS) for delivering local anesthesia and an integrated TDS subsequently eliminating the need for general anesthesia in an operating room setting. These investigators evaluated behavioral support techniques used during a clinical study of the new technology for pediatric in-office tube placement without general anesthesia or physical restraints. As part of an institutional review board (IRB)-approved, prospective, 9-center case series, pediatric patients requiring tube insertion underwent in-office treatment using the new procedure. The behavior management techniques included preparation, distraction, coaching, and reinforcement for co-operation. The entire procedure was videotaped, and two independent coders used the validated FLACC scale to code behavioral distress across five procedural phases. A total of 70 pediatric patients aged eight 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 zero to one [MDN = 0, inter-quartile range (IQR) = 0.05], which indicated "mild" distress. During iontophoresis, eardrum tap (anesthesia assessment), and tube delivery, older children displayed lower distress and girls had higher FLACC scores during the eardrum tap procedural phase. The authors concluded that when combined with the evidence-based behavioral techniques, office-based local anesthesia and tube delivery resulted in minimal distress, suggesting that the new procedure may be a viable method of conducting tympanostomy tube placement in children without having to use general anesthesia. A randomized trial with a comparison or control group is needed to establish the efficacy of in-office tympanostomy tube placement without general anesthesia.

Zeiders et al. (2015, included in the 2022 Hayes Evidence Analysis Research Brief). conducted a prospective, single-arm study at nine otolaryngology sites in the US. Participants included pediatric patients aged six months to less than 22 years who required tube placement. The participants were prepared for the procedure using behavioral support techniques and tube placement was attempted under local anesthesia using the IPS in conjunction with the TDS. No physical restraints were allowed nor was the use of anxiolytics, analgesics, or sedatives permitted. Safety was evaluated via the occurrence of AEs and success rates for tube placement under local anesthesia were determined. The 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 one device was required in nine 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 two weeks was 99.1%. As only 15 patients were enrolled who were three years old or younger, the ability to generalize these results to younger patients was limited. The authors concluded that the use of the IPS and TDS technologies enabled safe, reliable, and tolerable placement of tubes in awake, unrestrained pediatric patients. This study was limited by lack of a control group or relevant efficacy outcomes.

## Reference(s)


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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 |
|---|---|
| 0594T | Osteotomy, humerus, with insertion of an externally controlled intramedullary lengthening device, including intraoperative imaging, initial and subsequent alignment assessments, computations of adjustment schedules, and management of the intramedullary lengthening device |

**Osteotomy, humerus, with insertion of an externally controlled intramedullary lengthening device, including intraoperative imaging, initial and subsequent alignment assessments, computations of adjustment schedules, and management of the intramedullary lengthening device is considered unproven and not medically necessary due to insufficient evidence of efficacy.**

## Clinical Evidence

In 2023, ECRI assessed the clinical evidence of the Maxframe AutoStrut Multi-axial Correction System (DePuy Synthese) for fracture fixation, limb lengthening, and deformity correction. The assessment uncovered the device to appear safe and work as intended to fix fractures and correct deformities in children and adults. However, the available studies provided only very low-quality evidence and assessed too few individuals to allow conclusions. To effectively evaluate the safety and effectiveness of the device, randomized controlled trials comparing Maxframe AutoStrut with other fixation systems and reports on longer-term patient-oriented outcomes are necessary.

In a single-center study, Laufer et al. 2022 assessed 44 individuals with severe shortening of the upper extremities and functional impairments who underwent humeral lengthening. After exclusion, the retrospective study examined the results from 28 individuals for a median follow-up time of 6 years. Medical charts were evaluated for improvement in function and autonomy, and a nine-item questionnaire was administered to assess the individual's functional progress in activities of daily living, physical appearance, and overall satisfaction. The results of this study showed all participants reported improvement at their most recent follow-up compared with scores obtained before treatment [median (IQR) 24 (16 to 28) before surgery vs. 44 (42 to 45) at the latest follow-up, a difference of medians 20 points, $p < 0.001$]. A total of 89% (25 of 28) of those achieved the desired 8 cm of lengthening in both arms. A total of 50% (14 of 28) of individuals experienced a significant complication. Specifically, 39% (11 of 28) had an unplanned reoperation, 39% (11 of 28) had a radial nerve palsy, 18% (5 of 28) had a refracture of the regenerate, and 4% (1 of 28) concluded treatment with a severe limb length discrepancy. In addition, 82% (23 of 28) of individuals experienced minor complications that resolved without further surgery and did not involve radial nerve symptoms. Radial nerve palsy was observed immediately in eight of 13 segments and 1 to 7 days postoperatively in five of 13 segments. The treatment goal was not achieved because of radial nerve palsy in 5% (3 of 56) of lengthened segments, which occurred in 7% (2 of 28). Complete functional recovery of the radial nerve was observed in all participants after a median (IQR) of 3 months (2 to 5). Refractures of bone regeneration were observed in 11% (6 of 56) of humeri in 18% (5 of 28). Of those refractures, 1 of 6 individuals was treated nonsurgically with a hanging cast, while 5 6 underwent revision surgery with intramedullary rodding. The authors concluded that bilateral humeral lengthening with a monolateral external fixator should only be considered for individuals with severe functional impairments because of rhizomelic shortening of the upper extremities. Internal lengthening devices are preferable, as these are generally associated with higher comfort and decreased complication rates than external fixators.

In 2022 the National Institute for Health and Care Excellence (NICE) produced interventional procedures guidance for intramedullary distraction for upper limb lengthening. The recommendations are as follows:

- Evidence on the safety and efficacy of intramedullary distraction for upper limb lengthening needs to be improved in quantity and quality. But because this is a rare condition with limited alternative treatments, the procedure can be considered as long as special arrangements for clinical governance, consent, and audit or research are in place.
- Clinicians wanting to use intramedullary distraction for upper limb lengthening should:
    - Inform the clinical governance leads in their healthcare organization.
    - Give people (and their families and caregivers as appropriate) clear written information to support shared decision-making, including NICE's data for the public.
    - Ensure that people (and their families and caregivers as appropriate) understand the safety and efficacy and any uncertainties about the procedure.
    - Audit and review clinical outcomes of everyone having the procedure. The primary efficacy and safety outcomes identified in this guidance can be entered into NICE's interventional procedure outcomes audit tool (for use at local discretion).
    - Discuss the procedure's outcomes during their annual appraisal to reflect, learn and improve.
- Healthcare organizations should:
    - Make sure systems are in place that support clinicians to collect and report data on outcomes and safety for everyone having this procedure.
    - Regularly review data on outcomes and safety for this procedure.

- This technically challenging procedure should only be done in specialist centers using a multidisciplinary approach by surgeons with specific training and experience in upper limb lengthening techniques.
- Report any problems with a medical device using the Medicines and Healthcare Products Regulatory Agency's Yellow Card Scheme.
- Further research, which could be registry data, should report patient selection, device selection, the technique used, procedural outcomes, and long-term outcomes, including quality of life, the need for repeat interventions or surgery, and complication rates.

In 2020, ECRI produced a clinical evidence assessment on the intramedullary devices for lengthening the humerus. The evidence assessment included:
- One single-center
- Single-surgeon
- A retrospective, nonrandomized comparative study
- One multicenter, retrospective case series; and
- One multicenter, retrospective case series

The included studies are at extremely substantial risk of bias due to single-surgeon and single-center focus, small sample size, retrospective design, and lack of controls, blinding, and randomization. The evidence needed more conclusive, of poor quality, and more data.

A clinical evidence assessment on TrueLok Ring Fixation System (Orthofix, Inc) for fracture fixation, limb lengthening, and deformity correction in 2014; updated 2021. The evaluation results uncovered studies at an elevated risk of bias due to small sample sizes and lack of randomization and blinding. The overall evidence was inconclusive and had too little data on outcomes of interest.

The FDA announced the Precice Intramedullary Limb Lengthening System (NuVasive Specialized Orthopedics, Inc) approval. The Precice Intramedullary Limb Lengthening System is indicated for limb lengthening, open and closed fracture fixation, pseudarthrosis, malunions, nonunion, or bone transport of long bones for individuals aged 18 years and older and indicated for limb lengthening of the femur and tibia in the pediatric population (greater than 12 years old). For use in segmental bone loss treatment. For more information, refer to the following website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K220234. (Accessed May 22, 2023)

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ECRI. TrueLok Ring Fixation System (Orthofix, Inc.) for fracture fixation, limb lengthening, and deformity correction. Plymouth Meeting (PA): ECRI; 2021 May. (Clinical Evidence Assessment).

Laufer A, Rölfing JD, Gosheger G, et al. What are the risks and functional outcomes associated with bilateral humeral lengthening using a monolateral external fixator in patients with achondroplasia? Clin Orthop Relat Res. 2022 Sep 1;480(9):1779-1789.

National Institute for Health and Care Excellence (NICE). IPG722. Intramedullary distraction for upper limb lengthening. April 2022.


| Code | Description |
|---|---|
| 0600T | Ablation, irreversible electroporation; 1 or more tumors per organ, including imaging guidance, when performed, percutaneous |
| 0601T | Ablation, irreversible electroporation; 1 or more tumors, including fluoroscopic and ultrasound guidance, when performed, open |

**Ablation, irreversible electroporation (IRE), and percutaneous are unproven because there are insufficient studies supporting the safety and efficacy of the procedure and demonstrating improvement in health outcomes compared to other standard treatments. Ablation, irreversible electroporation (IRE), open, is unproven due to insufficient clinical evidence of safety and efficacy.**

## Clinical Evidence

The NanoKnife System uses irreversible electroporation (IRE) for nonthermal tissue ablation of soft tissue during open, laparoscopic, or percutaneous procedures. NanoKnife uses high-voltage direct current to induce cell death by permeabilizing cell membranes. NanoKnife is not labeled explicitly for tumor ablation, but it is sometimes used for individuals to treat unresectable liver tumors. In the 2023 ECRI Clinical Evidence Assessment on the NanoKnife System (AngioDynamics, Inc) for treating liver cancer, evidence was inconclusive and very low quality. Evidence from two systematic reviews (SRs) with meta-analysis of low-quality studies, two small randomized controlled trials, and five nonrandomized comparison studies suggests NanoKnife works as intended to ablate tissue in the liver. However, how well NanoKnife works compared with other ablation modalities cannot be determined because comparative studies are at a high risk of bias and assess too few subjects per comparison. The studies also pooled outcomes for individuals with different cancer types, stages, or tumor locations, which limited generalization across studies. The SRs lack control groups, and IRE's effectiveness in improving patient-oriented outcomes cannot be interpreted without control groups.

In the 2023 ECRI Clinical Evidence Assessment on the NanoKnife System (AngioDynamics, Inc) For Treating Pancreatic Cancer, evidence was inconclusive and of very low quality. Evidence from five systematic reviews (SRs) of very-low-quality studies and four additional nonrandomized comparison studies do not permit conclusions about IRE's risks and benefits for treating pancreatic cancer. The SRs reported median overall survival (OS) of 6 to 27 months and OS rates of 55% at 1-year and 33.8% at 2-year follow-up, but whether IRE improves outcomes when used as an alternative to other ablation modalities or an adjunct to radiotherapy and chemotherapy remains unclear because comparative studies are of low quality and report few and inconsistent findings.

The evidence was inconclusive in the 2022 ECRI Clinical Evidence Assessment on NanoKnife System (AngioDynamics, Inc) For Treating Prostate Cancer. Two systematic reviews (SRs) that include case series and two other case series provide very low-quality evidence and do not permit conclusions on IRE's safety and effectiveness for treating prostate cancer. Reported recurrence rates varied widely (3% to 39%). Severe complication rates were low, but NanoKnife's safety is unclear because no studies compared it with other ablative treatments.

In 2022 Yu and Li conducted a meta-analysis to gauge the efficacy and safety of IRE for treating malignant hepatic tumors, with a particular interest in the damage to the gastrointestinal tract, bile ducts, and vital vessels. Twenty-six studies were uncovered, encompassing 807 participants and 1115 lesions. IRE's complete ablation rate of liver cancer was 86% (95% CI: 81%-90%). IRE-related complications were 23% (95% CI: 17%-28%); however, many were minor. The authors concluded that the meta-analysis confirmed that IRE ablation is safe and effective for treating liver cancer. This study has several limitations: the retrospective nature of the studies, differences in design and treatment methods, heterogeneity between studies, and bias. The significant differences in PLR cut-off values could affect the study results.

Through a prospective single-center, double-arm clinical trial, Liu et al. (2022) compared the efficacy, safety, and intermediate-term outcomes of IRE and radiofrequency (RF) therapy for malignant liver tumors. Included in the trial were twenty-four individuals with primary or secondary liver malignancies. In random order, participants were divided into either the IRE or RF group. Outcomes measured were efficacy (local ablation control evaluation at 90 days), safety (procedure-related complications at ≤ 90 days), and intermediate-term survival (at 24 months). The ablation assessment at 90 days after surgery with mRECIST for IRE compared to RF was 70%, 20%, 0%, and 10% versus 92.9%, 7.1%, 0%, and 0% (CR, PR, SD, and PD, respectively). The complication rates of IRE compared to RF with Clavien-Dindo classification were 16.7%, 25%, 0%, 8.3%, and 8.3% versus 8.3%, 50%, 0%, 0%, and 0% (Grade I, II, III, IV, and V, respectively). On average, the overall survival (OS) was 17.55 months in the IRE group (95% CI 15.13-22.37) and 18.75 months in the RF group (95% CI 12.48-22.61). Statistical differences between the IRE and RF groups in terms of efficacy ($p = 0.48$), safety ($p = 0.887$), or 24-month OS ($p = 0.959$) were absent. The authors concluded that IRE ablation showed comparable efficacy and safety in a short-term follow-up and similar OS in mid-term survival as RF ablation in treating malignant hepatic tumors. Follow-up was inhibited due to the COVID-19 epidemic for individuals in the later stages. Telephone follow-up was conducted, and basic information was obtained regarding follow-up.

Yaxley and colleagues (2022) steered a retrospective review of prospectively gathered data to assess histological in-field clearance of prostate cancer at ≥ 12 months for individuals post-IRE. To be considered a 'significant recurrence,' individuals would have results of ≥ 6 mm core Gleason 3 + 3 or ≥ Gleason 3 + 4 with ≥ 4 mm tumor length. Any focus of the International Society of Urological Pathology (ISUP) ≥ 2 was also investigated. For the entire cohort, the median follow-up is 23 months (range 3-39 mo). For 64 primary IRE procedures, surveillance biopsy was performed in 40/50 (80.0%) with ≥ 12 months follow-up. Significant in-field recurrence occurred in 3/40 (7.5%) or 4/40 (10.0%) with any focus of ISUP > 2. Significant out-of-field

recurrence was demonstrated in 5/40 (12.5%). Three individuals (3/6, 50.0%) in salvage IRE have undetectable prostate-specific antigen levels, two have no residual cancer on biopsy, and one had an out-of-field recurrence. Erectile function was maintained in 24/28 (85.7%) primary IRE for sexually active men. For primary IRE, there was no incontinence developed (0/64). The authors concluded that primary focal IRE for prostate cancer is correlated with 90% infield ablation of any ISUP grade > two cancer with a low risk of urinary incontinence or impotence. Prostate biopsies are required to exclude progression surveillance, regardless of a standard post-IRE multiparametric magnetic resonance imaging (mpMRI). The data shows salvage IRE is an encouraging option for localized recurrence after prostate radiotherapy with low morbidity. Limitations to the study included relatively short follow-up and the retrospective review of a prospective database (which resulted in an underestimated complication rate).

In 2022, Li and associates guided a retrospective longitudinal study for individuals ineligible for thermal ablation and underwent computed tomography-guided IRE for hepatic tumors at the hepatorenal confluence. The authors analyzed the individuals and tumor characteristics, IRE procedure details, treatment-related complications, and prognosis to carry out the analysis. Twenty-one of the 38 lesions were at the hepatorenal confluence, and complete ablation was accomplished in all cases. Of the ablated tumors, local and distant recurrence was seen in 4.8% (1/21) and 42.6% (9/21), respectively. All postcava remained perfused at follow-up, except for 1 (4.8%) hepatic vein near the lesion, found to be temporarily occluded and reestablished within one month. At 1-, 3-, and six months post-procedure, the ratio of the maximum diameter of ablation area compared to directly after IRE was 0.68 (0.50-0.84), 0.49 (0.27-0.61), and 0.38 (0.25-0.59), respectively. Progression-free survival of the individuals with recurrence was 121 (range, 25-566) days. The median OS was 451.5 (range, 25-716) days, as four (19.0%) individuals died at the end of follow-up. The authors concluded that added data is required to solidify the indications for using IRE for treating hepatic tumors at the hepatorenal confluence. When thermal ablation is inappropriate, its safety profile and sustainable rate have favored IRE as a safe and viable treatment option. The high success and low local recurrence rates indicate the efficacy of IRE, although these results are to be proven with a longer follow-up time in a more significant number of individuals. For additional benefits, Synergistic therapy may be the trend of IRE.

The FDA has cleared the NanoKnife® System (510 K number K183385) for the surgical ablation of soft tissue. Additional information can be found at:

- https://www.accessdata.fda.gov/cdrh_docs/pdf18/K183385.pdf. (Accessed May 22, 2023)
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K183385. (Accessed May 22, 2023)

The National Comprehensive Cancer Network (NCCN) Guidelines for pancreatic adenocarcinoma report that irreversible electroporation (IRE) is an ablative technique in which electric pulses are used to create nanopores that induce cell death similar to apoptosis. This technique has been used for individuals with locally advanced pancreatic cancer. IRE may be safe and feasible and may improve survival outcomes. However, due to concerns about complications and technical expertise, the panel does not currently recommend IRE for treating locally advanced pancreatic cancer (V1 2023).

The NCCN Guidelines for Hepatocellular Carcinoma report that IRE has some advantages over RFA, notably the lack of a "heat sink" effect and the ability to treat near vessels, bile ducts, and other critical structures. However, IRE can cause cardiac arrhythmias and uncontrolled muscle contractions. Some small studies have shown that IRE treatment for unresectable HCC is safe and feasible. In a small nonrandomized trial including 30 participants with malignant liver tumors, none of the eight people with HCC experienced a recurrence through a 6-month follow-up. Recurrences have been reported following IRE for larger tumors. Larger studies are needed to determine the effectiveness of IRE for local HCC treatment. Although inconclusive, available evidence suggests that the choice of ablative therapy for individuals with early-stage HCC should be based on tumor size, location, underlying liver function, and available local radiologist expertise and experience. Ablative therapies are most effective for tumors.

The 2019 NICE guideline for irreversible electroporation of primary liver cancer states: evidence on the safety of irreversible electroporation for primary liver cancer shows serious but infrequent and well-recognized complications.

- Evidence of its efficacy needs to be improved in quantity and quality. Therefore, this procedure should only be used in the context of research. A multidisciplinary team should make patient selection.
- The procedure should only be done in specialist centers by clinicians with experience and specific training.
- Further research could be in case series or registry-based research. It should include details of patient selection, tumor position, and size; long-term outcomes, including overall survival, progression-free survival, and tumor regression; and patient-reported outcomes, including quality of life.

The 2017 NICE guideline for irreversible electroporation for treating pancreatic cancer states: Current evidence on the safety and efficacy of irreversible electroporation for treating pancreatic cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. Further research, preferably in the form of randomized controlled trials, should assess the effect of the procedure on local tumor control, survival, pain control, and quality of life.

The 2016 NICE guideline for irreversible electroporation for treating prostate cancer states: Current evidence on the safety and efficacy of irreversible electroporation for treating prostate cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. Studies should include randomized controlled trials comparing the procedure with current standards of care. They should report details of patient selection and short- and long-term outcomes, including patient-reported outcomes and the effect on any future prostate surgery.

The 2013a National Institute for Health and Care Excellence (NICE) guideline on irreversible electroporation for treating liver metastases states: Current evidence on the safety and efficacy of irreversible electroporation for treating liver metastases is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumor control and survival.

The 2013c National Institute for Health and Care Excellence (NICE) guideline on irreversible electroporation for treating renal cancer states: Current evidence on the safety and efficacy of irreversible electroporation for treating renal cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumor control and patient survival.

The 2013b National Institute for Health and Care Excellence (NICE) guideline on irreversible electroporation for treating primary lung cancer and metastases of the lung states: Current evidence on the safety and efficacy of irreversible electroporation for treating primary lung cancer and metastases in the lung is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research. In particular, studies should report the effect of the procedure on local tumor control and patient survival.

The European Network for Health Technology Assessment (EUnetHTA) reported on the Rapid Relative Effectiveness Assessment for IRE for the treatment of liver and pancreatic cancer:

### *Pancreatic Cancer*

- There is insufficient evidence to establish whether IRE is more effective than, or at least as effective as, the conventional standard of care (CHEMO, CRT, or palliative therapy) for treating unresectable LAPC.
- There is insufficient evidence to establish whether IRE is safer than, or at least as safe as, the conventional standard of care (CHEMO, CRT, or palliative therapy) for treating unresectable LAPC.
- The existing evidence raises doubts regarding the efficacy of IRE for achieving complete ablation of unresectable LAPC.
- The existing evidence raises doubts regarding the efficacy of IRE as the sole primary local treatment for LAPC. It is unclear whether IRE needs to be combined with CHEMO and, if so, which regimens are optimal.
- There are uncertainties regarding severe AEs when IRE is used to treat unresectable LAPC.

### *Liver Cancer*

- There is a lack of data to establish whether IRE is more effective than, or at least as effective as, the conventional standard of care (TACE, sorafenib, or palliative therapy) for treating individuals with primary or secondary unresectable liver cancer that is not suitable for thermal ablation.
- There is a lack of evidence to establish whether IRE is safer than, or at least as safe as, the conventional standard of care (TACE, sorafenib, or palliative therapy) for treating individuals with primary or secondary unresectable liver cancer that is not suitable for thermal ablation.
- The existing evidence raises doubts regarding the efficacy of IRE for achieving complete ablation of primary or secondary unresectable liver tumors unsuitable for thermal ablation.
- The existing evidence raises doubts regarding the efficacy of IRE as a sole primary local treatment for primary or secondary liver tumors unsuitable for thermal ablation.
- There are uncertainties regarding the occurrence of severe AEs when IRE is used to treat liver tumors unsuitable for thermal ablation (Zapata-Cachafeiro et al., 2019).

The German Society of Urology (Borkowitz et al., 2022) S3 Evidence-Based Guidelines on Focal Therapy in Localized Prostate Cancer states that the available data are insufficient to assess the oncological effectiveness and safety of focal irreversible electroporation (IRE), in particular, concerning long-term outcomes (evidence-based statement, level of evidence 4, overall agreement: 97%).

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| Code | Description |
|---|---|
| 0607T | Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; set-up and patient education on use of equipment |
| 0608T | Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center; analysis of data received and transmission of reports to the physician or other qualified health care professional |

**Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-hyphen derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hyphen hour attended surveillance center as well as the analysis of data received and transmission of reports to the physician or other qualified health care Professional is unproven due to insufficient clinical evidence of safety and efficacy.**

## Clinical Evidence

ZOLL® µCor™ HFAMS is an FDA-cleared patch-based, wireless system that employs novel radiofrequency technology to monitor pulmonary fluid levels, an early indicator for heart failure decompensation. ZOLL® HFAMS is intended for use in patients who

are 21 years of age or older requiring fluid management in outpatient clinic and home settings. The HFAMS sensor is non-invasive and can be worn by patients 24 hours a day. ZOLL® HFAMS continuously records, stores, and transmits patient data, including Thoracic Fluid Index, heart rate, respiration rate, activity, posture, and heart rhythm (ECG), and alerts physicians to signs of worsening patient condition (ZOLL® Medical Corporation, 2019). The Remote Dielectric Sensing (ReDs) Wearable System is another example of an external pulmonary fluid monitor; however, it is larger in size than the HFAMS.

A comparison study by Wheatley-Guy et al. (2020) was conducted to validate the ability of radiofrequency (RF) to assess lung fluid via a wearable patch device compared to thoracic CT in order to characterize volume overload. A total of 120 subjects were studied: 66 acute heart failure (AHF) inpatients and 54 subjects without AHF (Control – 44 healthy and 10 stable HF). All underwent supine thoracic CT scans and supine RF readings from the wearable patch device placed on the left mid-axillary line (age = 74 ±16 vs. 57 ±15 yrs.; female = 38 vs. 44%; BMI = 33.2 ±9.0 vs. 27.3 ±5.1, AHF vs. Control respectively). Reflected RF signals and subject-specific anthropometric data were used to calculate the RF-determined lung fluid content. CT Lung fluid was reported as a percentage of lung volume. Classification analyses were used to compare RF and CT performance. AHF presented with higher lung fluid than controls by both CT and RF (CT: 20.1 ±4.2% vs. 15.4 ±2.4%; RF: 20.7 ±5.6% vs. 15.6 ±3.3%; $p < 0.05$ for all). The correlation between lung fluid measured by CT vs. RF was $r = 0.7$ ($p < 0.001$). RF determined lung fluid performed as well as CT in distinguishing AHF from control subjects: Sensitivity: 70% vs. 86%; Specificity: 82% vs. 83%; Positive Predictive Value: 82% vs. 86%; Negative Predictive Value: 69% vs. 83%, CT vs. RF respectively. The authors concluded that noninvasive nonionizing RF determined lung fluid provides a potential alternative to other measures for diagnosing and monitoring pulmonary fluid overload. The RF technology described in the current study cannot be used to determine total body water overload or purely right sided heart failure peripheral edema as the device only looks measures at the lung fields. Furthermore, it is unclear if RF can detect intravascular congestion. The findings of this study need to be validated by well-designed studies. Further investigation is needed before clinical usefulness of this service is proven.

An ECRI Clinical Evidence Assessment (2020) Product Brief for ReDS Wearable Systems (Sensible Medical Innovations Ltd.) for Noninvasive Monitoring of Lung Fluid was published following review and evaluation of 1 non-randomized before-and-after study, and 3 diagnostic cohort studies from January 1, 2013, through February 14, 2020 (244 individuals). Evidence from 1 before-and-after study suggests that adding ReDS to standard, at-home practices for monitoring lung fluid in patients with HF may reduce hospitalization rates, but the study is at too high a risk of bias to be conclusive. 3 diagnostic cohort studies are too small and of too poor quality to determine ReDS's accuracy for monitoring lung fluid. Findings require validation in larger (n > 100) prospective cohort studies. Studies are also needed to assess inpatient monitoring with ReDS and to compare ReDS with chest impedance cardiography and manometry. Evidence is inconclusive because of too few data.

## Reference(s)


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| Code | Description |
|---|---|
| 0615T | Eye-movement analysis without spatial calibration, with interpretation and report |

**Eye-movement analysis without spatial calibration, is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.**

## Clinical Evidence

There is insufficient quality evidence to conclude that eye-movement analysis without spatial calibration is effective. Additional research involving larger, well-designed studies is needed to establish its safety, efficacy, and clinical utility as compared to conventional clinical assessment.

The EyeBOX was granted de novo approval as the first non-invasive, baseline-free tool directed at diagnosing concussions from the U.S. Food and Drug Administration (FDA) in 2018 (product code QEA). According to FDA documentation:

- The EyeBOX is intended to measure and analyze eye movements as an aid in the diagnosis of concussion within one week of head injury in patients 5 through 67 years of age in conjunction with a standard neurological assessment of concussion.

A negative EyeBOX classification may correspond to eye movement that is consistent with a lack of concussion.

A positive EyeBOX classification corresponds to eye movement that may be present in both patients with or without concussion. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm. (Accessed June 7, 2023)

Jain et al. (2022) conducted an observational study to determine if there were differences in objective eye tracking metrics that characterize eye position, saccadic movement, and pupillary dynamics between uninjured adolescents, adolescents with acute concussion symptoms (≤ 28 days since injury), and adolescents with persistent concussion symptoms (> 28 days since injury). Uninjured adolescent athletes (n = 180) and concussed adolescent participants (n = 224), with acute or persistent symptoms, ages 13 to 17 years old were included in the study. Eye movements were recorded using EyeBOX. Two hundred fifty-six eye tracking metrics were compared. Two metrics of eye position were worse in those with concussion than uninjured adolescents, and only one metric was significantly different between acute cases and persistent cases. Concussed adolescents had larger left and right mean, median, minimum, and maximum pupil size than uninjured controls. Concussed adolescents had greater differences in mean, median, and variance of left and right pupil size. Twelve metrics distinguished female concussed participants from uninjured; only four were associated with concussion status in males. A logistic regression model including clinical and demographics data and transformed eye tracking metrics performed better in predicting concussion status than clinical and demographics data alone. The authors concluded that after concussion, objective eye tracking technology can identify vision and pupillary disturbances and could be used to augment existing clinical concussion assessments. The authors recommend future studies to investigate additional visual stimuli and paradigms to ascertain if other standard assessments of oculomotor function can be used to identify deficits in concussed children, and modifying and consolidating these metrics with existing clinical measures to monitor recovery in the adolescent concussion populations. Limitations include participant population of only adolescents and lack of assessment of the clinical utility above and beyond patient history and clinical findings, Furthermore, these findings need to be reproduced in an independent sample.

Samadani et al. (2022) conducted a study to validate the sensitivity and specificity of a baseline-free eye movement tracking algorithm as a classifier for identifying concussion. The study included both adult and pediatric subjects and were separated in to two groups, concussed (n = 46) and the non-concussed (n = 236). Eye tracking while watching a short film clip for 220 seconds, alteration of consciousness, and Sports Concussion Assessment Tool (SCAT3) subsets were collected then validated against a pre-specified algorithm with a cutoff for concussed vs. non-concussed. The sensitivity and specificity of eye tracking were calculated after plotting of the receiver operating characteristic curve and calculation of the AUC (area under curve). When concussion is defined by SCAT3 subsets, the sensitivity and specificity of an eye tracking algorithm was 80.4 and 66.1%, The area under the curve was 0.718. The misclassification rate (n = 282) was 31.6%. The authors concluded eye tracking has a sensitivity and specificity that is useful to aid in diagnosis of concussion. The authors recommend future, larger clinical trials to define how specific attributes or deficiency in eye-tracking ability are associated with symptoms, brain imaging, and outcomes. Limitations include small sample size, lack of assessment of the clinical utility above and beyond patient history and clinical findings, and the study was partially funded by the manufacturer.

Oldham et al. (2021) conducted a cross-sectional study to evaluate the relationship between eye tracking, self-reported symptoms, and gait performance in both concussed participants (n = 30) and healthy controls (n = 30). Symptoms were collected using the Post-Concussion Symptom Scale (PCSS) and triaxial inertial measurement units were used to measure gait speed. The study examined the relationship between PCSS and the BOX score (a metric of pupillary disconjugacy) and a two-way mixed effects analysis of variance to examine the effect of group on single- and dual-task gait speed. There was a significant association between total PCSS score and BOX score in the concussion group but not in the control group. There were no significant associations between PCSS symptom profiles and BOX scores in the concussion or control groups. There were also no significant differences in single-task or dual-task gait speed. The authors concluded that following concussion, there appeared to be an association between eye tracking and clinical symptoms. However, it did not appear that abnormal eye tracking was influenced by a single symptom domain. The authors also note the concussion group had worse overall total symptom severity and higher scores on each of the five symptom profiles than those in the control group. The authors state that following concussion, eye tracking could be a clinically useful tool for identifying ocular and motor deficits and further research was recommended. Limitations include small sample size, predominantly female participants, and lack of blinding.

ECRI (2020) published a Clinical Evidence Assessment for EyeBOX (Oculogica, Inc.) intended for use as a neurologic assessment to identify a concussion diagnosis when used within one week of head injury. ECRI found the evidence for EyeBOX, which consisted of two cohort studies, to be inconclusive and provided insufficient evidence to determine clinical validity and clinical utility for managing patients with concussion signs. The assessment states future randomized clinical trials (RCTs) and larger diagnostic cohort studies are needed to determine whether EyeBOX improves patient management and outcomes.

Samadani et al. (2015) prospectively tracked 75 trauma patients with either a positive head computed tomography (CT) scan (n = 13), negative head CT (n = 39), or nonhead injury (n = 23) and compared them to a normal, healthy control group (n = 64) to explore whether eye tracking would reveal the disconjugate gaze associated with both structural brain injury and concussion. Participants eye movements were tracked while they watched music videos on a viewing monitor of a binocular tracking device. Eye movements were recorded with an Eyelink 1000 eye tracker at a fixed distance of 55 cm from a computer monitor over a time period of 220 sec. Five out of five measures of horizontal disconjugacy were increased in positive and negative head CT patients relative to noninjured control subjects. Only one of five vertical disconjugacy measures was significantly increased in brain-injured patients relative to controls. Linear regression analysis of all 75 trauma patients demonstrated that three metrics for horizontal disconjugacy negatively correlated with SCAT3 symptom severity score and positively correlated with total Standardized Assessment of Concussion score. Abnormal eye-tracking metrics improved over time toward baseline in brain-injured subjects observed in follow-up. The authors concluded eye tracking may help quantify the severity of ocular motility disruption related to concussion and structural brain injury. Limitations include small sample size, and conflicts of interest which may limit the study's conclusions.

Two clinical trials were found for EyeBOX. One trial is active, not recruiting (NCT05047003), and one is not yet recruiting (NCT05527041). For further details refer to the following:

- https://www.clinicaltrials.gov/ct2/show/NCT05047003?term=eyebox&recrs=abdf&cond=concussion&draw=2&rank=1
- https://www.clinicaltrials.gov/ct2/show/NCT05527041?term=eyebox&recrs=abdf&cond=concussion&draw=2&rank=2

(Accessed June 7, 2023)

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Samadani U, Spinner RJ, Dynkowski G et al. Eye tracking for classification of concussion in adults and pediatrics. Front Neurol. 2022 Dec 1;13:1039955.


| Code | Description |
|---|---|
| 0616T | Insertion of iris prosthesis, including suture fixation and repair or removal of iris, when performed, without removal of crystalline lens or intraocular lens, without insertion of intraocular lens |
| 0617T | Insertion of iris prosthesis, including suture fixation and repair or removal of iris, when performed; with removal of crystalline lens and insertion of intraocular lens |
| 0618T | Insertion of iris prosthesis, including suture fixation and repair or removal of iris, when performed; with secondary intraocular lens placement or intraocular lens exchange |
| C1839 | Iris prosthesis |

**Insertion of iris prosthesis is unproven and considered not medically necessary due to insufficient evidence of safety and/or efficacy.**

## Clinical Evidence

Through a multicenter, prospective, unmasked, nonrandomized, interventional clinical trial, Ayres et al. (2022) reported on the results of the United States Food and Drug Administration Clinical Trial of the Custom Flex Artificial Iris to evaluate the safety and efficacy of the device, for treating congenital and acquired iris defects. The trial consisted of participants with photophobia, sensitivity secondary to partial or complete congenital or acquired iris defects, or both. The individuals were evaluated on day 1, week 1, and 1,3, 6, and 12 months after surgery. The outcomes measured were slit-lamp findings, intraocular pressure, implant position, subjective visual symptoms, and complications. At 3, 6, and 12 months, corrected distance visual acuity (CDVA) and endothelial cell density (ECD) were measured as added safety evaluations. The 25-item National Eye Institute Visual Function Questionnaire (NEIVFQ-25) was utilized to assess the health-related quality of life affected by vision. And to evaluate cosmetic results, the Global Aesthetic Improvement Scale was used. The results showed at 12 months postoperatively, a 59.7% reduction in marked to severe daytime light sensitivity ($p < 0.0001$), 41.5% reduced marked to extreme nighttime light sensitivity ($p < 0.0001$), 53.1% marked to severe daytime glare reduction ($p < 0.0001$), and 48.5% severe nighttime glare reduction ($p < 0.0001$) uncovered. The NEIVFQ-25 scores showed a 15.4-point improvement ($p < 0.0001$), with 98.3% of individuals showing an improvement in cosmesis, measured by the Global Aesthetic Improvement Scale at 12 months following the surgery. No loss of CDVA of > 2 lines related to the device was found, and a median ECD loss was 5.3% at six months post-operative and 7.2% at 12 months post-surgery. The authors concluded that the artificial iris (AI) surpassed all critical safety endpoints for an adverse device, IOL, or implant surgery-related adverse events. The AI also met all the essential efficacy endpoints, including decreased light and glare sensitivity, improved health-related quality of life, and satisfaction with cosmesis appearances created by congenital or acquired iris defects. The findings are limited by lack of comparison group.

Romano et al. (2022) conducted a systematic review to evaluate the literature on the use of AI implants in congenital aniridia, focusing on the different surgical implantation techniques, the clinical outcomes achieved, complications, and the risk of bias of the studies included. All the studies were retrospective, with a relatively small sample size, and without a control group. Even if the low incidence of aniridia makes clinical studies with adequate sample size complex, strong scientific evidence is needed, and thus conclusions drawn from the literature may be considered less dependable. The major drawback of small studies is that they are vulnerable to overestimating the size of an association, which is a limitation of this review. All reviewed papers were single-surgeon studies, and due to the rarity of individuals with aniridia, there were no strict inclusion criteria, resulting in selection bias (Figueiredo and Synder [2020], and Ayres et al. [2022] are included in this systematic review).

In a 2022 Hayes evolving evidence review, the CustomFlex Artificial iris (HumanOptics AG, Clinical Research Consultants Inc.) for aniridia, clinical evidence from poor or very poor-quality studies without control groups suggested that the implantation of an AI is technically possible. The AI was associated with improved glare, photosensitivity, aesthetics, and quality of life. Complications and adverse events were commonly reported and may be related to the additional ophthalmic comorbidities and the invasiveness and complexity of the procedures. Without control groups, it was unclear which complications can be attributed to AI implantation. A guideline against using AI insertion for congenital aniridia outside research settings was identified. No ongoing clinical studies were identified. A review of full-text clinical studies suggests minimal support for using CustomFlex Artificial Iris (HumanOptics AG) to treat aniridia. A review of full-text systematic reviews offers no/unclear support for using CustomFlex Artificial Iris (HumanOptics AG) for treating aniridia, as no relevant systematic reviews were identified. Based on a review of full-text clinical practice guidelines and position statements, the guidance confers strong support against using CustomFlex Artificial Iris (HumanOptics AG) to treat aniridia (Figueiredo and Synder [2020], Rickman et al. [2016], and Spitzer et al. [2016] were included in this evolving evidence review).

In a 2021 ECRI Clinical Evidence Assessment on CustomFlex Artificial Iris Prosthesis (HumanOptics AG) for Repairing Iris Defects, the evidence found was inconclusive and exceptionally low quality. CustomFlex improves light and glare sensitivity and eye aesthetics for individuals with aniridia based on very low-quality evidence from one large and four small case series. However, available studies are at too high a risk of bias to permit conclusions. CustomFlex's safety still needs to be clarified because some of the small case series report frequent adverse events (AEs). Large, prospective, multicenter studies are required in order to confirm findings and validate CustomFlex for individuals with congenital and acquired aniridia, but none are ongoing (Figueiredo and Snyder [2020] is included in this clinical evidence assessment).

Figueiredo and Snyder (2020) evaluated the effectiveness and safety of the CustomFlex device when used to treat photic symptoms in individuals with congenital aniridia. The retrospective single-surgeon case series involving 50 individuals and 96 eyes included those with more than six months follow-up (mean follow-up 44 months, 36 ±36 months). Pre- and post-operative data were collected regarding CDVA, subjective photophobia and glare, keratopathy, glaucoma, intraocular pressure (IOP), glaucoma drops, and other comorbid pathologies. Additional post-operative data were collected regarding post-operative

complications, prosthesis decentration, and further surgeries. In all cases, additional procedures were performed during implantation, including phacoemulsification, intraocular lens (IOL) implantation repositioning or replacement, limbal relaxing incision, keratectomy (superficial and lamellar), or vitrectomy. Intraoperative complications were reported in 14 eyes (14.6%). Regarding photophobia, 95.7% (89/93) reported a reduction in symptoms, 3.2% (3/93) reported no change in symptoms, and 1.1% (1/93) reported a worsening of symptoms. The results were similar for the subjective reporting of glare; 95.2% (79/83) reported a reduction in symptoms, 3.6% (3/83) reported no change in symptoms, and 1.2% (1/83) reported a worsening of symptoms. When preoperative visual acuity (VA) was compared to the last measured post-operative VA, 58.3% (56) of the eyes improved two or more lines, 32.3% (31) of the eyes stayed within two lines of preoperative measurements, and 9.4% (9) of the eyes dropped two or more lines. Compared to the best-measured post-operative VA, there were declines during the post-operative follow-up period. These declines were attributed to underlying comorbidities, including worsening of the ocular surface, aniridia fibrosis syndrome (AFS), retinal detachment, and posterior capsule opacification. Aniridic keratopathy, which was present in 84.4% (81) of the eyes preoperatively, was present in 85.4% (82) at the last visit. A total of 28.4% (23) of the eyes with preoperative keratopathy had progression of the disease. At the earlier visit, aniridic glaucoma was present in 33.3% (32) of the eyes preoperatively and in 51.0% (49). A total of 53.1% (17) of the eyes with preoperative glaucoma had progression of the disease. Added complications included AFS (3.1%; 95% confidence interval (CI): 0.6 to 8.9%), prosthesis decentration (9.4%), choroidal folds/effusion secondary to ocular hypotony (2.1%), retinal detachment (1.0%), cystoid macular edema (1.0%) and vitreous hemorrhage (1.0%). During the follow-up period, 33.3% (32) of eyes required added surgical intervention, with a mean of 2.97 ±1.87 surgeries performed/eye. While the study was limited to individuals with congenital aniridia, the group had significant heterogeneity related to aniridic pathology. The findings are further limited by lack of contemporary comparison group.

In 2020a, interventional procedures guidance produced by NICE on AI insertion for congenital aniridia states:

- Evidence on the safety and efficacy of AI implant insertion for congenital aniridia needs to be improved in quantity and quality. Therefore, this procedure should only be used in the context of research.
- Research could include the use of observational data from cohort studies or high-quality case series. Studies should report details of patient selection and the type of implant used. Outcomes should include quality of life and other patient-reported results.

The 2020b interventional procedures guidance produced by NICE on AI insertion for acquired aniridia states:

- Evidence on the safety and efficacy of AI implant insertion for acquired aniridia is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.
- Research could include using observational data from cohort studies or high-quality case series. Studies should report details of patient selection and the type of implant used. Outcomes should consist of quality of life and other patient-reported results.

In 2019, Mayer and colleagues, through an interventional case series in a single center study, described previously unrecognized late complications associated with AI implantation by evaluating the effect of an AI implant on the remnant iris. Individuals with remnant iris tissue who underwent AI implantation between June 2011 and December 2016 (n = 42) were evaluated to decide the influence of the prosthesis on the residual iris. A retraction of the residual iris was detected in 7 individuals. In all cases, the syndrome was seen via photographic comparisons rather than by the treating ophthalmologists or the treated individual. A total of 4 of the 7 affected individuals showed severe complications, including highly raised IOP, pigment dispersion associated with glaucoma, and recurrent bleeding into the anterior chamber. Several individuals needed additional invasive procedures, including glaucoma shunt surgery and an implant explanation. This study underscores the need for long-term data to predict better risks associated with specific techniques or comorbidities and to monitor for unanticipated complications.

The U.S. Food and Drug Administration on May 30, 2018, approved the first stand-alone prosthetic iris in the United States, a surgically implanted device to treat adults and children whose iris (the colored part of the eye around the pupil) is completely missing or damaged due to a congenital condition called aniridia or other damage to the eye. Additional information is available: https://www.fda.gov/news-events/press-announcements/fda-approves-first-artificial-iris. (Accessed May 23, 2023)

Spitzer et al. (2016) retrospectively evaluated the functional, cosmetic, and complication outcomes in 34 individuals who received the AI implant. Individuals with a history of a severe globe injury with total or subtotal iris loss in one eye who received an AI were included. Distance visual acuity, IOP, and the rate of complications (long-term inflammation and corneal decompensation leading to corneal transplantation) were evaluated. The median follow-up period was 24 months.

Postoperatively, 14 individuals had a VA improvement between 0.2 and 2.1 logMAR units, 11 had a VA change of less than 0.2 logMAR units, and nine individuals (26%) reduced VA (between 0.2 and 1.4 logMAR units). The median group VA was unchanged following AI implantation. Complications were noted. Post-operative hypotony was reported in ten individuals, 7 of whom had low pressure before AI implantation. In 2 of these individuals, the low IOP led to phthisis and blindness, and, ultimately, enucleation. Hypertony was seen in 6 individuals, 3 of whom had pre-existing glaucoma. Other complications, including persistent intraocular inflammation (9%) and macular edema (12%), were noted. A total of 12 individuals required corneal transplantation following AI implantation, with 6 of these cases showing endothelial decompensation post-AI implantation. Suspected post-operative endophthalmitis was recorded in one case. In many instances, other procedures, such as keratoplasty, repositioning of the AI, or strabismus surgery, were required. The authors noted that several factors could have contributed to the variability in responses to the AI, including pathophysiology related to the original trauma, complications or surgeries post-AI implantation, which were independent of the AI, and complications resulting from the AI implantation itself. While 34 individuals were included in the case series, only 20 of these participants were available to report subjective symptoms such as discomfort and glare. The findings are further limited by lack of contemporary comparison group undergoing a different treatment approach.

In a retrospective interventional case series, Rickmann et al. (2016) evaluated the long-term clinical outcome (2 years or greater) and complication spectrum after AI implantation in 34 individuals with congenital, traumatic, or iatrogenic aniridia. Cases included individuals with complete and partial aniridia. Before implantation, five eyes were hypotonic, ten eyes had glaucoma, six had pre-existing keratopathy, and in 4 eyes, there was silicone oil in the anterior chamber. Complications included glaucoma (3), keratopathy (2), silicone oil in the anterior chamber (3), hemorrhage of the remnant iris (1), and retinal detachment (2). Consecutive surgery was needed in 5 eyes. When the VA at baseline was compared to the final examination, 16 eyes gained two or more VA lines, 15 remained stable, and three lost two or more VA lines. There was no significant difference in the mean IOP when the baseline was compared to the final examination. With the study being single-center and single-surgeon, additional studies are needed to improve the generalizability of the results. Furthermore, no comparison group was present and selection of only participants with two-year follow-up could have introduced biases in the findings.

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Spitzer MS, Nessmann A, Wagner J, et al. Customized humanoptics silicone iris prosthesis in eyes with posttraumatic iris loss: outcomes and complications. Acta Ophthalmol. 2016; 94(3):301-306.


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

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

## Clinical Evidence

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

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

Katzenschlager et al. (2022) conducted a randomized controlled trial (RCT) to assess microcirculatory alterations during trauma resuscitation care using HSI in a dedicated trauma resuscitation room of a level one trauma center. The study included 51 adult patients who were admitted to the trauma resuscitation room. Patients were allocated in a 1:1 ratio to the HSI group (intervention) (n = 25) and control group (n = 26). In addition to the standard of care, patients in the intervention group had two hyperspectral recordings (HSR) of their hand palm taken using the Tivita® Tissue System (Diaspective Vision GmbH, Am Salzhaff, Germany. Primary outcomes were the treatment duration of the primary survey (until end of ABCDE-evaluation, ultrasound and evaluation by the trauma team) and the total resuscitation room care (until transport to definitive care) as well as the ability to perform measurements from all HSR. Secondary outcomes were analyses from the intervention group compared to HSI measurements of 26 healthy volunteers including an analysis based on the ISS (Injury severity score) (< 16 vs. ≥ 16). Caregivers, and those assessing the outcomes were blinded to group assignment. Statistically, there was shorter median duration of the primary survey in the control group (03:22 min [Q1–Q3 03:00–03:51]) compared to the intervention group (03:59 min [Q1–Q3 03:29–04:35]) with a difference of −37 s (95% CI −66 to −12). Total resuscitation room care was longer in the control group, but without significance: 60 s (95% CI −60 to 180). From 52 HSI, the authors were able to perform hyperspectral measurements on all images, with differences noted between injured patients and healthy volunteers. 30 days follow-up was conducted either by e-mail or a phone call. One patient was lost in the control group to 30 days follow-up. In the control group, 5 (21.5%) patients had to be admitted to the ICU and 3 (12.5%) patients underwent surgery immediately. Another 3 (12.5%) patients were discharged on the same day. In the intervention group, 8 (30.8%) patients were admitted to the ICU and 5 (19.2%) went to the OR. No patient was discharged on the same day. In both groups, all patients were alive throughout the 30 days follow up-period. The authors concluded that HSI proved to be feasible during resuscitation room care and can provide valuable information on the microcirculatory state. This RCT has several limitations that should be considered for the interpretation of the results. First, it was only conducted at a single trauma center, limiting its external validity. Secondly, the study sample size was too small to analyze subgroups with severe trauma or shock. This is reflected in the non-significance when assessing HSI measurements in patients with an ISS < 16 and ≥ 16. Further investigation including impact on patients' outcomes is needed before clinical usefulness of this procedure is proven.

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

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

Kohler et al. (2021) performed a prospective observational study including 22 patients with soft tissue reconstruction to explore HSI as a new tool in flap monitoring to improve sensitivity compared to established monitoring tools. Flap perfusion was assessed by standard clinical parameters, Doppler ultrasound, and HSI on t0 (0 h), t1 (16–28 h postoperatively), and t2 (39–77 h postoperatively). HSI records light spectra from 500 to 1000 nm and provides information on tissue morphology, composition, and physiology. These parameters contain tissue oxygenation (StO2), near-infrared perfusion- (NIR PI), tissue hemoglobin- (THI), and tissue water index (TWI). Total flap loss was seen in n = 4 and partial loss in n = 2 cases. Every patient with StO2 or NIR PI below 40 at t1 had to be revised. No single patient with StO2 or NIR PI above 40 at t1 had to be revised. Significant differences between feasible (StO2 = 49; NIR PI = 45; THI = 16; TWI = 56) and flaps with revision surgery [StO2 = 28 ($p < 0.0001$). The authors concluded HSI provides valuable data in free fap monitoring. The technique seems to be superior to the gold standard of flap monitoring. StO2 and NIR PI deliver the most valuable data and 40 could be used as a future threshold in surgical decision making. The limitations of this study include its small sample size and the heterogeneity of the study's endpoint. Also, to improve selectivity in future studies with higher case numbers, the authors suggested that it may be of interest to split individual flap composition (fasciocutaneous, myocutaneous) and by the entity (e.g., ALT, latissimus dorsi, subscapular). Findings from this proof-of-concept study are however insufficient to demonstrate the validity and clinical utility of this technology.

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

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

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

Chin et al. (2011, included in Saiko 2020 and Ma 2019 systematic reviews above) conducted a diagnostic study on 126 patients to determine if HIS could accurately assess the presence or absence of PAD and accurately predict PAD severity. All patients underwent standard noninvasive lower extremity arterial flow studies, including measurement of the ankle-brachial index (ABI); segmental pressures for the upper thigh, lower thigh, calf, dorsalis pedis, posterior tibial, metatarsal, first digit areas, and second to fifth digits if first digit pressures were < 50 mm Hg and arterial Doppler waveforms of the dorsalis pedis and posterior tibial arteries. HSI data for participants was collected using the OxyVu system and the vascular technicians were blinded to the results. The primary comparative analysis showed no significant differences in hyperspectral oxyhemoglobin values for patients with versus without PAD. In contrast, the analysis of the deoxyhemoglobin values showed statistically significant differences for non-PAD vs PAD limbs. Data also suggested a significant correlation between deoxyhemoglobin values and ABI ($p = 0.001$).

The authors concluded that HSI presents an interesting new development for the diagnostic imaging and evaluation of PAD but does not provide a breakthrough to replace existing bedside technology. Future study and understanding of how this technology works may identify it as a valuable tool for the prediction of wound healing in severely ischemic patients. The findings of this study do not demonstrate the incremental clinical utility of this approach over other established non-invasive approaches, such as ABI.

The U.S. Food and Drug Administration (FDA) cleared the HyperView™ Hyperspectral Tissue Oxygenation Measurement system under its 510(k) premarket notification process as substantially equivalent to predicate devices. For additional information, refer to the following:

- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K161237
- https://www.accessdata.fda.gov/cdrh_docs/pdf16/K161237.pdf

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| Code | Description |
|---|---|
| 0640T | Noncontact near-infrared spectroscopy (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation), other than for screening for peripheral arterial disease, image acquisition, interpretation, and report; first anatomic site |
| 0859T | Noncontact near-infrared spectroscopy (e.g., for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation), other than for screening for peripheral arterial disease, image acquisition, interpretation, and report; each additional anatomic site (List separately in addition to code for primary procedure) |

**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 an indication of wound healing.

Lindelauf et al. (2022) conducted a systematic review evaluating the use of near infrared spectroscopy (NIRS) versus hyperspectral Imaging (HSI) to detect flap failure in reconstructive surgery compared to standard monitoring such as clinical assessment and a handheld doppler. PubMed and Embase were searched in August 2021 with studies selected by two independent reviewers. Five HSI and sixteen NIRS studies totaling 3,662 flap procedures carried out in 1,970 patients using NIRS and 90 patients using HSI were included. The flap survival of HSI was 92.5% and NIRS 99.2% with statistically significant

differences observed in flap survival, flaps returned to OR, and partial flap loss rate. The literature concludes NIRS and HSI are reliable, accurate and user-friendly, however according to recent available literature, no concrete conclusions can be made regarding non-invasive monitoring techniques superiority.

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

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

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

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

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

## Reference(s)


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

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

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| Code | Description |
|---|---|
| 0647T | Insertion of gastrostomy tube, percutaneous, with magnetic gastropexy, under ultrasound guidance, image documentation and report |

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

## Clinical Evidence

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

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

In a prospective, single-arm clinical trial with historical matched controls, Accorsi et al. (2021) conducted a study of PUG insertion in 25 adult patients and compared its safety and efficacy to 25 patients who received PRG. Out of 150 adult patients referred to have PUG insertion, 25 adult patients were enrolled in this study. For comparison, a retrospective cohort of 25

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

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

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

The US Food and Drug Administration (FDA) approved the PUMA-G system for gastrostomy insertions under 510(k) (K183057) on April 10, 2019. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm. (Accessed March 16, 2023)

For information on current clinical trials studying percutaneous ultrasound gastrostomy techniques, refer to the following website: www.clinicaltrials.gov. (Accessed March 16, 2023)

## Reference(s)


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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

On May 22, 2023, the FDA granted De Novo Clearance for the Navicam®, MCE (AnX Robotica, Inc. Dover, DE). The Navicam consists of a WCE, a magnetic-guidance robot, a data recorder and a computer workstation for real-time observation and capsule navigation control. According to the FDA approval letter, the Navicam magnetically controlled capsule endoscope is intended for visualization of the stomach of adults (≥ 22 years old) with a BMI less than 38. The system can be used in clinics and hospitals, including ER settings.

Xi et al. (2022) in a prospective study attempted to validate whether the Kyoto classification of gastritis could be applied to magnetically controlled capsule endoscopy (MCCE) and if *H. pylori* infection status could be accurately assessed on MCCE. 227 participants who underwent both MCCE and urea breath tests (UBT) were recruited. Two physicians who were blinded to the UBT results independently made the diagnosis of H. pylori infection status according to 10 findings listed in the Kyoto classification of gastritis after reviewing MCCE images. The author's developed 2 predictive models to assess *H. pylori* infection status by combining these 10 findings. The MCCE overall diagnostic accuracy for *H. pylori* infection status was 80.2%. The sensitivity, specificity, and diagnostic odds ratio (DOR) for current infection were 89.4%, 90.1% and 77.1, respectively. In the two prediction models, the area under the curve (AUC) values for predicting noninfection and current infection were 84.7 and 84.9, respectively. Study limitations included a design in which approximately half of the included participants were not infected with *H. pylori* (44.5%), while the amount of past-infection participants was particularly low (15.9%); therefore, selective bias could not be avoided; the Kyoto classification system was modified because the degrees of atrophy and intestinal metaplasia on MCCE could not be rated; and lastly, the participants might have had natural eradication of *H. pylori* which would have resulted in an underestimation in diagnostic accuracy. The author's concluded that *H. pylori* infection status could be accurately assessed on MCCE according to the Kyoto classification of gastritis. Additional studies are needed to confirm these results and the clinical utility of the technology compared to usual care.

Geropoulos et al. (2021) performed a systematic review and meta-analysis assessing MCCE versus conventional gastroscopy. 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%. MCCE had minimal adverse events and was tolerated by most. The time of MCCE is also much longer than conventional gastroscopy. Authors note that the MCCE demonstrated an acceptable sensitivity of identifying gastric lesions. But well-designed randomized studies are needed to identify the risks and benefits of this new technique, as well as to determine its role as a replacement for conventional gastroscopy. The study by Liao et al (2016) described below is included in this systematic review.

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

In a comparative study, Liao et al. (2016) compared the performance of MCCE with conventional gastroscopy in detecting gastric lesions. A MCCE system was designed to explore the stomach. A multicenter blinded study comparing MCCE 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 MCCE, followed by conventional gastroscopy 2 hours later, without sedation by an interventionist blinded to the findings of the MCCE. The sensitivity, specificity, positive predictive value, and negative predictive value of detection of gastric focal lesions by MCCE was calculated, using gastroscopy as the standard. MCCE 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%). MCCE 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%). MCCE 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%). MCCE detected 1 advanced gastric carcinoma, 2 malignant lymphomas, and 1 early-stage gastric tumor. MCCE 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 MCCE over gastroscopy (95.7%). There are study limitations including, the MCCE preparation is slightly longer than conventional gastroscopy and it takes longer to perform an MCCE (approx. 30 minutes). Lastly, the preference of MCCE over gastroscopy observed in this study might be biased because the gastroscopy was performed without sedation. The author notes that this novel MCCE 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.

## Reference(s)


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

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

## Clinical Evidence

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

In the updated 2023 practice guideline for cutaneous melanoma, the National Comprehensive Cancer Network (NCCN) states that patients presenting with a suspicious pigmented lesion should undergo an excisional biopsy (elliptical, punch or saucerization). If excisional biopsy is inappropriate due to the location or the lesion is very large, a full thickness incisional or punch biopsy of the thickest portion is an acceptable option. In the common follow up recommendations for all patients, this guideline states that pre-diagnostic clinical modalities and other imaging technologies (et, reflectance confocal microscopy, electrical impedance spectroscopy) may aid in surveillance for new primary melanoma in patients with a high mole count and/or the presence of clinically atypical nevi.

A 2023 Hayes health technology assessment evaluated the use of electrical impedance spectroscopy (EIS) with nevisense for diagnosis of cutaneous melanoma. Based on the assessment evaluating the clinical validity EIS is reasonably safe and has some capacity to diagnose cutaneous melanoma; however, there is not sufficient evidence to determine whether EIS improves

melanoma diagnosis. A small body of very low-quality evidence is not sufficient to conclude that EIS as an adjunct to standard tests (clinical examination and dermoscopy) improves diagnosis or health outcomes compared with standard tests without use of EIS. No studies were identified that provided statistical analysis of the accuracy of EIS versus conventional techniques. Additional larger long-term studies are needed to evaluate the optimal clinical role of EIS in melanoma diagnosis and management, including its effects on treatment decision-making and health outcomes in patients with melanoma.

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

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

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

In a 2019 clinical practice guideline of care for the management of primary cutaneous melanoma (CM), the American Academy of Dermatology acknowledged emerging diagnostic technologies, and stated that bedside diagnosis will continue to improve with further Investigation of existing, noninvasive imaging/electrical data acquisition and evaluation tools including electrical

impedance spectroscopy combined with digital dermoscopy. Despite these emerging technologies, biopsy with histopathological examination remains the first step in establishing a definitive diagnosis of CM. (Swetter et al. 2019).

Svoboda et al. (2019) conducted a comparative study reviewing clinician accuracy for diagnosing melanoma on the basis of electrical impedance spectroscopy score plus morphology versus lesion morphology alone. In total, 164 dermatology trainees completed an online survey presenting clinical images of 45 pigmented lesions (28 benign, 17 melanoma). For each image, respondents were asked if they would recommend biopsy on the basis of morphologic assessment alone, and then asked again once presented with the corresponding EIS score (along with positive and negative predictive values4). The proportion of clinical decisions for which the addition of EIS score altered the decision to biopsy was calculated. In addition, the sensitivity, specificity, and proportion of missed melanomas and benign biopsies were determined for morphologic assessment alone and for morphologic assessment plus EIS score. Significance testing was performed using McNemar test for categorical variables and paired t tests for continuous variables. Overall, 7380 clinical decisions (164 respondents 3 45 lesions) were made on the basis of morphology alone and 7380 were made on the basis of morphology plus EIS score. The decision to biopsy was made in 4527 of 7380 cases on the basis of morphology alone and 4553 of 7380 cases on the basis of morphology plus EIS. The EIS results altered the individual biopsy decision in 24.3% of cases (Table I). The addition of the EIS score resulted in 402 fewer missed melanomas and a net decrease of 376 benign biopsies. When including the EIS score, the mean sensitivity of respondents for ruling out melanoma increased from 80.7% to 95.2% and mean specificity from 50.4% to 58.6%. A diagnostic device is only useful if it affects clinical management and improves accuracy. In this study, EIS score led to a change in the decision to biopsy in 25% of cases and improved diagnostic accuracy, resulting in fewer biopsies of benign lesions and more biopsies of melanomas, without significantly changing the total number of biopsies. A higher specificity was seen in this study compared with the EIS pivotal trial (58.6% vs 34.4%),4,5 which measured the specificity of the device alone. This suggests that respondents utilized the EIS information synergistically with the clinical image, rather than basing decisions solely on the EIS results. The authors concluded that EIS had a meaningful impact on the decision to biopsy pigmented lesions with atypical features. When combined with morphologic assessment, EIS score led to improved accuracy without significantly changing the overall biopsy rate. A limitation of this study was that additional clinical data, such as patient history, risk factors, and dermoscopic images, were not available to participants. In addition, as this study only included trainees, the results might not extrapolate to more experienced clinicians.

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

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

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| Code | Description |
|---|---|
| 0659T | Transcatheter intracoronary infusion of supersaturated oxygen in conjunction with percutaneous coronary revascularization during acute myocardial infarction, including catheter placement, imaging guidance (e.g., fluoroscopy), angiography, and radiologic supervision and interpretation |

**Transcatheter intracoronary infusion of supersaturated oxygen in conjunction with percutaneous coronary revascularization during acute myocardial infarction is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.**

The ZOLL Medical Corporation website states they have developed a proprietary medical technology called SuperSaturated Oxygen ($SSO_2$) Therapy (TherOx®). The system includes three device components: a console, cartridge, and $SSO_2$ catheter, which are intended to create and deliver SuperSaturated Oxygen (SSO2) Therapy to a patient following an acute heart attack. The premise is that "$SSO_2$ Therapy creates a highly oxygenated saline solution and combines it with the patient's arterial blood to provide focal hyperoxemic oxygen therapy to ischemic (oxygen-deprived) tissue".

## Clinical Evidence

In January 2023, Zoll Medical Corporation announced the start of the REAL $SSO_2$ post-market observational study, assessing the clinical utility and cost-effectiveness of the TherOx® system. They expect to enroll 750 individuals, consisting of $SSO_2$-treated and control subjects. As of May 2023, this trial was still recruiting subjects. ClinicalTrials.gov Identifier: NCT05156996.

In a clinical evidence assessment of TherOx DownStream SuperSaturated Oxygen Therapy System, ECRI (2021) looked at two multicenter randomized controlled trials (RCTs), and one prospective, nonrandomized comparison study of this system/procedure. Among the limitations of these RCTs were only short-term results, and too few patients. Additionally, it was felt that the comparison study was at high risk of bias because of the retrospective design and lack of randomization. ECRI concluded that there were too few data to come to a conclusion on this system and that the evidence is inconclusive.

In the IC-HOT study, David et al. (2019) (referenced in the ECRI report listed above), evaluated the safety of SSO2 used in acute anterior MI. SSO2 therapy was administered to 100 individuals with anterior ST-segment elevation myocardial infarction (STEM in a single-arm study design. SSO2 use was successful in 98% of patients. At 30 days, NACE occurred in 7.1% of patients, with no deaths, one stent thrombosis, and one case of severe heart failure. The authors concluded that SSO2 infusion following primary percutaneous coronary intervention in acute anterior STEMI showed a favorable early safety profile. The findings are limited by the single arm design. In the IC-HOT study follow-up report, Chen et al. (2021) report, (referenced in the ECRI report listed above), on 1 year clinical outcomes of supersaturated oxygen therapy ($SSO_2$) after successful percutaneous coronary intervention (pPCI) in patients with anterior STEMI. One hundred individuals were evaluated in this prospective open-label, single -arm study. These individuals were compared with a control group of similar patients enrolled in the INFUSE-AMI trial (which evaluated the effect of myocardial infarction on the heart tissue and function). The authors found that treatment with $SSO_2$ was associated with a lower 1-year rate of the composite endpoint of all-cause death or new-onset heart failure (HF) or hospitalization for HF (0.0% vs. 12.3%, p = .001). All-cause mortality, driven by cardiovascular mortality, and new-onset HF or HF hospitalization were each individually lower in $SSO_2$ -treated patients. There were no significant differences between groups in the 1-year rates of reinfarction or clinically driven target vessel revascularization. The authors concluded that $SSO_2$ Infusion following pPCI in patients with anterior STEMI was associated with improved 1-year clinical outcomes including lower rates of death and new-onset HF or HF hospitalizations and that study is required to examine the salutary benefits of SSO2 delivery following pPCI in patients with anterior STEMI. The findings are limited by lack of contemporary comparison group and lack of randomization.

In 2009, Stone et al. (referenced in the ECRI report listed above), conducted a prospective, multicenter trial to investigate SSO2's role in reducing infarct size in early use in individuals with large STEMIs undergoing PCI within 6 hours of symptom onset. Three hundred and one patients were randomized to SSO (2) infusion in the left anterior descending artery infarct territory (n = 222) or control (n = 79). Among 281 randomized patients with tc-99m-sestamibi single-photon emission computed tomography data in AMIHOT II, median (interquartile range) infarct size was 26.5% (8.5%, 44%) with control compared with 20% (6%, 37%) after SSO (2). The pooled adjusted infarct size was 25% (7%, 42%) with control compared with 18.5% (3.5%, 34.5%) after SSO (2) (P(Wilcoxon) = 0.02; Bayesian posterior probability of superiority, 96.9%). The Bayesian pooled 30-day mean (+/- SE) rates of major adverse cardiovascular events were 5.0 +/-1.4% for control and 5.9 +/-1.4% for SSO (2) by intention-to-treat, and 5.1 +/-1.5% for control and 4.7 +/-1.5% for SSO (2) by per-protocol analysis (posterior probability of noninferiority, 99.5% and 99.9%, respectively). The authors concluded that at 30 days, SSO2 infusion into the left anterior descending artery infarct territory resulted in a significant reduction in infarct size with noninferior rates of major adverse cardiovascular events. The findings are limited by lack of blinding or sham control and the clinical significance of the findings is unclear.

The TherOx DownStream System (Product Code MWG) received U.S. Food and Drug Administration (FDA) premarket approval on April 2, 2019 for the preparation and delivery of SuperSaturated Oxygen Therapy (SSO2 Therapy) to targeted ischemic regions perfused by the patient's left anterior descending coronary artery immediately following revascularization by means of percutaneous coronary intervention (PCI) with stenting that has been completed within 6 hours after the onset of anterior acute myocardial infarction (AMI) symptoms caused by a left anterior descending artery infarct lesion. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P170027. (Accessed June 20, 2023)

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Zoll Medical Corporation, Corporate Headquarters, 269 Mill Road, Chelmsford, MA 01824-4105.

| 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.**

## Clinical Evidence

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

A clinical evidence assessment from ECRI (2017, updated 2022) reveals the evidence for treating AUFI with UTx is inconclusive. Only one systematic review was found, and current available evidence lacked the volume of patients to conclusively characterized the risks and successes for the procedure. Additional robust studies are needed to further evaluate the safety and efficacy of this technology.

Johannesson et al. (2022) reviewed transplant and birth outcomes of uterus transplant recipients in the US since 2016. In this study, five years of transplant data was collected from 3 centers throughout the U.S. The authors reviewed the data for 33 uterine transplant recipients and found a one- year graft survival rate in 23 of 31 recipients. Eighty- three of these delivered a live born child. Overall, 19 of the 33 patients delivered 21 live-born children. The authors concluded that the uterus transplant

surgical therapy allows women with uterine-factor infertility to safely and successfully gestate and deliver children, and the data herein may be used to counsel women with uterine factor infertility on treatment options.

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

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

In a scientific paper from the Royal College of Obstetricians and Gynaecologists (Jones 2021), it suggests while UTx offers an alternative possibility for women with AUFI, it is still under investigation.

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

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

Clinical trials for uterus transplantation are currently ongoing. Refer to the following website for more information: https://clinicaltrials.gov/ct2/home. (Accessed March 22, 2023)

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

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

## Clinical Evidence

Transurethral and transvaginal RF therapy involves the use of non-ablative thermal levels of RF 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 System). 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.

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

Zhang et al. (2023) conducted a systematic review and meta-analysis of only randomized controlled trials (RCT) to evaluate the efficacy and safety of vaginal energy-based therapies, including CO2 laser, RF and Er: YAG laser, in comparison to placebo intervention in treating SUI. The primary outcome was International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) score, and the secondary outcomes included the 1-hour pad test and cure rate. A total of 577 patients from 6 studies (including two studies comparing RF to sham described below) were included in the meta-analyses. The results showed that energy-based therapies did not significantly improve the ICIQ-SF score at all visits (1,3 and 6 months). The subgroup analysis showed that there was no significant improvement in ICIQ-SF score in the CO2 laser group compared to the placebo group at all visits (1, 3 and 6 months) Meta-analysis was not performed in Er: YAG laser and RF therapy due to insufficient trials, but the report of the two RF RCTs provided mixed findings with favorable findings on the ICIQ-SF score, but unfavorable or inclusive findings on pad weight. The authors concluded that based on limited clinical evidence, and heterogeneity among the included studies, there is no efficacy of energy-based therapy over placebo interventions. Furthermore, risks of complications of these interventions are acknowledged by the authors. Further research is needed and should address safety, clarification and consistency in terms of intervention sessions, intervals, and parameters of device use, as well as the impact of population characteristics such as age, body mass index (BMI) and severity of SUI.

In a 2022 prospective double blind randomized controlled trial, Seki et al. (included in the Zhang systematic review above) compared the efficacy of CO2 laser and radiofrequency (RF) compared to sham control (SCT) for the treatment of SUI. One hundred and thirty -nine women were randomized to have CO2 laser (42), RF (47) or to SCT (50). A total of 114 women, 38 in each group, reached the 12-month follow-up. Treatment consisted of three consecutive monthly sessions of 15 minutes and follow up occurred at 1,6 and 12 months. The primary outcomes were the participants subjective observation of improved SUI on the Linkert Scale, and an objective cure which was evaluated by three negative tests for the following: stress test (tested with comfortably full bladder in a gynecological and standing position), pad test and an absence of any urinary leakage in the 7-day voiding diary. Secondary outcomes assessed included the impact on quality of life, sexual function, urinary loss during intercourse and associated symptoms such as urgency and nocturia. Subjective improvement and objective cure results were reported by intention-to-treat (ITT) and per protocol (PP) analysis, with significant improvements seen in QOL scores, and no

significant difference in sexual function among any groups before or after treatment. The results showed at 12 month follow up, the subjective outcomes showed significant improved in the laser and RF treatment groups compared to the SCT. Objective incontinence measurements also showed better results in the groups that received energy -based therapies, and results were significantly better in mild cases of SUI in premenopausal women with pure SUI. No major complications were identified. The authors concluded that CO2 laser and RF are effective outpatient treatment options compared to sham treatment, especially in premenopausal women with pure SUI. This study is limited by a lack of comparison to established treatments for SUI; further research is needed.

In a 2022 evidence based clinical consensus statement on vaginal energy -based devices (EBD), the American Urogynecologic Society (AUS) was unable to reach consensus due to a lack of evidence, and it is unknown if EBD therapy offers better success rates than pelvic floor exercise or midurethral slings for treatment of stress urinary incontinence.

The American College of Obstetricians and Gynecologists (ACOG) Committee Opinion (2020) states that the FDA's 2018 Safety Communication warns against the use of energy-based devices (commonly radiofrequency or laser) to perform vaginal “rejuvenation,” cosmetic vaginal procedures, or nonsurgical vaginal procedures to treat symptoms related to menopause, urinary incontinence, or sexual function and prospective studies that use validated measures of quality of life, body image, and sexual function are needed to understand the true benefits and harms of these procedures, noting that the FDA has not cleared or approved any energy-based medical device for the treatment of vaginal symptoms related to menopause, urinary incontinence or sexual function. They recommend prospective studies that use validated measures of quality of life, body image and sexual function to understand the true benefits and harms of these procedures be done by those without a financial interest in the outcomes.

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

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

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

Leibaschoff et al. (2016, included in the Zhang systematic review above) conducted a prospective, descriptive double blind single site RCT on the effects of non-ablative, monopolar transcutaneous temperature -controlled radiofrequency (TTCRF) technology versus sham on the vaginal walls in 20 postmenopausal women with symptoms of SUI and vaginal relaxation

syndrome. Baseline QOL scores as well as VHI and VAS were statistically not different between the two groups. Treatment protocol was three treatments, 4 weeks apart using the ThermiVa device for 3-5 minutes in the labia majora and minora and vaginal canal. Participants were randomized equally and were followed for three months. The primary outcomes assessed were subjective QOL improvements assessed by the International Consultation On Incontinence Short Form (ICQ-SF) and the Urogenital Distress Inventory (UDI-6), and VAS at baseline and at least three months after treatment. Objective outcomes were assessed by histological changes at the urethravesical junction. The results showed statistically significant improvements in urinary leakage, and the measurement tools used all showed statistical improvement from baseline to the end of treatment. Seven out of ten patients treated had a negative stress test. The authors concluded that TTCRF is an effective treatment for SIU. This trial is limited by a small number of participants and a lack of long term follow up, and further research with larger populations and longer follow up is needed to validate these findings.

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

To assess treatment efficacy and quality of life in women with stress urinary incontinence 3 years after treatment with nonsurgical transurethral radiofrequency collagen denaturation (Renessa), Elser et al. performed a prospective study including 139 women with stress urinary incontinence due to bladder outlet hypermobility. Radiofrequency collagen denaturation was performed using local anesthesia in an office setting. Assessments included incontinence quality of life (I-QOL) and urogenital distress inventory (UDI6) instruments. In total, 139 women were enrolled and 136 women were treated (mean age 47 years). At 12 months, significant reductions existed from baseline in the median number of daily (-0.61) and weekly (-4.0) leaks caused by activity, and 50% of the subjects experienced at least 50% fewer leaks compared with baseline (52% of evaluable participants). (Elser 2009) At the 18-month follow-up, data were available on 60 women (44%). The study found incontinent episodes decreased whereas quality of life and participant satisfaction with the procedure increased (Elser 2010). At 36 months, 63 patients were lost to follow-up and 76 patients remained. With the intent-to-treat analysis (n = 139) revealed significant improvements in quality of life at 36 months. Mean I-QOL score improved 17 points from baseline (p = .0004), while mean UDI-6 score improved (decreased) 19 points (p = .0005). The authors concluded that transurethral collagen denaturation is a low-risk, office-based procedure that results in durable quality-of-life improvements in a significant proportion of women for as long as 3 years. The long-term durability of this minimally invasive procedure in women with SUI may be a beneficial intervention for women with this condition who wish to avoid or postpone surgery. The results also confirm that the treatment has a good safety

profile, with no serious adverse events reported at any time during this or previous trials. Limitations of this study include the dropout rate with regard to patients completing all of the in-office assessments and a lack of a control group. (Elser 2011).

On January 17, 2017, the Thermi Temperature Controlled Radiofrequency (RF) System (ThermiGen, L.L.C, Irving TX) received FDA clearance under the 510 (k) process. The device is approved for use in dermatological and general surgical procedures for electrocoagulation and hemostasis, and to create lesions in nervous tissue. Use for incontinence is considered off label use.

Refer to the following websites for additional information on this device and subsequent accessories:

- https://www.accessdata.fda.gov/cdrh_docs/pdf17/K173582.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf16/K161661.pdf
- https://www.accessdata.fda.gov/cdrh_docs/pdf17/K170116.pdf

(Accessed April 13, 2023)

In 2018, the FDA issued a warning regarding the use of laser and energy-based devices to treat gynecological conditions, including vaginal rejuvenation, symptoms related to menopause, urinary incontinence or sexual function, beyond those for which the devices have been approved or cleared. Refer to the following website for more information: Statement from FDA Commissioner Scott Gottlieb, M.D. on agency's efforts to advance development of gene therapies | FDA.
(Accessed April 13, 2023)

In 2006, the U.S. Food and Drug Administration (FDA) approved the Viveve® 2.0 System (Viveve Medical, Inc.) under its 510(k) premarket notification process as substantially equivalent to predicate devices for use in general surgical procedures for electrocoagulation and hemostasis. (501K 1254). Refer to the following website for more information: K193611.pdf (fda.gov).
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| Code | Description |
|---|---|
| 0692T | Therapeutic ultrafiltration |

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

## Clinical Evidence

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

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

In a 2022 Cochrane Database Systematic Review, Srivastava et al. assessed the efficacy of UF compared to diuretic treatment in clinical trials that compared clinical outcomes including mortality and rehospitalization rates, in patients with acute heart failure (AHF). This review included 14 randomized controlled trials (RCT) with 1190 participants with clinical signs of hypervolemia. Participants with ischemia or hemodynamic instability were excluded. Two trials used UF in conjunction with diuretics, and the remainder used UF alone. On all-cause mortality at 30 days or less [risk ratio (RR) 0.61, 95% confidence interval (CI) 0.13 to 2.85; 3 studies, 286 participants; very low-certainty evidence], and longest follow up (RR1.00, 95% CI 0.73 to1.36; 9 studies, 987 participants; low-certainty evidence), the results showed very low-certainty evidence of an effect. On all cause rehospitalization, the results showed low certainty evidence and moderate certainty evidence for an impact on heart failure related rehospitalization. The results showed UF may have little or no effect on serum creatinine change at 30 days since discharge may increase the risk of new initiation of renal replacement therapy at longest available follow-up. The authors concluded that there is insufficient evidence to determine the impact of UF on AHF. There was high risk of bias in some studies, particularly with deviations from the intended protocols from high cross-overs as well as missing outcome data for long-term follow-up. Future research should consider evaluating UF in conjunction with current therapies and focus on outcomes such as heart failure-related rehospitalization, cardiac mortality and renal outcomes at medium- to long-term follow-up. (Publications by Wobbe 2021, Costanzo 2016, Costanzo 2010, Bart 2012 which were previously cited in this policy, are included in this systematic review).

In a 2022 systematic review and meta-analysis, Ullah et al. reported on 10 clinical trial results comprised of 838 participants (413 received UF, 425 received diuretics) that compared UF and diuretics in patients with decompensated HR with reduced ejection fraction (HFrEF). The primary endpoint was major adverse cardiovascular event (MACE) which is a composite of all-cause mortality and all-cause re-hospitalizations. Secondary outcomes included components of MACE, need for HF-related re-hospitalization, change in the mean creatinine level, change in blood pressure, total fluid loss, mean change in weight, and mean change in sodium level. The results showed at a median follow-up of 90 days, there was no significant difference in the odds of MACE (odds ratio 0.71, 95% CI 0.47–1.07). The need for emergency department visits, all-cause admissions and heart failure-related re-hospitalization was also not statistically significantly different between the two groups. The in-hospital risk for hypotension and post-therapy creatinine rise > 0.3 mg/dL was also not significantly different between the UF and diuretics arms. The authors concluded that in patients with HFrEF, UF appears to be safe but might not provide significant benefits in terms of reducing the risk of mortality or readmission rates compared with those treated with diuretics. This analysis is limited by inclusion criteria not limited to RCT. (Publications by Wobbe 2021, Costanzo 2016, Bart 2012 which were previously cited in this policy, are included in this systematic review).

Wang et al. (2021) conducted a meta-analysis to assess the safety and efficacy of UF. A total of 12 studies were included with 1197 patients that were over the age of 18 and had a diagnosis of AHF; in each of the 12 studies there was an ultrafiltration

group of patients and a group on diuretics. Outcomes assessed were all-cause rehospitalizations, fluid and weight loss, adverse events and mortality. The authors found that UF was more effective at removing fluid than diuretics; this was contributed to the speed and duration of fluid and that it could be more easily controlled for specific patient conditions. In addition, the patients in the study had already been exposed to diuretics thus possibly decreasing their efficiency. There was inconsistent agreement about which group had more adverse effects, but the authors agreed rehospitalizations for patients with HF were less frequent for the UF group. The conclusion was UF appears to be suitable for certain kinds of patients but, future studies should identify what types of patients are best suited to receive UF and the safety and efficacy of its use. Limitations included a high heterogeneity about weight loss and lack of information to assess the bias of the RCT.

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

The 2014 National Institute of Health and Care Excellence (NICE) guideline, updated in 2021, on the diagnosis and management of acute heart failure states that ultrafiltration should not be used routinely for people with acute heart failure but can be considered for people with confirmed diuretic resistance (diuretic resistance is defined as dose escalation beyond a person's previously recognized dose ceiling or a dose approaching the maximum recommended daily dose without incremental improvement in diuresis).

Clinical trials of aquapheresis and ultrafiltration are currently ongoing. Refer to the following website for more information: https://clinicaltrials.gov/ct2/home. (Accessed April 12, 2023)

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

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

On February 24, 2020, the FDA granted premarket approval for the Aquadex FlexFlow® System (K192756) for continuous ultrafiltration therapy for temporary or extended use in adult and pediatric patients weighing 20 kilograms or more whose fluid overload is unresponsive to medical management, including diuretics. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192756.pdf. (Accessed April 12, 2023)

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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.**

## Clinical Evidence

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 |
|---|---|
| 0695T | Body surface-activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of implant or replacement |
| 0696T | Body surface-activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of follow-up interrogation or programming device evaluation |

**Electrocardiographic body surface mapping is unproven and not medically necessary for the evaluation or treatment of cardiac disorders.**

## Clinical Evidence

In a multi-center, prospective, randomized trial of patients with heart failure, Rickard et al. (2023) evaluated the efficacy of the ECG Belt System (EBS) in patients who were less likely to respond to cardiac resynchronization therapy (CRT) and whether EBS use in lead placement guidance and device programming was superior to standard CRT. The study included 408 participants (79.2% male and 65.9% had an American College of Cardiology/American Heart Association class II indication for CRT) from 43 centers in Europe and North America who were implanted with a CRT device and LV lead. Participants were randomized into either the ECG Belt arm (n = 200) or a control arm (n = 208). For patients in the ECG Belt arm, the EBS was applied to the patient's chest and back to be worn during the CRT implant procedure to guide left ventricular (LV) lead placement while patients in the control arm had their leads implanted per standard of care. The authors reported that both groups had an improvement in left ventricular end-systolic volume and that there was no significant statistical difference in relative change from baseline. The authors noted that patients with a higher baseline standard deviation of the activation times derived greater left ventricular reverse modeling but that improvement in electrical dyssynchrony did not correlate with the extent of reverse modeling. The authors concluded that their study did not support the use of EBS-guided therapy for CRT management of heart failure with reduced ejection fraction. Study limitations include some patient dropout, and the use of AdaptivCRT in 22% of the EBS arm but not in any of the control arm (as per protocol) and the open-label design, which could have introduced biases.

Bank et al (2018) used a body-surface activation mapping (BSAM) system in a study to quantify changes in electrical synchrony and the potential for optimization with CRT. The study included 94 patients with a history of heart failure with ejection fraction ≤ 40% (mean 25.7 ±7%) who were at least four months post-CRT and were clinically stable. The authors reported that CRT programmed clinically at baseline settings reduced electrical dyssynchrony by 20% and that this improvement was greater in left bundle branch block (LBBB) patients but similar in patients with and without QRS ≥ 150 milliseconds (ms). The authors also reported that, at individualized optimal device settings based on BSAM, there is a further 26% improvement in standard deviation of activation times (SDAT) as compared to current programming. Limitations of the study include the study design (single-center, retrospective, observational), and the lack of evaluating other atrio-ventricular, ventricular-ventricular delays, and/or pacing vectors or patient-centered outcomes. The authors concluded that BSAM can noninvasively quantify electrical dyssynchrony at multiple device settings and identify the setting in an individual patient that provides the lowest electrical dyssynchrony.

In a single-arm, single-center feasibility study to characterize changes in electrical heterogeneity during biventricular (BiV) pacing from different LV pacing sites during device implantation, Johnson et al (2017) computed two EH metrics-standard deviation of activation times and mean left thorax activation times from isochronal maps that were based on 53-electrode body surface mapping. The body surface mapping was done during baseline AAI pacing and biventricular (BiV) pacing from different pacing sites in coronary veins in 40 patients that cardiac resynchronization was indicated. The authors reported that the greatest combined reduction in standard deviation of activation times and left thorax activation times from baseline to BiV pacing was hemodynamically optimal in 35 of the 40 patients (88%) and that sites with the longest right ventricle-left ventricle (RV-LV) and narrowest paced QRS were hemodynamically optimal in 26 of the 40 patients (65%) and 28 of the 40 patients (70%) respectively. Limitations of the study include the study design (single center, single arm), lack of long-term follow-up, and the lack of clarity regarding the degree of acute hemodynamic improvements that correlates with the degree of chronic improvement in symptoms in patients using CRT. The authors concluded that changes in EH from baseline to BiV pacing more accurately identified hemodynamically optimal sites than RV-LV delays or paced QRS shortening and that optimization of LV lead location by minimizing EH during BiV pacing with the use of body surface mapping may improve cardiac resynchronization therapy response.

Revishvili et al. (2015) performed a single-arm, single-center study to validate the mapping accuracy of an epi- and endocardial electrophysiology system (NEEES). Their study included 29 patients (79% male, mean age 62 ±11 years) with previously implanted devices who were being seen for regular check-up at a pacemaker clinic. Study participants included 21 (72%) with a history of ischemic cardiomyopathy, 7 (24%) with a history of dilated cardiomyopathy and one (4%) with a history of restrictive cardiomyopathy. Each patient received pacing from a total of 76 pacing sites (21 in the right atrium, 29 in the right ventricle and 26 in the left ventricle). The authors reported that the mean distance from the non-invasively predicted pacing site to the anatomic reference site was 10.8 ±5.4 mm for the right atrium, 7.7 ±5.8 mm for the right ventricle, and 7.9 ±5.7 mm for the left ventricle activated via the coronary sinus lead and that there was no significant difference in accuracy for the left vs. right ventricular sites, while the difference in accuracy was significant when they compared the ventricular and atrial sites. The authors stated that the NEEES is capable of mapping both the endo- and epicardial surface when compared with other non-invasive mapping systems that rely on epicardial surface information. Limitations included the use of different systems with inherent differences in the geometries created, the small study size and the single-center study design. The authors concluded that the NEEES was able to correctly identify the site of pacing from various endo- and epicardial sites with high accuracy and they recommended future studies to assess the feasibility of the NEEES to correctly diagnose the origin of focal or re-entry arrhythmia within the human heart.

The U.S. Food and Drug Administration (FDA) has cleared several body surface mapping systems under its 510(k) premarket notification process as substantially equivalent to predicate devices. Refer to the following website for more information (use product code DQK): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed June 5, 2023)

## Reference(s)


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

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

## Clinical Evidence

Transcutaneous magnetic stimulation (tMS), also known **as p**eripheral magnetic stimulation (PMS), is a non-invasive method of delivering a rapidly pulsed, high-intensity magnetic field to the periphery other than the brain.

Park et al. (2023) evaluated the effect of peripheral magnetic stimulation (PMS) on acute and chronic postoperative pain. A search was conducted using MEDLINE, Cochrane CENTRAL, EMBASE, ProQuest International Dissertations, and ClinicalTrials.gov. A total of seventeen RCTs and one non-randomized clinical trial totaling 958 patients were included for review. PMS was described as pulsed electromagnetic field therapy in all studies and the length of PMS varied from the first 24 hours following surgery to 60 days. The frequency of pulses were identified as either 40 Hz, 75 Hz, or 27.12 MHz and the number of pulses varied amongst the studies. The primary outcome of this review was acute postoperative pain intensity within the first 7 days following the surgical procedure. Secondary outcomes included postop opioid consumption, acute pain

intensity 1-3 months following surgery, chronic pain scores greater than 3 months after surgery and any adverse events. For acute postoperative pain, the authors found seven of ten studies showed a benefit of PMS when compared to sham or no intervention; the other three studies did not provide a benefit of PMS over other interventions. For subacute postoperative pain, two of seven studies found a significant improvement in pain with PMS. For chronic post-surgical pain, the authors found only one study at three months that identified significantly lower pain scores when compared to the sham group. The remaining studies found continued pain or no significant difference between the control and sham groups. The authors concluded that PMS may be a potentially beneficial adjunct service for postoperative pain management, however results are limited by heterogeneity and generally low-quality trials, as well as low or very low quality of evidence according to the GRADE framework. Future high-quality and robust studies are needed to confirm the benefits of PMS devices for postoperative acute and chronic pain along with their safety and efficacy. Limitations included lack of trials on this specific topic, small study bias and a large number of participants that dropped out from several studies with no specific reasons documented. Also, if a study did not see any significant improvements in pain, it was unclear whether it was due the ineffectiveness of the PMS, or patient noncompliance.

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

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

Clinical trials for transcutaneous magnetic stimulation are currently ongoing. Refer to the following website for more information: https://clinicaltrials.gov/ct2/home. (Accessed April 26, 2023)

## Reference(s)


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

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

Park S, Park R, Westwood D, et al. Effect of peripheral magnetic stimulation on acute and chronic pain after surgery: A systematic review and meta-analysis. J Pain. 2023 Mar 4:S1526-5900(23)00071-8.


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

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

## Clinical Evidence

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

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.

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 |
|---|---|
| 33289 | Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision and interpretation, and pulmonary artery angiography, when performed |
| 93264 | Remote monitoring of a wireless pulmonary artery pressure sensor for up to 30 days, including at least weekly downloads of pulmonary artery pressure recordings, interpretation(s), trend analysis, and report(s) by a physician or other qualified health care professional |
| C2624 | Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components |

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

**Notes**:
- Monitoring – For members with an existing implanted device, monitoring is a covered service.
- Removal – Removal of an implantable wireless PAP sensor is a covered service in the rare instance when it might be required.

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

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

## Clinical Evidence

Cowie et al. (2022) conducted a prospective, open-label, unblinded, single-arm, post-market study to evaluate the safety, efficacy, and feasibility of hemodynamic-guided HF management using an implanted sensor in the pulmonary artery of NYHA Class III HF patients. The primary clinical endpoint compared annualized HF hospitalization rates after one year of hemodynamic-guided management vs. the year prior to sensor implantation and a previous HF hospitalization. Freedom from device/system-related complications and pressure sensor failure after two years were the primary safety endpoints. At baseline, all patients (n = 100) were in NYHA Class III, 70% were male, mean age was 69 ±12 years, and 39% had an etiology of ischemic cardiomyopathy. The annualized HF hospitalization rate after 12 months was 82% lower than the previous 12 months (0.27 vs. 1.52 events/patient-year, respectively, $p < 0.0001$). Freedom from device/system-related complications and pressure sensor failure at two years was 100% and 99%, respectively. The authors concluded remote hemodynamic guided HF management that uses frequent assessment of PAP was safe and significantly reduced hospitalization in high-risk patients. Limitations include lack of a contemporary control group, small study size, and the study was funded by the manufacturer.

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

A Hayes technology assessment concluded that low-quality evidence suggests the use of CardioMEMS implantable hemodynamic monitor as an adjunct to standard care for managing adult patients with symptomatic NYHA class III HF failure benefits health outcomes by leading to a consistent reduction of hospitalization risk and mean PAP values with some

improvements in cardiac function. However, data on the effects of the device on mortality and health related QOL were inconclusive due to inconsistent findings, short duration of follow-up and variability in reported outcome measures. The device appears to be safe and poses no major risks. Additional large well-designed comparative studies that conduct long-term assessments extending beyond 1-year post implantation are needed (Hayes, 2022).

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

### *MONITOR-HF*

The MONITOR-HF study (Brugts et al., 2023), a prospective, multicenter, open-label, randomized controlled trial, investigated the effectiveness of remote hemodynamic monitoring on QOL and HF hospitalizations compared to contemporary standard of care in the Netherlands. This was the first randomized controlled trial to investigate the benefits of using a PAP sensor (CardioMEMS) in a European healthcare system. A total of 348 patients were randomly assigned (1:1) to HF management with guideline-directed medical therapy (GDMT) and diuretics (control group; n = 172) or to HF management with GDMT and diuretics with the addition of hemodynamic monitoring using a PAP sensor (CardioMEMS-HF group; n = 176). Eligible patients had chronic HF, any ejection fraction, NYHA class III symptoms and a previous HF hospitalization or urgent visit requiring intravenous diuretics in the past 12 months. All patients were scheduled to be seen by their clinician at 3 months and 6 months, and every 6 months thereafter. All patients were followed for at least 12 months. The average duration of follow-up was 18 months and the maximum was 48 months. The primary endpoint was the change in QOL measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months. The secondary endpoint was the number of HF hospitalizations and/or urgent visits requiring intravenous diuretics during follow-up. The primary safety endpoints were device-related or system-related complications and sensor failures. All analyses were by intention-to-treat. The mean change in KCCQ overall summary scores between baseline and 12 months among patients in the CardioMEMS-HF group was + 7.05 (95% CI 2.77 to 11.33; p = 0.0014), compared with −0.08 points among those in the standard care group (−3.76 to 3.60; p = 0.97). During a mean follow-up of 1.8 years there were 117 HF hospitalizations or urgent visits in the monitoring group and 212 in the control group. The freedom of device-related or system-related complications and sensor failure were 97.7% and 98.8%, respectively. This study is limited by its open-label design.

### *CHAMPION*

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

randomized clinical trial setting, as well as in a follow-up setting more typical of clinical practice (Abraham et al., 2011; Abraham et al., 2016). Clinicaltrials.gov NCT00531661.

### *GUIDE-HF*

The GUIDE-HF trial (Lindenfeld et al., 2021) evaluated whether hemodynamic-guided management using remote PAP monitoring could reduce HF events and mortality in patients with HF across the spectrum of symptom severity, including patients with elevated natriuretic peptides but without a recent HF hospitalization. The randomized arm of 1000 patients was a multicenter, single-blind study at 118 centers in the U.S. and Canada. Following successful implantation of a PAP monitor, patients with all ejection fractions, NYHA class II–IV HF, and either a recent HF-related hospitalization or elevated natriuretic peptides were randomly assigned (1:1) to either hemodynamic-guided HF management based on PAP (n = 497) or standard of care (n = 503). The primary endpoint was a composite of all-cause mortality and total HF events (HF-related hospitalizations and urgent HF-related hospital visits) at 12 months assessed in all randomly assigned patients. Safety was assessed in all patients. There were 253 primary endpoint events (0·563 per patient-year) in the treatment group and 289 (0·640 per patient-year) in the control group [hazard ratio (HR) 0·88, 95% CI 0·74–1·05; p = 0·16]. The overall study analysis did not show a benefit of hemodynamic-guided management of HF on the primary outcome of mortality and HF events compared with the control group. However, a pre-COVID-19 impact analysis showed a possible benefit for the primary endpoint, driven by a reduction in HF hospitalizations. The authors reported no apparent benefit on all-cause mortality at 12 months. Study limitations include single blinding which has the potential to introduce investigator bias during communication with patients, the 12-month duration of follow-up and the effects of the COVID-19 pandemic in limiting data collection. The trial also includes an ongoing, single-arm, observational study (n = 2600). Clinicaltrials.gov NCT03387813.

### *PASSPORT-HF*

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

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

- In selected adult patients with NYHA class III HF and history of a HF hospitalization in the past year or elevated natriuretic peptide levels, on maximally tolerated stable doses of guideline-directed medical therapy (GDMT) with optimal device therapy, the usefulness of wireless monitoring of PAP by an implanted hemodynamic monitor to reduce the risk of subsequent HF hospitalizations is uncertain.
- In patients with NYHA class III HF with a HF hospitalization within the previous year, wireless monitoring of the PAP by an implanted hemodynamic monitor provides uncertain value.

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

Class of Recommendation: 2b (weak).

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

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

## Reference(s)

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Abraham WT, Stevenson LW, Bourge RC, et al.; CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. Lancet. 2016 Jan 30;387(10017):453-61.

Brugts JJ, Radhoe SP, Clephas PRD, et al.; MONITOR-HF investigators. Remote haemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF): a randomised clinical trial. Lancet. 2023 May 19:S0140-6736(23)00923-6.

Cowie MR, Flett A, Cowburn P, et al. Real-world evidence in a national health service: results of the UK CardioMEMS HF System post-market study. ESC Heart Fail. 2022 Feb;9(1):48-56.

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Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145(18):e895-e1032. Erratum in: Circulation. 2022 May 3;145(18):e1033. Erratum in: Circulation. 2022 Sep 27;146(13):e185.

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National Institute for Health and Care Excellence (NICE). IPG711. Percutaneous implantation of pulmonary artery pressure sensors for monitoring treatment of chronic heart failure. November 2021.

Thakker RA, Abu-Jazar D, Cabello R, et al. Outcomes in hospitalization in patients with heart failure undergoing remote pulmonary artery pressure monitoring: a systematic review and meta-analysis of major trials. Curr Probl Cardiol. 2022 Oct;47(10):100980.

| 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. A normal amount of effort is still required to urinate, and the pressure from the balloons will help guard against unintentional urine loss, such as during a sneeze or cough. The ACT® device is used for women, and the balloons are surgically placed on either side of the bladder neck, providing compression. The ACT device currently has FDA Investigational Device Exemption (IDE) and in March 2021, the first patients were enrolled in a clinical trial.

On November 24, 2015, the ProACT device received FDA Premarket Approval as a Class III device to treat adult men who have developed stress urinary incontinence following prostate surgery. Further information may be found at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P130018. (Accessed April 17,2023)

The 2023 European Association of Urology (EAU) guideline on non- neurogenic male urinary tract symptoms (LUTS), including benign prostatic obstruction (BPO) states that the non-circumferential compression device (ProACT®) is effective for treatment of PPI SUI and seems to be a reasonable alternative for male UI however, it is associated with a high failure and complication rate leading to frequent explanation and should not be offered to men who have had pelvic radiation therapy. Additionally, the procedure should only be performed in specialized centers.

A Hayes Health Technology Assessment on the ProACT device implantation for the treatment of post-prostate surgery induced urinary incontinence (UI) in adult men unresponsive to 6 to 12 months of more conservative treatment found an overall low-quality body of evidence that demonstrated improvement from baseline in key clinical outcomes among men receiving ProACT implantation. The body of evidence lacks controlled studies to determine if the ProACT device is similar, better, or worse than other available treatments with respect to patient outcomes. Single-arm studies consistently reported improvements from

baseline in some key clinical outcomes. Other patient outcomes were assessed by too few studies or assessed inconsistently across studies, precluding firm conclusions. Available evidence regarding potential harms suggests that the ProACT device may be associated with a moderate risk of complications, including revision and explanation; however, there is insufficient evidence to determine the relative safety of the ProACT device compared with other available treatments (Hayes, 2022).

An ECRI 2018 Clinical Evidence Assessment, updated in 2021, focused on ProACT's safety and effectiveness and how it compares with artificial urinary sphincters (AUSs) or other adjustable continence balloons (ACBs) for male stress urinary incontinence resulting from prostate surgery. One systematic review with meta-analysis that included 1264 participants was included. Although evidence from many case series synthesized in a meta-analysis supports limited conclusions on ProACT's safety and effectiveness the failure and complication rates may outweigh benefits for more than one-fifth of treated patients. Multicenter controlled trials that directly compare ProACT with other ACBs, AUSs, and other treatment options for SUI are needed. An ongoing single-arm study will assess long-term (five-year) adverse events (AE) and QOL scores. The report overall conclusion is that evidence for this device is inconclusive.

Munier et al. (2020) conducted a two center retrospective case series of 26 patients implanted with the ProACT device to treat persistent stress urinary incontinence (SUI) after radical prostatectomy who had insufficient improvement from sub urethral slings. The primary endpoint was continence, defined as 0 pads per day (PPD). The secondary endpoints were 50% decrease in PPD and increases in the Incontinence Quality of Life score (IQOL). Refilling and complications were also reported. The mean follow-up was 36 months (±20; min 14-max 128). Five patients have had adjuvant radiotherapy (18%). All patients presented with persistent stress urinary incontinence, using 2.3 PPD (±1; min 1-max 6), and only one sling was removed due to infection. After ProACT with an average 3 mL refilling (±1.2 min 2-max 6), 18 patients (66.7%) were continent. Eight of the remaining patients (29.6%) were improved; their number of PPD decreased from 2.6 to 1. The average IQOL score of those 8 patients increased by 20 points, from 53.4 up to 74.2 ($p = .005$). Overall, 26 patients (96.3%) were improved. The remaining patient was not implanted because of an intraoperative urethral injury and is considered a failed case (3.7%). He had instead an AUS implantation. Three patients (14.8%) needed peri-urethral balloon replacement. The authors concluded that ProACT implantations are effective and without significant complications. This study is limited by a small number of participants, and a lack of a comparison group.

Angulo et al. (2019, included in the ECRI and Hayes reports above) completed a systematic review and meta-analysis on adjustable devices ATOMS and ProACT. The objective of this study was to assess efficacy and safety of Adjustable Transobturator Male System (ATOMS) compared to Adjustable Continence Therapy (proACT) for male SUI according to literature findings. Combined data of 41 observational studies with 3059 patients showed higher dryness (68 vs. 55%; $p = .01$) and improvement (91 vs. 80%; $p = .007$) rate for ATOMS than ProACT. Mean pad-count (-4 vs. -2.5 pads/day; $p = .005$) and pad-test decrease (-425.7 vs. -211.4 cc; $p < .0001$) were also significantly lower. Satisfaction was higher for ATOMS (87 vs. 56%; $p = .002$) and explant rate was higher for proACT (5 vs. 24%; $p < .0001$). Complication rate for ProACT was also higher, but not statistically significant (17 vs. 26%; $p = .07$). Mean follow-up was 25.7 months, lower for ATOMS than ProACT (20.8 vs. 30.6 months; $p = .02$). The rate of working devices favored ATOMS at 1-year (92 vs. 76; $p < .0001$), 2-years (85 vs. 61%; $p = .0008$) and 3-years (81 vs. 58%; $p = .0001$). Significant heterogeneity was evidenced, due to variable incontinence severity baseline, difficulties for a common reporting of complications, different number of adjustments and time of follow-up and absence of randomized studies. Despite the limitations that studies available are exclusively descriptive and the follow-up is limited, the authors concluded that literature findings confirm ATOMS is more efficacious, with higher patient satisfaction and better durability than ProACT to treat male stress incontinence.

Nash et al. (2019, included in Angulo systematic review and Hayes report above) presented a paper with the 4-year follow-up results for patients enrolled in a pivotal study conducted to support an FDA premarket approval application (PMAA). The study evaluated the safety and efficacy of the ProACT Adjustable Continence Therapy for the treatment of post-prostatectomy SUI. The clinical study involved 11 clinical sites. A total of 124 subjects met study criteria and 123 were implanted with ProACT. Baseline and outcomes for 68 patients who completed 4-year follow-up visits are reported. Endpoints included 24-h pad weight, Incontinence Quality of Life Questionnaire (I-QOL), UCLA Prostate Cancer Index-Urinary Function (PCI-UF), residual volume, and incidence and severity of device or procedure-related adverse events. The results showed statistically significant improvements during follow-up observed in 24-h pad weight, for which the mean pre-implant urine loss was 293 g, which was reduced at 4 years to 73 g ($p < 0.001$). Reductions in pad weight were observed across all levels of pre-implant SUI severity. Significant improvements were also seen in quality of life as measured by the I-QOL ($p < 0.001$) as well as measures of urinary function and pad use. One procedure-related SAE (retention) was reported among the 68 subjects; the SAE was resolved without clinical meaningful sequalae. The authors concluded that these results confirm the long-term safety and efficacy of this

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

Noordhoff et al. (2019, included in Angulo systematic review, and Hayes report above) conducted a retrospective multicenter case series to evaluate the outcome of adjustable continence balloons in the treatment of SUI after transurethral resection of the prostate (TURP). In two tertiary centers, adjustable continence balloons were implanted in 29 patients with post-TURP SUI between 2007 and 2018. Endpoints of this were patient-reported changes in pad count and complications. Dry was defined as no pad or one security pad. Preoperative UI was mild in 7 (24%), moderate in 12 (41%), and severe in 10 (35%) patients. The median follow-up duration was 21 months. The results showed within 30 days postoperatively, a Clavien-Dindo grade less than or equal to II complication occurred in 24% of the patients. Reintervention rate was 24%. Six and 12 months after implantation, the International Prostate Symptom Score (IPSS) quality-of-life item improved significantly from 5 preoperatively to 3 and 1 respectively. At the last visit (median 21 months after implantation), the outcome on continence had improved in 76% of the patients, including, 45% dry patients. After a median follow-up of 28 months, all but one patient reported improvement on the Patient Global Impression of Improvement (PGI-I) scale. In detail, 10 patients reported "very much better" condition compared with before the implantation, 10 patients "much better," two patients "a little better," and one patient "no change." Daily pad use decreased from three (IQR, 2-5) to one (IQR, 0-2) pads/day ($p < 0.001$). According to the authors, this is the first study reporting results of adjustable continence balloons in the treatment of post-TURP SUI. They concluded that the therapy was found to be safe and efficient. These findings are limited by lack of comparison group and small sample size.

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

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

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

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

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

Crivellaro et al. (2016, included in Angulo systematic review and Hayes report above) conducted a systematic review to report the results in terms of efficacy (pad count, 24-hour pad test, QOL questionnaires) and safety (complication rate and type of complications) of all surgical devices approved for the treatment of SUI after radical prostatectomy (RP). Inclusion criteria were number of patients higher than 30, mean follow up longer than 12 months and definition of a successful outcome as the use of

0 to 1 safety pads a day. 51 papers met the inclusion criteria with a total sample size of 4022 patients. Efficacy (0-1 safety pads) was on average 65.7% for AUS, 48.2% for Invance Sling, 48.8% for Advance Sling, 64.2% for ProACT. The overall complication rate was 19.43% for AUS, 7.4% for Invance Sling, 12.3% for Advance Sling, 12.3% for ProACT. The authors concluded that due to the poor overall quality of available studies, it was not possible to identify or refute clinically important differences between the alternative surgical procedures. The data seems to suggest that while AUS has the highest efficacy in the treatment of SUI following RP it is also associated with the highest complication rate, but this may be due to the longest follow up. Larger rigorous trials are needed in order to support this evidence.

Venturino et al. (2015, included in Angulo systematic review above) conducted a case series to evaluate the functional results, morbidity, and quality of life of the adjustable continence balloons ProACT for the treatment of male SUI after prostate surgery considering both short- and long-term results. Between 2002 and 2012, twenty-two consecutive male patients were implanted with the ProACT device. Continence was defined by the use of 0 pads daily, and the quality of life was assessed by validated questionnaires. Only 1 patient (4.5%) was immediately continent after ProACT implantation, and the other 21 men (95.5%) needed ≥ 1 balloon refillments postoperatively. The baseline daily pad number decreased from a mean of 5.9 pads (range, 3-12 pads) to a mean of 1.7 pads (range, 0-5 pads) per day after refilling but increased to a mean of 3.9 (range, 0-10) at the last follow-up visit. After balloon adjustments, 4 patients (18%) were continent and 18 patients (82%) showed an improvement with a 95% rate of subjective satisfaction. Revision and explanation rates were 73% and 55%, respectively. At a median follow-up of 57 months, only 1 patient (4.5%) remained dry, and only 10 patients (45%) remained satisfied with the procedure, whereas 12 patients (55%) were unchanged and dissatisfied. The authors concluded that the ProACT device appears to be safe and efficacious in the short term, and that the postoperative readjustment allows the achievement of a short-term continence status. They also note that in the long term, the ProACT does not appear to be an ideal device for durable continence and patients' satisfaction. This study is limited by the lack of comparison group and small sample size.

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

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

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

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

## Clinical Evidence

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

Krogshede et al. (2022) conducted a prospective randomized controlled trial that included twenty-six participants to investigate whether balloon dilation of the Eustachian tube (BDET) can improve ventilation of the middle ear among adult patients with a mild chronic Eustachian tube dysfunction (ETD) via tympanometry and otomicroscopy. Criteria included adults aged eighteen and older with a unilateral, persistent ETD despite completion of 2 months of daily use of nasal steroid and Valsalva's maneuver (NSVM treatment). Participants were randomized 1:1 between the treatment and control groups. The results of at each follow-up were categorized as either "improvement" or "no improvement." Tympanometry results in the BDET group showed an improvement in nine out of thirteen patients at 6 months, while four out of thirteen either maintained their tympanogram type or worsened. In the control group, three out of eleven showed improvement at 6 months, while eight out of eleven either maintained their tympanogram type or worsened. Otomicroscopy showed an improvement to either bulging or normal in nine out of thirteen patients at 6 months, while four out of thirteen showed no improvement. In the control group, zero out of eleven showed improvement at 6 months, and all patients showed no improvement. There was no significant difference in mean ETDQ-7 score between the two groups at follow-up, and there were no complications from the intervention. The authors concluded that BDET may be a beneficial treatment compared to control treatment in a selected group of adult patients with mild, chronic ETD. The limitations of this study include a small number of participants and lack of blinding due to ethical considerations which may have affected outcome measures. Further high-quality research with longer follow, sham procedure, masking, and demonstrated benefit on patient-centered outcome is needed to validate these findings.

A systematic review was conducted by Aboueisha et al. (2022) to determine the efficacy and safety of BDET amongst the pediatric population. A search was conducted using PubMed, Embase, Web of Science, Cochrane, Clinicaltrials.gov and CINAHL which returned seven studies and included 408 patients for assessment. Inclusion criteria consisted of children < 18 years of age with an intervention of BDET either alone or in combination with a tympanostomy or myringoplasty. Preoperatively Type B tympanogram was the most common presentation with an air bone gap (ABG) mean of 22.8 dB. Following BDET, the authors found Type B tympanograms reduced from 64.2% to 16.1% and the main adverse effect was epistaxis. When comparing BDET to ventilation tubes, there was no statistical significance, however BDET demonstrated a statistically significant post op reduction in ABG along with a lower failure rate. Limitations included a small number of studies for analysis, lack of RCTs, limited number of comparative studies, and use of multiple types of balloons. Future RCTs in the pediatric population may help to better determine the best candidates for BDET.

In a 2022 systematic review, Raymond et al. examined eleven studies (all case series or case reports) of eighty-one patients on the effectiveness of balloon Eustachian tube dilation for the treatment of baro-challenge eustachian tube dysfunction. Seventy-two patients from ten studies underwent balloon eustachian tube dilation; nine patients in one study underwent laser

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

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

A Hayes health technology assessment, states that the overall body of evidence for the use of eustachian tube balloon dilation (ETBD) for treatment of chronic ETD refractory to medical management (MM) while large in size, is considered to be low quality. Based on the results of four RCTs, one case control, one retrospective and five pre/post studies, it was concluded that patients treated with ETBD experience symptom relief and improved function, and it appears to be comparable or better than the standard of care with no major safety concerns identified, however additional high-quality studies are warranted. Furthermore, it is acknowledged that evaluating the treatment response is difficult and a combination of patient reported, and objective treatment outcomes are necessary for future research. Well-designed studies are underway that will provide additional evidence regarding the efficacy and safety of this technology. The authors concluded that this approach has potential but unproven benefit (Hayes 2021; updated April 2023).

A systematic review and meta-analysis by Froehlich et al. (2020) examined the effectiveness of ETBD for the treatment of eustachian tube dysfunction. A search was conducted and identified thirty-five articles of which twelve met the criteria for inclusion. Inclusion criteria consisted of balloon dilation of the ET for the treatment ETD in adults. Data was collected on four primary outcomes: 1) ETDQ7 scores, 2) tympanometry, 3) otoscopy findings, and 4) ability to perform the Valsalva maneuver. Results were collected at baseline, 6 weeks (+/- 2 weeks) and 3 to 12 months. The authors found three studies reported improvement in ETDQ7 scores, nine studies reported improvement in tympanograms and seven studies reported abnormal otoscopy exams decreased by 30%. Seven studies reported an increase in ability to perform successful Valsalva maneuver by 81% from baseline to long-term. The authors found the ETBD may be associated with improved patient outcomes along with stable improvement through twelve months following the dilation procedure. Limitations include lack of comparison to other therapeutic approaches, variation in surgical techniques amongst the studies, use of three different balloon devices, variation in protocols, and increased risk in heterogeneity. While patients have benefited from this procedure, further studies are needed to determine the efficacy of this specific treatment modality.

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

Using data from a prospective, multicenter, randomized, controlled trial, Anand et al. (2019-included in Hayes and ECRI reports and Froehlich (2020 systematic review) analyzed and investigated the durability of BDET for obstructive eustachian tube dysfunction (OETD) plus medical management (MM) treatment outcomes through 52 weeks. Among subjects randomized to BDET + MM, the overall number with normalized tympanograms and ETDQ-7 scores remained comparable to those reported at 6- versus 52-week follow-up: tympanograms, 73 of 143 (51.0%) versus 71 of 128 (55.5%); ETDQ-7, 79 of 142 (55.6%) versus 71 of 124 (57.3%). The overall number of ears with normalized tympanograms also remained comparable, with 117 of 204 (57%) versus 119 of 187 (63.6%). The author's conclusions suggested that the beneficial effects of BDET + MM on tympanogram normalization and symptoms of subjects with refractory OETD demonstrated significant durability that is clinically relevant through 52 weeks. This publication, however, is limited to the analysis of one of the randomized arms and does not allow comparison to a different treatment approach.

Meyer et al. (2018, included in Hayes report above and Froehlich (2020 systematic review)) compared eustachian tube balloon dilation versus continued medical therapy for treating persistent ETD in a prospective, multicenter, randomized controlled trial. Sixty participants were randomized to either a balloon dilation group or a control group; after 6 weeks, the control participants had the option to undergo balloon dilation if symptoms persisted. No complications were reported in either study group. Among participants with abnormal baseline assessments, improvements in tympanogram type and tympanic membrane position were significantly better for balloon dilation than control. Technical success was 100% and most procedures (72%) were completed in the office under local anesthesia. Improvements in the ETDQ 7scores were maintained through 12 months after balloon dilation. A limitation of the study was the inability to blind the participants to their treatment which can lead to a placebo effect, but since significant improvements were seen in the objective findings such as tympanometry, otoscopy, and Valsalva maneuver in the balloon dilation arm and not in the control arm, the author's believed that any placebo effect was minimal and that the improvements observed in the ETDQ-7 scores were reliable and indicated true symptom improvement. Another limitation is the short-term duration (six weeks) of the randomized portion of the study. The author's concluded balloon dilation is a safe and effective treatment for persistent ETD. Based on improved ETDQ-7 scores, balloon dilation is superior to continued medical management for persistent ETD. Symptom improvement is durable through a minimum of 12 months and procedures are well tolerated in the office setting under local anesthesia.

In a prospective, multicenter, randomized, controlled trial, Poe et al. (2018- included in Hayes and ECRI reports and Froehlich (2020 systematic review)) assessed balloon dilation of the eustachian tube with eustachian tube balloon catheter in conjunction with medical management as treatment for eustachian tube dilatory dysfunction. Patients aged 22 years and older were assigned in a ratio of 2:1 and underwent balloon dilation of the Eustachian tube with balloon catheter in conjunction with medical management or medical management alone. The data suggest superiority of balloon dilation of the Eustachian tube with balloon catheter plus medical management compared to medical management alone: Tympanogram normalization at 6-week follow-up was observed in 51.8% (72/139) of investigational patients versus 13.9% (10/72) of controls ($p < .0001$). However, the short duration of the study limits the conclusion that can be drawn for the duration of the effect.

Wang et al. (2018- included in ECRI report) performed a meta-analysis examining balloon dilatation and laser tuboplasty for the treatment of ETD. Pub Med, Cochrane and Embase databases were searched in April of 2018 with the following results: two retrospective and eleven 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.

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

In a 2017 ECRI clinical evidence assessment, updated in 2021 on the Acclarent Aera Eustachian Tube Dilation System (Acclarent, Inc) for treating persistent ETD states that based on the results of one randomized controlled trial (RCT) and 4 additional small, low-quality studies, eustachian tube (ET) dilation with the Aera balloon system is safe and, when added to medical therapy, may relieve symptoms from 6 weeks up to 1 year in select patients whose ETD has not responded to medical therapy alone. Limitations include the RCT comparative outcomes only included up to 6-week follow up due to the cross-over design, and device and control group participants dropping out before receiving treatment, and at follow up. Additionally,

studies are limited by one or more of the following: small study size, single-center focus, retrospective design, and lack of randomization, blinding, and control groups. While the authors consider the evidence somewhat favorable, additional RCTs would be useful to validate results.

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

The U.S. Food and Drug Administration (FDA) approved the Audion ET dilation system under 510(K) (K220027) on April 12, 2022. The device is intended for use in dilating the cartilaginous portion of the Eustachian tube for treating persistent Eustachian tube dysfunction in patients aged eighteen and older using a transnasal approach. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf22/K220027.pdf. (Accessed April 18, 2023)

The U.S. Food and Drug Administration (FDA) approved the NuVent Eustachian Tube Dilation Balloon 510(K) (K210841) on August 16, 2021. The device is indicated in patients aged eighteen and older who need treatment for persistent Eustachian tube dysfunction. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf21/K210841.pdf. (Accessed April 18, 2023)

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 18, 2023)

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 eighteen and older. Additional information is available at: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171761.pdf. (Accessed April 18, 2023)

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| Code | Description |
|---|---|
| 80145 | Adalimumab |
| 80230 | Infliximab |
| 80280 | Vedolizumab |

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

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

## Clinical Evidence

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

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

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

### *Adalimumab (Humira)*

In 2022, D'Haens et al. reported the results of the SERENE CD phase 3, randomized, double-blind, multicenter trial that was done across 93 sites in 19 countries that evaluated higher vs standard adalimumab induction dosing as well as clinically adjusted (CA) vs therapeutic drug monitoring (TDM) maintenance in patients with moderate to severe CD. Participants were first randomized to the higher induction regimen or standard induction regimen followed by 40 mg every other week from week

4 onward. Primary end points included clinical remission at week 4 and endoscopic response at week 12. At week 12, patients were re-randomized to maintenance therapy optimized by the Crohn's Disease Activity Index and C-reactive protein or serum adalimumab concentrations and/or clinical criteria. A 44 week double blind maintenance study was added with all participants. Exploratory end points were then evaluated at week 56. The results showed similar proportions of patients receiving higher induction regimen and standard induction regimen achieved clinical remission at week 4 and endoscopic response at week 12. Week 56 efficacy was similar between CA and TDM. The authors concluded that a higher induction regimen was not superior to standard induction regimen, and CA and TDM maintenance strategies were similarly efficacious. Maintenance dose adjustment primarily by serum adalimumab levels was not more efficacious than clinically adjusted dosing. The SERENE CD trial confirms the appropriateness of the approved adalimumab Induction dose regimen. Although exploratory, no clinical advantage for TDM over clinical adjustment during maintenance therapy was observed.

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

In a cross-sectional study of 66 patients receiving maintenance therapy with ADA for CD or UC, Yarur et al. (2016) assessed the relationship between random serum ADA levels and histologic and endoscopic healing in patients with IBD. The results showed that mean random ADA levels were significantly lower in patients with histologic and endoscopic inflammation [9.2 (SD: 8.4) versus 14.1 (6.4) μg/mL, p = 0.03 and 8.5 (SD: 7.8) versus 13.3 (SD: 7.7), p = 0.02, respectively]. The ADA level that was best associated with histologic healing was 7.8 μg/mL [receiver operating characteristic: 0.76 (p = 0.04)], whereas the ADA level that was best associated with endoscopic healing was 7.5 μg/mL [receiver operating characteristic: 0.73 (p = 0.02)]. The presence of anti-ADA antibodies (AAA) was associated with lower random ADA levels (5.7 versus 12.5 μg/mL, p = 0.002) and higher C-

reactive protein levels (30.3 versus 12.0, p = 0.01). The authors concluded that the measurement of random ADA levels and anti-drug antibodies may guide therapy and edify the course of incomplete responses. Further studies with larger patient populations are needed to evaluate optimal levels of ADA.

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

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

### *Golimumab (Simponi)*

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

### *Infliximab (Remicade)*

Bossuyt et al. (2022, included in Hayes report below) conducted a pragmatic trial to compare outcomes of an ultra-proactive TDM algorithm of infliximab based on point of care testing, with reactive TDM in patients with IBD on maintenance infliximab for at least 14 weeks. The trial was conducted in two large non-academic IBD centers, one focused on ultra-proactive TDM in 115 patients and the other focused on reactive TDM in 72 patients. The primary endpoint was failure of IFX therapy after 1 year, defined as infliximab discontinuation, IBD-related surgery or hospitalization, add-on treatment, and allergic reaction to infliximab. One secondary endpoint included sustained clinical remission based on physician global assessment which included the number of trough level (TL) measurements per patient per year, the percentage of interval changes, the percentage of patients with infliximab discontinuation, and percentage of patients with sustained clinical remission. Another secondary endpoint included mucosal remission based on endoscopy and/or fecal calprotectin between 6 and 12 months. The results showed a significant difference in the use of TL measurements between the two groups, with the patients in the ultra-proactive TDM cohort having a mean number of 8.8 TL measurements per year compared with only one TL measurement per year in the reactive group. The higher number of TL measurements led to a significant difference in dose flexibility in the ultra-proactive TDM group. Half of the patients in the ultra-proactive cohort had an interval shortening compared with only 15% in the reactive group. Additionally, more interval prolongations and bidirectional changes were applied in the ultra-proactive group. However, no differences were seen in infliximab failure rates after 2 year of follow-up: 19% of patients in the ultra-proactive cohort versus 10% in the reactive cohort. For the secondary clinical outcomes, no difference was seen in infliximab discontinuation rate nor in the sustained clinical remission rate. There was a significant difference in the proportion of patients with mucosal remission, with 79% in the reactive TDM cohort compared with 52% in the ultra-proactive TDM cohort, however these results need to be interpreted with caution as the assessment based on endoscopy or fecal calprotectin was part of standard of care and was only taken into account between 6 and 12 months and data were only available in 71 patients. The authors concluded that these results show that ultra-proactive TDM has no superior impact on clinical outcomes over reactive TDM which remains the strategy of choice during maintenance infliximab treatment. It is acknowledged that this pragmatic trial

only addresses patients on maintenance treatment and further studies are needed for TDM during induction treatment. The findings are limited by lack of randomization.

In 2022, Hayes completed a health technology assessment on the use of anti-infliximab antibody levels to monitor Infliximab treatment in patients with Crohn's Disease. (Hayes 2022). Based on the results of 3 randomized controlled trials (RCTs), 3 prospective cohort studies, 4 retrospective cohort studies, 1 prospective trial with historical controls, and 1 retrospective registry analysis it was concluded that there has not been enough high quality evidence to demonstrate sufficient diagnostic or prognostic accuracy or capacity to improve management or health outcomes, and additional well-designed studies are needed.

In a 2021 randomized clinical trial, Syversen et al. assessed whether proactive TDM during maintenance therapy with infliximab improves treatment efficacy by preventing disease worsening compared with standard infliximab therapy without TDM. The trial included 458 adult patients with Immune-mediated inflammatory diseases and included rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, or psoriasis who had been undergoing maintenance therapy with infliximab for a minimum of 30 weeks and a maximum of 3 years. Patients were randomized 1:1 to receive either TDM In the TDM group, in which infliximab dosing was adjusted according to an algorithm designed to maintain infliximab levels within the therapeutic range of 3 to 8 mg, or standard therapy in which administration was based on clinical judgement. The primary outcome was sustained disease control without worsening during the study period of 52 weeks. The results showed this outcome was achieved for 74% of patients in the TDM group and 56% in the standard therapy group. Secondary outcomes reflected disease activity, remission rate and patient reported outcomes at week 52 and there were no significant differences between the two groups. Adverse events were reported in 60% and 63% patients in the TDM and standard therapy groups, respectively the number of infections was higher in the TDM group. Three patients in the standard therapy group and none in the TDM group experienced an infusion reaction. The authors concluded that proactive TDM was more effective than treatment without TDM in sustaining disease control during maintenance therapy without disease worsening, and further research is needed to compare proactive TDM with reactive TDM to validate these findings.

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

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

In a systematic review and meta-analysis, Moore et al. (2016) evaluated studies that reported serum IFX levels according to outcomes in IBD. The primary outcome was clinical remission, and secondary outcomes included endoscopic remission, and

CRP levels. A total of 22 studies met the inclusion criteria, including 3483 patients; 12 studies reported IFX levels in a manner suitable for determining effect estimates. During maintenance therapy, patients in clinical remission had significantly higher mean trough IFX levels than patients not in remission: 3.1 µg/ml versus 0.9 µg/ml.

The standardized mean difference in serum IFX levels between groups was 0.6 µg/ml [95% confidence interval (CI) 0.4-0.9, p = 0.0002]. Patients with an IFX level > 2 µg/ml were more likely to be in clinical remission [risk ratio (RR) 2.9, 95% CI 1.8-4.7, p < 0.001], or achieve endoscopic remission (RR 3, 95% CI 1.4-6.5, p = 0.004) than patients with levels < 2 µg/ml. The authors concluded that there is a significant difference between serum IFX levels in patients with IBD in remission, compared with those who relapse, and a trough threshold during maintenance > 2 µg/ml is associated with a greater probability of clinical remission and mucosal healing.

In an observational study, Vande Casteele et al. (2015, include in Hayes report above) 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, included in Hayes report above) studied 128 consecutive patients (105 patients with CD, 23 patients with UC) who restarted IFX after a median 15-month discontinuation (range, 6-125 months) to investigate correlations among response to treatment, infusion reactions, treatment modalities, trough levels, and antibodies to IFX. The absence of antibodies to infliximab at T + 1 [hazard ratio (HR), 0.14; 95% confidence interval (CI), 0.026-0.74; p = .021] and re – initiation with concomitant immunomodulator therapy were associated with short-term responses (HR, 6.0; 95% CI, 1.3-27; p = .019). Based on the results, the authors concluded that reinitiating IFX therapy can be safe and effective for patients with CD or UC after a median 15-month discontinuation period. Additional studies are needed to validate these findings.

In a pilot retrospective observational study, Vaughn (2014, included in Hayes report above) 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.

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

### *Vedolizumab (Entyvio)*

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. The 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 patients with UC on VDZ maintenance therapy were included. Per-event analysis was performed. Histological healing was defined as a Nancy histological index ≤ 1. The results showed that histological healing was associated with higher VDZ trough levels during maintenance therapy in UC. Based on this analysis, the authors found that a VDZ trough level threshold of 25 μg/mL proved most optimal to predict histological healing according to the Nancy histological index. Confirmation of these data in larger, independent cohorts is needed.

In a retrospective cohort study, Dreesen et al. (2018) investigated the correlation between VDZ exposure and response to identify patient factors that affect exposure and response. Serum concentrations of VDZ were drawn on 179 consecutive patients (66 with UC and 113 with CD) before all infusions and up to week 30. Effectiveness endpoints included endoscopic healing (UC, Mayo endoscopic sub-score ≤ 1; CD, absence of ulcers), clinical response (physicians' global assessment), and biologic response or remission (based on level of CRP) and were assessed at week 14 (for patients with UC) and week 22 (for patients with CD). VDZ trough concentrations > 30.0 μg/mL at week 2, > 24.0 μg/mL at week 6, and > 14.0 μg/mL during maintenance therapy associated with a higher probability of attaining the effectiveness endpoints for patients with UC or CD (p < .05). Higher body mass and more severe disease (based on high level of CRP and low level of albumin and/or hemoglobin) at the start of VDZ therapy associated with lower trough concentrations of VDZ over the 30-week period and a lower probability of achieving mucosal healing (p < .05). Mucosal healing was achieved in significantly more patients with UC than patients with CD,

even though a diagnosis of UC was not an independent predictor of higher VDZ trough concentrations. Prospective studies are needed to evaluate the impact of TDM on clinical management.

### *Ustekinumab (Stelara)*

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

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

### *Clinical Practice Guidelines*

#### American College of Gastroenterology (ACG)

In a 2018 clinical guideline on the management of CD in adults, the AGA states that therapeutic drug monitoring has become very common in the management of CD especially among patients who initially responded to biologic therapy but then developed loss of clinical response. While a detailed critical examination of the role of therapeutic drug monitoring was beyond the scope of this guideline, if active CD is documented, the assessment of biologic drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered.

In a 2019 clinical guideline on the management of ulcerative colitis in adults, the AGA states the following:

- The patient with nonresponse or loss of response to therapy should be assessed with therapeutic drug monitoring to identify the reason for lack of response and whether to optimize the existing therapy or to select an alternate therapy.
- There is insufficient evidence supporting a benefit for proactive therapeutic drug monitoring in all unselected patients with UC in remission.

#### American Gastroenterological Association (AGA)

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).

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 includes the following:

- In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive TDM to guide treatment changes. (Conditional recommendation, very low quality of evidence).
- In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring due to a knowledge gap.
- There are several knowledge gaps in TDM that have been identified for which prospective observational and RCTs are warranted, which have been highlighted in the Technical Review that accompanies this guideline (Vande, Casteele et al., 2017).
- It is unclear whether TDM should be performed during induction therapy in patients with suboptimal response (as opposed to empiric dose escalation) and, if it is performed, what the target trough concentrations should be.

- Similarly, target trough concentrations when performed in the reactive setting in patients on maintenance therapy with different agents is unclear, and whether it should be different based on disease phenotype, disease state, and treatment target (clinical remission vs mucosal healing).
- Further studies are also needed to better define clinically meaningful vs insignificant anti-drug antibodies, based on titers and/or persistence on repeated testing, and at which titers can anti-drug antibodies be suppressed before needing to change drug therapies.
- Additionally, well-designed RCTs are needed that compare routine proactive TDM vs reactive TDM, and empiric dosing changes on patient relevant outcomes, and also the frequency and timing of proactive TDM.
- Finally, as newer biologic agents are approved, the use of TDM to optimize these drugs will need to be evaluated.

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

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

## Clinical Evidence

The Vectra DA test (Crescendo Bioscience Inc., a wholly owned subsidiary of Myriad Genetics Inc.) is a multi-biomarker blood test that measures levels of 12 key proteins. A weighted algorithm based on the levels of these markers is used to calculate the multi-biomarker disease activity (MBDA) score, resulting in a single number ranging from 0 to 100 to rank disease activity. The Vectra DA test, also referred to as the MBDA test, is intended to measure disease activity in individuals who have rheumatoid arthritis (RA), with the goal of informing treatment decisions in conjunction with standard clinical assessment. The Vectra DA test is regulated under the Food and Drug Administration's (FDA) Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the FDA is not required for this test (Hayes, 2018. Updated February 2021).

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

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

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

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

Ma et al. (2020) used the multi-biomarker disease activity (MBDA) test to explore the role of biomarkers in predicting point remission and sustained remission. RA patients on > 6 months stable therapy in stable low disease activity (DAS28-ESR ≤ 3.2) were assessed every 3 months for 1 year. Baseline, intermittent (IR) and sustained (SR) remission were defined by DAS28-ESR, DAS28-CRP, simple disease activity index (SDAI), clinical disease activity index (CDAI) and ACR/EULAR Boolean criteria. Patients not fulfilling any remission criteria at baseline were classified as 'low disease activity state' (LDAS). Patients not fulfilling any remission criteria over 1 year were classified as 'persistent disease activity' (PDA). MBDA score was measured at baseline/3/6 months. The baseline MBDA score, the 6-month time-integrated MBDA score and MBDA biomarkers were used for analyses. The area under the receiver operating characteristic curve (AUROC) assessed the ability of the MBDA score to discriminate between remission and non-remission. Biomarkers were analyzed at baseline using the Mann-Whitney test and over time using the Jonckheere-Terpstra trend test. Of 148 patients, 27% were in the LDAS, 65% DAS28-ESR remission, 51% DAS28-CRP remission, 40% SDAI remission, 43% CDAI remission and 25% ACR/EULAR Boolean remission at baseline. Over 1 year, 9% of patients were classified as PDA. IR and SR were achieved in 42%/47% by DAS28-ESR, 46%/29% by DAS28-CRP, 45%/20% by SDAI, 44%/21% by CDAI and 35%/9% by ACR/EULAR Boolean criteria, respectively. By all remission criteria, baseline MBDA score discriminated baseline remission (AUROCs 0.68-0.75) and IR/SR (AUROCs 0.65-0.74). The 6-month time-integrated MBDA score discriminated IR/SR (AUROCs 0.65-0.79). Baseline MBDA score and concentrations of IL-6, leptin, SAA

and CRP were significantly lower in all baseline remission criteria groups vs LDAS. They and the 6-month time-integrated values were lower among patients who achieved IR/SR vs PDA over 1 year. According to the investigators, this study demonstrated that the MBDA score and its biomarkers IL-6, leptin, SAA and CRP, differentiated between small differences in disease activity (i.e., between low disease activity and remission states). They were also predictors of remission over 1 year. The investigators indicated that the limitations of the study included the relatively small number of patients in sustained remission, particularly in the group meeting the ACR/EULAR Boolean definition and in the group with no remission at any time point, i.e., the PDA group. Secondly, because the different remission groups contained overlapping populations, it was not possible to formally compare them to each other. Thirdly, Anti-citrullinated protein antibodies (ACPA) status was not analyzed as a predictor of remission in REMIRA because the focus of this study was the MBDA score and its biomarkers and because ACPA data were incomplete. Lastly, BMI data was not collected in this study and the MBDA scores were not adjusted for adiposity.

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

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

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

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

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

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

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

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

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

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

## Clinical Evidence

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

In 2022, Ridner et al. (included in the 2023 Hayes updated below) reported results from a stratified, randomized international trial (PREVENT) of 1200 newly diagnosed breast cancer patient undergoing mastectomy/partial mastectomy, axillary treatment, radiation therapy, or taxane based chemotherapy. They compared rates of progression to chronic breast cancer related lymphedema following an intervention for subclinical lymphedema (S-BCRL) identified by bioimpedance spectroscopy (BIS) using the L-DexU400 (SOZO) (ImpediMed, Ltd. Brisbane) or by tape measurement (TM). Following post-surgery eligibility reassessment, randomization to prospective surveillance by BIS or TM occurred. A S-BCRL detection then triggered a 4-week, 12-hour per day, compression sleeve, and gauntlet intervention. The primary outcome was the rate of progression to complex decongestive physiotherapy (CDP) and was assessed over three years. Of the 1200 participants, 963 were randomized, and 879 were included in the analysis. 209 patients had a need for an intervention identified. The results showed a lower proportion of BIS patients triggered an intervention, and the median time from randomization to intervention was longer. 30 of these

participants progressed after intervention. Of those patients, no difference between the groups was observed in intervention completion rates. The participants that received BIS were less likely to progress to CDP than the TM group. The median follow-up months were not statistically significant between the groups. The authors concluded that the use of BIS for prospective BCRL surveillance, allows early intervention of CDP and reduces progression to C-BCRL. These results are likely related to the ability of BIS to detect an increase in extracellular fluid, as opposed to TM's ability to only detect an increase in whole arm volume. This study is limited in that it compares BIS to only one diagnostic for BCRL diagnosis and cannot be extrapolated to other well-established diagnostics.

In a 2021 randomized controlled trial, Boyages et al. compared the risk of subclinical BCRL (sBCRL) using BIS or tape measure (TM) by the extent of axillary surgery and regional nodal irradiation (RNI). 498 women with newly diagnosed breast cancer were included and randomized to receive BIS or TM surveillance. Postsurgical inclusion criteria included stage I-III invasive breast cancer or ductal carcinoma in situ with at least one the following: mastectomy, axillary treatment (ALND, SNB with greater than 6 nodes), radiation therapy, or taxane-based chemotherapy. Incidence of sBCRL by sentinel node biopsy or axillary lymph node dissection (ALND) with or without RNI was examined for 484 patients. Presurgical baseline measurements with BIS and TM using a nonflexible Gulick II TM with spring-loaded tension were taken patients were randomized after surgery, and postoperative assessments were conducted at 3,6,12,18, 24 and 36 months and at the end of any intervention. A BIS change of ≥ 6.5 L-Dex units, or TM change ≥ 5% but < 10% indicated sBCRL. BIS > 7.0 and TM volume change > 10% was considered clinical BCRL. Once sBCRL was identified, patients underwent 4 weeks of wearing a compression sleeve and gauntlet therapy for 12 hours per day. The overall results showed that the potential for sBCRL was identified in 30.8% for patients who underwent ALND and 19.2% for SNB with both techniques. For BIS, the rate was 24% after ALND and 13.5% after SNB. for TM, the incidence was 37.0% and 25.6%, respectively. The authors concluded that the likelihood of sBCRL increased with the extent of surgery and radiation and compared with TM, allows earlier detection which support its use for posttreatment surveillance. This study is limited by a relatively short follow up period to determine progression to clinical lymphedema, as well as potential for bias due to authors' affiliation with the manufacturer of the device.

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

A Hayes Health Technology Assessment (HTA), Bioelectrical Impedance (Bioimpedance) Analysis for Assessment of Lymphedema states that the clinical performance and accuracy of multiple frequency bioimpedance analysis (MFBIA), also referred to as bioimpedance spectroscopy (BIS) is similar to or somewhat lower than the accuracy of other techniques for lymphedema (LE) diagnosis, prediction of LE development, and guidance of treatment. With regard to guiding management of

patients at risk for LE, the evidence does not provide conclusive evidence of clinical utility and additional studies are needed on the clinical role of BIS relative to established techniques (2020; updated 2023).

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

Ridner et al. (2019) reported interim results from an ongoing RCT (PREVENT) 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.

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

Whitworth and Cooper (2018- included in Hayes health technology assessment, and Shah 2021 study) 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.

Bundred et al. (2015-included in Hayes health technology assessment) conducted a multi-center, case series study comparing multi-frequency BIS with perometry in the prediction of lymphedema. Women who were undergoing axillary node clearance had preoperative and postoperative measurements of arm volume by both methods. The primary outcome measure was the incidence of lymphedema (defined as a ≥ 10% arm volume increase compared to the contralateral arm by perometer) at 2- and 5-years following node clearance. A total of 612 women had 6 months of follow-up data, and the 1-month postoperative measurement was used as the baseline measurement. At 6 months, the perometer detected 31 patients with lymphedema vs. 53 patients detected with BIS. By 6 months, 89% of those with no lymphedema reported at least one symptom. There was moderate correlation between perometer and BIS at 3 months ($R^2 = 0.40$) and 6 months ($R^2 = 0.60$), with a sensitivity of 73%

and specificity of 84%. Univariate and multivariate analyses showed a threshold for early intervention of ≥ 5 to < 10% (p = 0.03). The authors concluded that even though the threshold for early intervention was ≥ 5 to < 10% symptoms alone do not predict lymphedema and that a modest correlation between methods at 6 months indicates that arm volume measurement remains the gold standard, although longer follow-up is also needed.

Erdogan et al. (2015, included in the Shah 2021 study) 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.

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (2023) recommend educating patients on lymphedema, monitoring for the condition, and referring for management as needed. Pretreatment measurement of both arms as a baseline for patients with risk factors for lymphedema should be considered. The use of BIS is not specifically mentioned.

The NCCN Guidelines for Survivorship states that early detection/diagnosis and early referral are key for optimal lymphedema management. Stages 0 and 1 are reversible, whereas stages 2 and 3 are less responsive to treatment. Survivors at risk of lymphedema should be regularly screened for lymphedema by symptoms assessment, clinical exam and if available, bioimpedance spectroscopy.

The 2011 National Lymphedema Network position statements states that all patients have pretreatment measurements of both arms. Post treatment measurements should be done on both arms at each visit with symptoms assessment for swelling, heaviness, and/or tightness in the affected arm/arms, and at-risk chest and truncal areas using consistent measurement methods. Circumferential tape measurements are acceptable when made with a flexible, non-elastic Gulick II (or similar) tape measure, and bioelectrical spectroscopy (BIS) or infrared perometry are suggested as alternative or adjunct methods.

The 2017 clinical practice guideline for the diagnosis of upper quadrant lymphedema secondary to cancer from the Oncology Section of the American Physical Therapy Association (Levenhagen et al.) makes the following recommendation for bioimpedance analysis:

- Bioimpedance analysis should be used to detect lymphatic transport impairments and diagnose subclinical and early stage lymphedema in patients at risk for breast cancer–related lymphedema (Stage 0 and 1). Evidence Quality: Level II reliability, validity and diagnostic accuracy; Recommendation Strength: Grade B.
    - L-Dex score of > 7.1 should be used as a diagnostic criteria for breast cancer–related lymphedema when no preoperative assessment is available. Evidence Quality: Level II diagnostic accuracy; Recommendation Strength: Grade B.
    - L-Dex score > 10 above preoperative baseline measures should be used as diagnostic criteria. Evidence Quality: Level II diagnostic accuracy; Recommendation Strength: Grade B.
- In moderate to late stage breast cancer–related lymphedema, as fibrosis and tissue changes occur, BIA may be utilized as a diagnostic tool; however, clinicians must be aware of the potential for decreasing extracellular fluid even with increased tissue volume. Evidence Quality: Level II diagnostic accuracy; Recommendation Strength B.

The U.S. Food and Drug Administration (FDA) cleared the MoistureMeterD (Delfin Technologies, Ltd.) under its 510(k) premarket notification process on August 11, 2017. The device is used to measure local fluid in tissues. For additional information, refer to the following website: https://www.accessdata.fda.gov/cdrh_docs/pdf14/K143310.pdf. (Accessed March 29, 2023)

The U.S. Food and Drug Administration (FDA) cleared the SOZO™ Impedance Plethysmograph (ImpediMed, Carlsbad, CA) under its 510(k) premarket notification process on August 11, 2017. The device is indicated for use on adults and utilizes impedance ratios that are displayed as an L-Dex ratio as an aid to the clinical assessment of unilateral lymphedema of the arm and leg in women and the leg in men. It is only indicated for patients who will have or who have had lymph nodes, from the axillary and pelvic regions, either removed, damaged or irradiated. For additional information, refer to the following website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K180126. (Accessed March 29, 2023)

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

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

## Clinical Evidence

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

Calafiore et al. (2022) conducted a systematic review and meta-analysis to assess the efficacy of Robot-assisted gait rehabilitation (RAGT) for gait recovery in subacute stroke survivors. A search of studies from inception through January 18, 2021, was performed to identify randomized controlled trials (RCTs) presenting stroke survivors in subacute phase (≤ 6 months) as participants; exoskeleton robotic devices as intervention; conventional rehabilitation as a comparator; and gait assessment,

through qualitative scales, quantitative gait scales or quantitative parameters, as outcome measures. In addition, a meta-analysis of the mean difference in the functional ambulation category (FAC) via the random effect method was performed. Out of 3188 records, 14 RCTs were analyzed in this systematic review. The 14 studies have been published in the last 14 years (from 2006 to 2021) and included 576 stroke survivors, of which 306 received RAGT, and 270 underwent conventional rehabilitation. Lokomat® robotic rehabilitation device was the most investigated robotic exoskeleton by the RCTs included (n = 9). The meta-analysis demonstrated an insignificant difference of -0.09 in FAC (95% CI: -0.22.0.03) between Lokomat® and conventional therapy. According to the PEDro scale, 11 (78.5%) were classified as good-quality studies, two as fair-quality studies (14.3%), and one as a poor-quality study (7.1%). The authors concluded the findings showed that RAGT might have a potential role in gait recovery in subacute stroke survivors. However, further RCTs comparing the efficacy of RAGT with conventional physical therapy are still warranted in the neurorehabilitation field. This systematic review provides information on the efficacy of RAGT in allowing subacute stroke patients to perform high-intensity gait training with a lower physical burden on PRM professionals. Limitations of this systematic review include the lack of meta-analysis for all the RAGT interventions assessed. Except for studies that investigated the Lokomat® (with FAC as outcome), all the other RCTs were heterogeneous, adopting different systems for RAGT and studied different outcomes. All studies showed a high heterogeneity of protocol session and duration of intervention. Further investigation is needed before clinical usefulness of this equipment is proven.

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

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

Calabro et al. (2021) conducted a systematic review to determine the scope, quality, and consistency of guidelines for robotic lower limb rehabilitation after stroke, in order to provide clinical recommendations. Stroke rehabilitation guideline recommendations between January 1, 2010, and October 31, 2020, were reviewed. Two independent reviewers used the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, and brief syntheses were used to evaluate and compare the different recommendations, considering only the most recent version. From a total of 1219 papers screened, ten eligible guidelines were identified from seven different regions/countries. Four of the included guidelines focused on stroke management, the other six on stroke rehabilitation. Robotic rehabilitation is generally recommended to improve lower limb motor function, including gait and strength. Unfortunately, there is still no consensus about the timing, frequency, training session duration and the exact characteristics of subjects who could benefit from robotics. The authors concluded their systematic review shows that the introduction of robotic rehabilitation in standard treatment protocols seems to be the future of stroke rehabilitation. However, robot assisted gait training (RAGT) for stroke needs to be improved with new solutions and in clinical practice guidelines, especially in terms of applicability. Guidelines development groups have used different methods to

create recommendations, leading to variability in both quality and scope. International guidelines are needed to overcome this issue. Further research with randomized controlled trials is needed to validate these findings.

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

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

Rodríguez-Fernández et al. (2021) completed a systematic review of 87 clinical studies that gathered information and measured the outcomes of wearable lower-limb exoskeletons while gait training overground for individuals with neuromuscular impairments. There were 25 exoskeletons included with only 6 containing FDA approval and/or commercially available. The results of the literature survey revealed that wearable exoskeletons have potential for a number of applications including early rehabilitation, promoting physical exercise, and carrying out daily living activities both at home and the community. Likewise, wearable exoskeletons may improve mobility and independence in non-ambulatory people and may reduce secondary health conditions related to sedentariness. However, the use of this technology is still limited by heavy and bulky devices, which require supervision and the use of walking aids. In addition, evidence supporting their benefits is still limited to short-intervention trials with few participants and diversity amongst clinical protocols. Wearable lower-limb exoskeletons for gait rehabilitation are still in the early stages of development and RCTs are needed to demonstrate their clinical efficacy.

Awad et al. (2020) conducted a multi-site clinical trial that included 44 patients with post-stroke hemiparesis to study the safety, reliability and feasibility of the ReWalk Restore soft robotic exosuit for post-stroke gait rehabilitation. The patients trained for five days with the Restore soft exosuit and 16 patients required an assistive device (Ankle foot orthosis (AF0), cane, ankle brace, walker) on the treadmill and overground. During the five days of training, each visit consisted of 20 minutes of overground and 20 minutes treadmill walking practice while wearing the Restore exosuit motor at the waist as it transmitted mechanical forces to points located proximally attached around the calf and distally to a shoe insole. During the study eight patients dropped out for various reasons. Of the 36 patients that finished the study, they found the Restore soft exosuit clinically feasible, less than 10% had safety issues ranging from mild to severe, no falls, and the device malfunctioned for 11.6%. After five days of training 61% of the patients increased their maximum walking speed. The authors concluded that the ReStore soft exosuit is safe and reliable for use 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.

Moucheboeuf et al. (2020) conducted a meta-analysis to investigate the effects of robot-assisted gait training after stroke and to elucidate the observed heterogeneity of results in previous meta-analyses. All RCTs investigating exoskeletons or end-effector devices in adult patients with stroke were searched in databases from inception to November 2019, as were bibliographies of

previous meta-analyses, independently by 2 reviewers. Variables collected before and after the rehabilitation program included gait speed, gait endurance, Berg Balance Scale (BBS), Functional Ambulation Classification (FAC) and Timed Up and Go scores. In addition, data on randomization method, blinding of outcome assessors, drop-outs, intention (or not) to treat, country, number of participants, disease duration, mean age, features of interventions, and date of outcomes assessment were extracted. A total of 33 studies involving 1466 participants were included. On analysis by subgroups of intervention, as compared with physiotherapy alone, physiotherapy combined with body-weight support training and robot-assisted gait training conferred greater improvement in gait speed [+ 0.09m/s, 95% confidence interval (CI) 0.03 to 0.15; p = 0.002], FAC scores (+ 0.51, 95% CI 0.07 to 0.95; p = 0.022) and BBS scores (+ 4.16, 95% CI 2.60 to 5.71; p = 0.000). A meta-regression analysis suggested that these results were underestimated by the attrition bias of studies. The authors concluded that the use of RAGT associated with CT and BWST would improve the efficiency of walking rehabilitation after stroke, with significant gait speed, FAC and BBS improvements. The findings of this study need to be validated by well-designed studies. Further investigation is needed before the clinical usefulness of this procedure is proven.

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

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

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

is an adjunct therapy for physical and functional recovery for patients with SCI. Future high-quality studies are warranted to investigate the effects of robot-assisted training on functional and cardiopulmonary recovery of patients with SCI.

Fisahn et al. (2016) completed a systematic review to determine if powered exoskeletons are effective as assistive and rehabilitation devices in improving locomotion in patients with SCI. Eleven publications were included in the review, 10 utilized the robotic exoskeleton Lokomat and the remaining study utilized the robotic exoskeleton MBZ-CPM1 [ManBuZhe (TianJin) Rehabilitation Equipment Co. Ltd., PR China]. Nine of the included randomized trials were of parallel design, and 2 were of crossover design. Most studies were of moderately high risk of bias. The authors of the review identified no comparison studies evaluating exoskeletons as an assistive device. Nine comparison studies (11 publications) evaluated the use of exoskeletons as a rehabilitative device. The 10-meter walk test velocity and Spinal Cord Independence Measure scores showed no difference in change from baseline among patients undergoing exoskeleton training compared with various comparator therapies. The remaining primary outcome measures of 6-minute walk test distance and Walking Index for Spinal Cord Injury I and II and Functional Independence Measure–Locomotor scores showed mixed results, with some studies indicating no difference in change from baseline between exoskeleton training and comparator therapies, some indicating benefit of exoskeleton over comparator therapies, and some indicating benefit of comparator therapies over exoskeleton. The authors of this review concluded that there is no data to compare locomotion assistance with exoskeleton versus conventional knee-ankle-foot orthoses (KAFOs). The authors also concluded that there is no consistent benefit from rehabilitation using an exoskeleton versus a variety of conventional methods in patients with chronic spinal cord injury and that trials comparing later-generation exoskeletons are needed.

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

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

## *Clinical Practice Guidelines*

### American Heart Association/American Stroke Association (AHA/ASA)

Guidelines on adult stroke rehabilitation and recovery published by the AHA and ASA state that no benefit was seen with robotic-based interventions compared with more traditional approaches. Robot-assisted movement training to improve motor

function and mobility after stroke in combination with conventional therapy may be considered. However, further studies are needed to clarify the optimal device type, training protocols, and patient selection to maximize benefits (Winstein, et al., 2016).

### National Institute for Health and Care Excellence (NICE)

According to NICE's guideline (2020) on stroke rehabilitation in adults, the standard of care for managing movement difficulties after stroke includes physiotherapy and fitness, strength and repetitive task training. Walking therapy is recommended for people who have had a stroke and who are able to walk, with or without assistance. Electromechanical gait training should only be used as part of a research study.

### U.S. Department of Veterans Affairs and U.S. Department of Defense (VA/DoD)

A VA/DoD joint clinical practice guideline for rehabilitation after stroke states that evidence supporting the use of robotics for stroke rehabilitation is weak. The quality of current evidence suggests offering robot-assisted movement therapy as an adjunct to conventional therapy in patients with deficits in upper-limb function to improve motor skill. In addition, there is insufficient evidence to recommend for or against the use of robotic devices during gait training (Sall et al., 2019).

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| Code | Description |
|---|---|
| A4542 | Supplies and accessories for external upper limb tremor stimulator of the peripheral nerves of the wrist |
| E0734 | External upper limb tremor stimulator of the peripheral nerves of the wrist |

**External upper limb tremor stimulators of the peripheral nerves of the wrist and the related monthly supplies to treat essential tremor or postural and kinetic hand tremor symptoms in adults with Parkinson's disease 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™ and Cala kIQ™) deliver non-invasive electrical stimulation to the peripheral nerves of the wrist (Cala Health, Inc. website).

In an ECRI clinical evidence assessment (2022; updated 2023), Cala Trio Wrist-worn Neuromodulation Therapy for Essential tremor was explored. ECRI reviewed one multicenter, double-blind randomized controlled trial (RCT) (Pahwa et al. 2019), one single-center, double-blind RCT (Lin et al. 2018), one prospective, multicenter, before-and-after study (Isaacson et al. 2020), one prospective, single-center, before-and-after study (Yu et al. 2020), and one retrospective, before-and-after study (Brillman et al. 2022). Studies assessing all Cala device generations were included in the review, as ECRI determined minor design changes were unlikely to affect clinical outcomes. ECRI concluded the Cala Trio is safe and appears to reduce tremor severity and improve activities of daily living in some patients with essential tremor at up to three-month follow-up. However, ECRI noted this conclusion was based on low-quality evidence from two small RCTs and two before-and-after studies. ECRI also noted the study findings do not permit firm conclusions on whether the Cala Trio's clinical benefits are sustained beyond three months. There were also no published studies comparing the Cala Trio with other treatments for essential tremor.

In a Hayes evolving evidence review (2022; updated 2023), Cala Trio for treatment for essential tremor was found to have minimal clinical studies, no systematic reviews, and guidelines with a weak support for the treatment. Clinical studies reviewed for the use of Cala Trio found one poor quality RCT which suggests some benefits over sham but no clear benefits or advantages (Pahwa et al 2019). Another poor quality pre and posttest study suggested benefits after 3 months of treatment, however the evidence does not address whether the device confers incremental gain over pharmacotherapy or whether its performance is inferior, equivalent, or improved versus alternative adjunctive treatment (Isaacson et al 2020).

Brillman et al. (2022, included in the Hayes and ECRI review) conducted a retrospective, post-marketing, observational study of 321 subjects (average age 71 years, 32% female) diagnosed with essential tremor to evaluate the real-world effectiveness of transcutaneous afferent patterned stimulation (TAPS) delivered by the Cala Trio wrist-worn device. The analysis included subjects who received TAPS therapy for at least 90 days and had a minimum of 10 sessions documented in device logs. Demographic information and tremor history were obtained from the prescription used to obtain the Cala Trio and a voluntary survey sent to subjects after 90 days of TAPS therapy. Usage and effectiveness information were compiled from Cala Trio device logs. These device logs provided session timestamps, device-prompted postural hold tremor accelerometry measurements, and self-ratings of post-session tremor impression (improved, no change, worsened). Of the total number of subjects, 216 had tremor measurements available for analysis and 69 completed the survey. The total use period of TAPS therapy by subjects ranged from 90 to 663 days, with 28% of patients having used the device for greater than one year. Subjects used the Cala Trio 5.4 ±4.5 (mean ±1 standard deviation) times per week. TAPS therapy was found to reduce tremor power, calculated using device postural hold accelerometry data, by 71% (geometric mean) across all sessions. Additionally, 59% of subjects reported experiencing a greater than 50% tremor reduction after TAPS therapy. Of the subjects who returned the voluntary survey, 84% reported improvements in eating, drinking, or writing; and 65% reported improvements in quality of life. Device-related safety complaints were reported as consistent with adverse events reported in prior clinical trials. There were no severe safety events were reported. The authors concluded the study results confirmed TAPS therapy as a safe and effective treatment for essential tremor. However, multi-year safety and effectiveness would be valuable. The authors noted some potential study confounders including the 90-day inclusion criteria and subject self-reported usage and effectiveness analyses could have introduced bias; only subjects who chose to complete the device-prompted postural holds and tremor improvement ratings were included in the analysis and a number of subjects and sessions were not analyzed for effectiveness due to data that was missing or of poor-quality; subjects were prompted to perform postural holds for measuring tremor only immediately

before and after stimulation sessions, thus, tremor measurements did not allow for characterization of duration of post-stimulation treatment effect; TAPS efficacy was captured after 1+ years of repeated use for some subjects, which was greater than 90-day efficacy established in prior clinical trials; factors such as caffeine, alcohol and medications are not controlled for in real-world usage; wrist-based accelerometry measures the joint-interaction torques produced by the hand tremor and not the hand tremor itself; and key patient-reported outcomes on activities of daily living were only assessed once and only by the voluntary survey, which may have been subject to recency and respondent-selection bias.

Isaacson et al. (2020, included in the Hayes and ECRI review) performed a prospective, multi-center, open-label, post-clearance, single-arm study to evaluate the efficacy and safety of Transcutaneous Afferent Patterned Stimulation (TAPS) delivered by an FDA-cleared wrist-worn device (Cala Health, Inc.). A total of 263 subjects were enrolled at 26 study sites. Of those, 205 subjects completed the study. Subjects were instructed to use the wrist-worn device for 40 minutes, twice daily, for three months. The co-primary efficacy endpoints were clinician-rated Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) and (patient-rated Bain & Findley Activities of Daily Living (BF-ADL) dominant hand scores. These endpoints were considered met ($p < 0.0001$), with 62% (TETRAS) and 68% (BF-ADL) of “severe” or “moderate” subjects improving to “mild’ or ‘slight”. Wrist-worn accelerometer recordings of tremor power showed that 92% of subjects improved and 54% of subjects experienced ≥ 50% improvement. Clinical Global Impression (CGI-I) scores showed that clinicians reported tremor improvement in 68% of patients. Patient Global Impression (PGI-I) scores showed 60% of subjects self-reported tremor improvement. Quality of Life in Essential Tremor (QUEST) surveys completed by subjects also showed improvement ($p = 0.0019$). Device-related adverse events occurred in 18% of subjects and included wrist discomfort, skin irritation, and pain. There were no device-related serious adverse events reported. The authors concluded that non-invasive neuromodulation therapy used at home over three months is safe and effective to treat patients with ET. This study had some limitations including the open-label, single-arm design; clinical raters were unblinded; while there were statistically significant reductions across the TETRAS and BF-ADL ratings, the extent of those reductions varied; and 58 subjects did not complete the study.

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

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

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| Code | Description |
|---|---|
| E2001 | 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.

Beeson et al. (2023) conducted a prospective, observational, quasi-experimental study to examine the effectiveness of an external female urinary management system (external urinary device for female anatomy [EUDFA]) in critically ill women unable to self-toilet and to identify rates of indwelling catheter use, catheter-associated urinary tract infections (CAUTIs), urinary incontinence (UI), and incontinence-associated dermatitis (IAD) before and after the introduction of the EUDFA. The sample included 50 adult female patients in 4 critical/progressive care units using an EUDFA at a large academic hospital in the Midwestern United States. All adult patients in these units were included in the aggregate data. The device studied was the Sage PrimaFit External Urine Management System for the Female Anatomy (Sage Products, a business unit division of Stryker, Cary, Illinois). This system is placed in the perineal area between the labia, against the urethra conforming to the female anatomy, and connected to low continuous suction providing a sump mechanism to divert urine into an external canister. Prospective data collected from the adult female patients over 7 days included urine diverted from the device to a canister and total leakage. Aggregate unit rates of indwelling catheter use, CAUTIs, UI, and IAD were retrospectively examined during 2016, 2018, and 2019. Means and percentages were compared using t tests or chi-square tests. EUDFA successfully diverted 85.5% of patients' urine. Indwelling urinary catheter use was significantly lower in 2018 (40.6%) and 2019 (36.6%) compared with 2016 (43.9%) ($p < .01$). The rate of CAUTIs was lower in 2019 than in 2016, but not significantly (1.34 per 1000 catheter-days vs 0.50, $p = .08$). The percentage of incontinent patients with IAD was 69.2% in 2016 and 39.5% in 2018-2019 ($p = .06$). The authors concluded that EUDFA was effective in diverting urine from critically ill female incontinent patients and indwelling catheter utilization. This study was limited by impacts of the COVID-19 pandemic, which interrupted and complicated patient enrollment and imposed significant burdens on staff. Additionally, data on IAD prevalence reflect only a single month in each observation year. Finally, the study time frame coincided with a period when the quality focus was on decreasing use of indwelling catheters and implementing a nurse-driven internal urinary catheter removal protocol. While the use of an effective EUDFA played a pivotal role in these initiatives, not all reductions in indwelling catheter use or CAUTIs can be attributed to the EUDFA. Further research with randomized controlled trials is needed to validate these findings.

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

Lem et al. (2022) conducted a retrospective study to compare CAUTI rate and the median number of days an indwelling urethral catheter (IUC) was used before and after availability of this female external urinary catheter device (EUCD) for surgical patients. This retrospective analysis consisted of adult female surgical patients admitted to a single academic institution who

received an IUC and/or EUCD was performed. Patients who received an IUC three months before (PRE) EUCD availability (08/2017 - 10/2017) were compared to patients receiving an IUC and/or EUCD 12 months after (POST) (11/2017 - 11/2018). Of 906 surgical patients receiving an IUC/EUCD, 127 received an EUCD in the POST cohort. Compared to the PRE, the POST had a higher rate of CAUTIs (infections per 1000 catheter days, 11.2 vs. 4.6, p = 0.017) and overall UTI rate (infections per 1000 catheter days, 5.4 vs. 4.8, p = 0.036), whereas IUC days were similar between cohorts (median, two vs. two days, p = 0.18). The POST cohort rate of EUCD UTI was 4.6 infections per 1000 device days. The authors concluded while EUCDs appear to be a promising alternative to IUCs for female surgical patients, this study found increased CAUTIs after introduction of an EUCD. Further research is needed to clarify if female EUCDs are effective in decreasing CAUTI prior to widespread adoption. This may be related to selection bias, with EUCDs being ordered for patients who would not have otherwise received any urinary collection device. The dermatologic injury from the pressure and stiffness of the device also should be taken into account when considering using an EUCD. This study suggests that future prospective randomized controlled trials with explicit indications for EUCD usage are needed to validate these findings.

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

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

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

Eckert et al. (2020) conducted a quality improvement, single center study comparing the use of an FEUC device with wall suction as an alternative to IDC. The outcomes were to determine if FEUCs reduced the risk of CAUTI rates. The FEUC device was trialed September 2015 through December 2015, using 60 FEUC devices on 30 female patients. Data collection on these patients for one year period after use of FEUC. In 2015, before the use of the FEUC device, the baseline female IDC utilization rate was 31.7% (7181 IDC device-days/22,656 patient stay days) and the female CAUTI rate was 1.11 (8 cases/7181 IDC device-days) per 1000 stay days. After implementing use of the FEUC device both IDC utilization and CAUTI rates declined. In 2016, the IDC utilization rate was 29.7% (p = .000) and the CAUTI rate was 0% (p =.005). In 2017 there was a reduction in IDC utilization rates of 26% (p = .000) but the CAUTI rate of 0.90% was not significantly different from the prior year rate (p = .726). The authors concluded they need to continue to prioritize the use of FEUCs over IDCS. Limitations of this study include lack of consistent sample size, short follow-up and lack of equal comparisons of FEUC and IDC patient usage.

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| Code | Description |
|---|---|
| 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 *Radiology & Cardiology Clinical Guidelines* at UHCprovider.com > Prior Authorization and Notification > Radiology Prior Authorization and Notification. (Accessed October 19, 2023)

## Clinical Evidence

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

On February 18, 2013, Oxford Performance Materials (OPM) received Food and Drug Administration (FDA) 510(k) clearance for the OsteoFab™ Patient Specific Cranial Device (OPSCD). OsteoFab is OPM's brand for Additively Manufactured (also called 3D Printing) medical and implant parts produced from polyetheretherketone (PEEK) polymer. Refer to the following for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf12/k121818.pdf. (Accessed April 28, 2023)

On January 19, 2017, the FDA granted OssDsign Cranial Patient-specific Implant (OssDsign AB), (Uppsala, Sweden) 510(k) marketing clearance for its three-dimensional (3-D) printed OssDsign® Cranial PSI (patient-specific implant). The customized implant is indicated for non-load-bearing applications to reconstruct cranial defects in adults for whom cranial growth is complete and with an intact dura with or without duraplasty. The OssDsign Cranial PSI is made from a calcium phosphate–based ceramic material, reinforced by a titanium skeleton. The implant's interconnecting tile design purportedly allows fluid movement through the device. Refer to the following for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf16/k161090.pdf. (Accessed April 28, 2023)

In a 2021 ECRI Clinical Evidence Assessment on AccuShape PEEK, patient-specific Cranial Implants (MedCAD) for Cranial reconstruction were evaluated. The report focused on determining the product's safety and efficacy for cranial reconstruction. No published studies addressed the technologies safety and efficacy for cranial reconstruction.

In a 2019 ECRI product brief, OssDsign AB for Cranial Reconstruction was assessed. The authors found significant limitations to the body of evidence. Limitations include small sample size, retrospective design, lack of control, randomization, blinding, lack of comparison, single-center studies, and studies conducted in different countries. Longer follow-up times are necessary to determine outcome measures to assess safety and efficacy.

Maricevich et al. (2019) evaluated the symptomatic and aesthetic improvement of patients with cranial defects secondary to decompressive craniectomies after cranial reconstruction with customized polymethyl methacrylate (PMMA) prostheses produced by 3D impression molds. This prospective study included 63 patients who underwent cranioplasties that were performed using customized PMMA prosthesis produced by 3D impression molds. All patients underwent a functional and aesthetic evaluation questionnaire in the preoperative period and in the sixth postoperative month. The mean area of the defect was 147 $cm^2$. The mean postoperative follow-up of the patients was 21 months, ranging from 6 to 33 months. Fifty-five patients attended the 6-month postoperative consultation. All patients presented symptomatic improvement after reconstruction of the skull. The infection rate was 3.2%, 4.8% of extrusion, 1.6% of prosthesis fracture, 7.9% of extradural hematoma, 17.4% of reoperation, 5% of wound dehiscence, and 4.8% of removal of the prosthesis. The authors concluded that cranioplasty, with a customized PMMA prosthesis, improved the symptoms and aesthetic appearance of all operated patients. The use of prototypes to customize cranial prostheses facilitated the operative technique and allowed the recovery of a cranial contour very close to normal. Limitations of this study include its case series design, the use of simple direct questions by the team that performed the cranioplasties to assess cognitive, motor, and QOL rather than the use of validated assessment tools, and the short follow-up period. Additional prospective, randomized controlled trials with longer follow-up are needed to examine the safety and efficacy of 3D printed cranial implants.

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

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

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

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| Code | Description |
|---|---|
| L8701 | Powered upper extremity range of motion assist device, elbow, wrist, hand with single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated |
| L8702 | Powered upper extremity range of motion assist device, elbow, wrist, hand, finger, single or double upright(s), includes microprocessor, sensors, all components and accessories, custom fabricated |

**The use of the upper limb orthotic known as the MyoPro™ is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy**.

## Clinical Evidence

MyoPro™ is a powered orthosis (brace) designed to help restore function to arms and hands paralyzed or weakened by CVA stroke, brachial plexus injury, cerebral palsy or other neurological or neuromuscular disease or injury. It works by reading the faint nerve signals (myoelectric signals) from the surface of the skin (fully noninvasive, no implants) then activating small motors to move the arm and hand as the user intends (no electrical stimulation) (Hayes, 2022).

A 2023 ECRI Clinical Evidence Assessment identified three case series and one case report 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, 2023) [Authors McCabe et al. (2019) and Peters et al. (2017)] which were previously cited in this policy are included in this study).

The current evidence does not indicate that the MyoPro orthosis (Myomo, Inc.) for upper extremity paralysis/paresis after stroke provides any additional benefit over repetitive task practice (RTP) alone. A report from Hayes (2023) on the MyoPro orthosis (Myomo, Inc.) identified minimal level of support for the device use following a review of five full-text clinical studies. In addition, there was no clear support for the use of the MyoPro device following an assessment of systematic reviews and practice guidelines or position statements.

Pundik et al. (2022) performed a prospective single arm mixed cohort interventional pilot study to evaluate MyoPro as a tool for motor learning-based therapy for individuals with chronic upper limb weakness. The study included thirteen individuals with chronic moderate/severe arm weakness due to either stroke (n = 7) or TBI (n = 6). The study consisting of two phases. The in-clinic phase included eighteen sessions (twice per week, 27 hours of face-to-face therapy) plus a home exercise program. The home phase included practice of the home exercise program. There was no control group. Outcomes were collected at baseline and at weeks 3, 5, 7, 9, 12, 15, and 18. Improvements were observed on Fugl-Meyer (+ 7.5 points). Gains were seen at week three, increased further through the in-clinic phase and were maintained during the home phase. Changes in the Modified Ashworth Scale, Range of Motion, and Chedoke Arm and Hand Activity Inventory were seen early during the in-clinic phase. Orthotic and Prosthetic User's Survey demonstrated satisfaction with the device throughout study participation. Both stroke and

TBI participants responded to the intervention. The authors concluded that MyoPro might be a useful tool for motor learning in individuals with chronic stroke and TBI. Reduction in impairment, gains in function, and satisfaction with the device were observed in response to the intervention. Further studies using a randomized controlled design is warranted.

A 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 thirty-four participants all exhibiting chronic, stable, moderate upper extremity impairment. Each participant was selected randomly for therapy consisting of Myomo combined with RTP, RTP only or Myomo therapy only. All three groups were supervised by a therapist and were administered therapies targeting their hemiparetic upper extremities. The primary outcome measure was the upper extremity section of the Fugl-Meyer Impairment Scale (FM); the secondary measurement was the Arm Motor Activity Test (AMAT). The therapies were one hour in duration, occurring 3 days/week for eight weeks. Upon completion of the study, all three groups showed a Fugl-Meyer (FM) score increase of + 2 points. On the secondary outcomes, the two groups that included Myomo had the same FM score increase of + 1 and the group with RTP only had a FM score increase of + 2.6. The authors concluded that outcomes in the group with Myomo and RTP were comparable to the RTP only group. Several limitations were identified by the authors, the device tested in the trial did not always work as expected and was somewhat cumbersome. Future studies would be strengthened by larger sample sizes.

A single-blinded randomized controlled pilot study was conducted by Park et al. (2020) to evaluate the differences in the clinical and kinematic outcomes between active-assistive and passive robotic rehabilitation among stroke survivors. Twenty stroke patients with upper extremity dysfunction were randomly assigned to the active-assistive robotic intervention (using an exoskeletal robot with robotic actuators; ACT) group or passive robotic intervention (using a passive exoskeletal robot without robotic actuators; PSV) group. Both groups completed twenty 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 et al. (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 but not limited to dietary deficiencies, allergies, hair loss, autism, schizophrenia, mood disorders, and environmental contamination. Hair has also been used as a specimen source for drug testing. Currently, in federally regulated programs, only urine specimens are collected for drug testing (SAMHSA). There are no widely accepted standards that specify how hair samples should be collected, stored, and analyzed, making results unreliable and inconsistent (ATSDR).

Hardy et al. (2021) conducted a pilot cohort study to compare the information obtained from the analysis of urine versus hair for exposure to pesticides. In ninety-three pregnant women, one urine and one hair sample were collected simultaneously. Samples were analyzed using GC-MS/MS analytical methods allowing for the detection of both parent pesticides and metabolites and designed to be as similar as possible between urine and hair for reliable inter-matrix comparison. Fifty-two biomarkers of exposure were targeted, including parents and metabolites of organochlorines, organophosphates, pyrethroids, carbamates, phenylpyrazoles and other pesticides. The results showed the number of different compounds detected ranged from 16 to 27 (median = 22) in hair, and from 3 to 22 (median = 12) in urine. In hair, 24 compounds were found in > 40% of the individuals, whereas only 12 compounds presented the same frequency of detection in urine. Among the chemicals detected in > 80% of both hair and urine samples, only one (pentachlorophenol) showed a signification correlation between hair and urine concentrations. The authors concluded that these results highlight multiple exposures and suggest that hair provides more

comprehensive information on pesticide exposure than urine analysis and supports the relevance of hair analysis in future epidemiological studies investigating association between exposure and adverse health effects.

In a 2019 systematic review and meta-analysis, Huang et al. sought to identify whether magnesium levels are lower in children with ADHD. A total of twelve studies were included. The results showed magnesium levels in the hair of children diagnosed with ADHD were significantly lower than those in controls (k = 4, Hedges' g = -0.713, 95% CI = -1.359 to -0.067, p = .031). In this meta-analysis, the authors found that children diagnosed with ADHD have lower serum and hair magnesium levels than children without ADHD. The authors concluded that further study is needed to investigate the behavioral influence on ADHD due to lower magnesium levels, the association between brain and serum magnesium levels, and the effects brought about by larger longitudinal cohort studies.

Khajuria et al. (2018) conducted a review designed to investigate the efficacy of chromatography for detection of drugs of abuse in hair. A comprehensive review of articles from last two decades on hair analyses via PubMed and similar resources was performed. The results showed a hair sample may be chosen over traditional biological samples such blood, urine, saliva or tissues due to its inimitable ability to provide a longer time frame for drug detection. Its collection is almost non-invasive, less cumbersome and does not involve any specialized training/expertise. Recent advances in analytical technology have resulted in better sensitivity, reproducibility and accuracy, thus providing a new arena of scientific understanding and test interpretation. The authors concluded that although recent studies have yielded insights into drug binding and drug incorporation in hair, the major challenge in hair analysis lies in the interpretation of results, which may be affected by external contamination and thus lead to false positives. Therefore, there is a need for more sensitive and selective analysis methods to be developed.

Mikulewicz et al. (2013) completed a systematic review to investigate the reference values of minerals in human hair. The five studies that met inclusion criteria reported reference ranges for the content of elements in hair: macro elements, microelements, toxic elements and other elements. Reference ranges were elaborated for different populations in the years 2000–2012. The analytical methodology differed, in particular sample preparation, digestion and analysis, as a result, the levels of hair minerals reported as reference values varied. The authors concluded standardization of procedures and detailed methodology are needed to validate hair mineral analysis. Only then it would be possible to provide meaningful reference ranges and take advantage of the potential that lies in Hair Mineral Analysis (HMA) as a medical diagnostic technique.

Wolowiec et al. (2013) conducted a systematic review on the relation between the mineral composition of hair and physical or mental disorders. Sixty-six studies were included in the review. Most of the studies reported that there exists a correlation between deficiency or excess of some elements in hair and occurrence of some diseases, such as: autism, cancer, hypertension, myocardial infarction, kidney disease and diabetes mellitus. However, not all results were consistent. The authors concluded that there is a need to standardize sample preparation procedures, in particular washing and mineralization methods.

A 2011 guideline for food allergy in children and young people from the National Institute for Health and Care Excellence (NICE) recommends against the use of hair analysis in the diagnosis of food allergy.

In their 2010 guidelines, the National Institute of Allergy and Infectious Diseases (NIAID) states that hair analysis for food allergies is non-standard and unproven. Additionally, the utility of these tests has not been validated for the diagnosis of FA and may result in false positive or false negative diagnoses.

In a 2014 joint practice parameter by the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), and the Joint Council of Allergy, Asthma & Immunology (JCAAI), hair analysis is listed as an unproven test for the evaluation of food allergies.

A practice parameter from the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology Society states that there is insufficient evidence to support the use of hair analysis for the diagnosis and evaluation of autism (Filipek et al., 2000. Reaffirmed August 2014).

In 2013, the American Society of Addiction Medicine (ASAM) published a document titled, Drug Testing: A White Paper of the American Society of Addiction Medicine. This document indicates that hair sample benefits include difficulty in falsifying sampling and a longer period of detection. However, the ASAM noted that recent exposures cannot be detected in hair

samples, and hair coloring can cause modest degradation of drugs in the matrix. The ASAM notes that one distinct disadvantage to hair testing is that some drug classes (e.g., benzodiazepines) are poorly detected in hair.

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# Policy History/Revision Information

| Date | Summary of Changes |
|---|---|
| 04/01/2024 | **Notice of Revision**: The following summary of changes has been modified. Revisions to the previous policy update announcement are outlined in red below. Please take note of the amended updates to be applied on **Apr. 1, 2024**.<br><br>**Coverage Rationale**<br>• Added coverage guidelines for:<br>***Automated Visual Evoked Potentials (VEPs) for Visual Acuity Screening (CPT code 0333T)***<br>○ Added language to indicate the use of automated visual evoked potentials (VEPs) for visual acuity screening is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy<br>***Electrocardiographic Body Surface Mapping (CPT codes 0695T and 0696T)***<br>○ Added language to indicate electrocardiographic body surface mapping is unproven and not medically necessary for the evaluation or treatment of cardiac disorders |

| Date | Summary of Changes |
|---|---|
| | ***Eye-Movement Analysis Without Spatial Calibration (CPT code 0615T)***<br>○ Added language to indicate eye-movement analysis without spatial calibration is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy<br>***Implantable Cardioverter-Defibrillator System with a Substernal (Extravascular) Electrode (CPT codes 0571T, 0572T, 0573T, 0574T, 0575T, 0576T, 0577T, 0578T, 0579T, 0580T, and 0614T)***<br>○ Added language to indicate insertion, repositioning, programming, interrogation, and evaluation of implantable cardioverter-defibrillator system with a substernal (extravascular) electrode are considered unproven and not medically necessary due to insufficient evidence of efficacy<br>***Insertion of Iris Prosthesis (CPT/HCPCS codes 0616T, 0617T, 0618T, and C1839)***<br>○ Added language to indicate insertion of iris prosthesis is unproven and considered not medically necessary due to insufficient evidence of safety and/or efficacy<br>***Irreversible Electroporation (IRE) Ablation (CPT codes 0600T and 0601T)***<br>○ Added language to indicate:<br>▪ Percutaneous irreversible electroporation (IRE) ablation is unproven because there are insufficient studies supporting the safety and efficacy of the procedure and demonstrating improvement in health outcomes compared to other standard treatments<br>▪ Open irreversible electroporation (IRE) ablation is unproven due to insufficient clinical evidence of safety and efficacy<br>***Osteotomy, Humerus with Insertion of an Externally Controlled Intramedullary Lengthening Device (CPT code 0594T)***<br>○ Added language to indicate osteotomy, humerus, with insertion of an externally controlled intramedullary lengthening device, including intraoperative imaging, initial and subsequent alignment assessments, computations of adjustment schedules, and management of the intramedullary lengthening device, is considered unproven and not medically necessary due to insufficient evidence of efficacy<br>***Radiostereometric Analysis (RSA) (CPT codes 0347T, 0348T, 0349T, and 0350T)***<br>○ Added language to indicate radiostereometric analysis (RSA) is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy<br>***Remote Monitoring of an External Continuous Pulmonary Fluid Monitoring System (CPT codes 0607T and 0608T)***<br>○ Added language to indicate remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (e.g., ECG data), transmitted to a remote 24-hour attended surveillance center, as well as the analysis of data received and transmission of reports to the physician or other qualified health care professional, is unproven due to insufficient clinical evidence of safety and efficacy<br>***Sonosalpingography (CPT code 0568T)***<br>○ Added language to indicate sonosalpingography, when used with a mixture of saline and air to confirm fallopian tube occlusion, is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy<br>***Transcatheter Intracoronary Infusion of Supersaturated Oxygen in Conjunction with Percutaneous Coronary Revascularization during Acute Myocardial Infarction (CPT code 0659T)***<br>○ Added language to indicate transcatheter intracoronary infusion of supersaturated oxygen in conjunction with percutaneous coronary revascularization during acute myocardial infarction is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy<br>***Transcatheter Placement of Extracranial Vertebral Artery Stent(s) (CPT codes 0075T and 0076T)*** |

| Date | Summary of Changes |
|---|---|
| | ○ Added language to indicate transcatheter placement of extracranial vertebral artery stent(s) is considered unproven and not medically necessary due to insufficient evidence of efficacy<br>***Transluminal Peripheral Atherectomy of Visceral, Renal, Abdominal, or Brachiocephalic Arteries (CPT codes 0234T, 0235T, 0236T, and 0237T)***<br>○ Added language to indicate transluminal peripheral atherectomy of visceral, renal, abdominal, or brachiocephalic arteries is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy<br>• Revised guidelines for:<br>***Biomarker Panel Based Algorithmic Analysis Test to Screen for Colorectal Cancer or Advanced Adenomas (CPT code 0163U)***<br>○ Replaced reference to "BeScreened" with "BeScreened™-*CRC*"<br>***External Upper Limb Tremor Stimulators of the Peripheral Nerves of the Wrist (HCPCS codes A4542 and E0734)***<br>○ Added language to indicate external upper limb tremor stimulators of the peripheral nerves of the wrist and the related monthly supplies to treat postural and kinetic hand tremor symptoms in adults with Parkinson's disease are unproven and not medically necessary<br>○ Updated list of applicable HCPCS codes to reflect annual edits:<br>▪ Added A4542 and E0734<br>▪ Removed K1018 and K1019<br>***Myringotomy and Tympanostomy Tube Placement Under Iontophoresis Local Anesthesia (Tula) System (CPT code 0583T)***<br>○ Replaced reference to "Tube Placement Under Local Anesthesia (TULA) System" with "Tube Placement Under *Iontophoresis* Local Anesthesia (Tula) System"<br>• Updated list of applicable CPT/HCPCS codes for:<br>***Cardiac Resynchronization Therapy (CRT) with Wireless Left Ventricular (LV) Endocardial Pacing (CPT codes 0515T, 0516T, 0517T, 0518T, 0519T, 0520T, 0521T, 0522T, 0861T, 0862T, and 0863T)***<br>○ Added 0861T, 0862T, and 0863T *(annual edits)*<br>○ Revised description for 0517T, 0518T, 0519T, and 0520T *(annual edits)*<br>***Contact or Non-Contact Near-Infrared Spectroscopy (NIRS) (CPT codes 0640T and 0859T)***<br>○ Added 0859T *(annual edit)*<br>○ Removed 0641T and 0642T *(annual edits)*<br>○ Revised description for ~~0641T~~ 0640T *(annual edit)*<br>***PureWick™ Female External Catheter and the PureWick™ Urine Collection System (HCPCS code E2001)***<br>○ Added E2001 *(annual edit)*<br>○ Removed K1006 *(annual edit)*<br>***Transcutaneous Magnetic Stimulation (tMS) (CPT codes 0766T and 0767T)***<br>○ Removed 0768T and 0769T *(annual edits)*<br>○ Revised description for 0766T and 0767T *(annual edits)*<br>• Removed guidelines for:<br>***Autologous Pancreatic Islet Cell Transplantation and Allogeneic Islet Cell Transplantation (CPT/HCPCS codes 0584T, 0585T, 0586T, 60659, G0341, G0342, and G0343)***<br>○ Refer to the Optum Clinical Guidelines titled Solid Organ Transplantation<br>***Cerebral Computed Tomography Perfusion (CTP) (CPT Code 0042T)***<br>○ CPT code 0042T no longer requires clinical review<br>***Fractional Carbon Dioxide Laser Treatment (CPT codes 0479T and 0480T)***<br>○ Refer to the Medical Policy titled *Light and Laser Therapy (for North Carolina Only)* |

| Date | Summary of Changes |
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| | ***Pulse-Echo Ultrasound Bone Density Measurement (CPT code 0508T)***<br>○ CPT code 0508T no longer requires clinical review *(annual edit)*<br>***Radiesse, Sculptra, Prolaryn, and Prolaryn Plus (HCPCS codes G0429, L8607, Q2026, and Q2028)***<br>○ HCPCS codes G0429, L8607, Q2026, and Q2028 no longer require clinical review<br>***Right Ventricular Leadless Pacemakers (CPT codes 33274 and 33275)***<br>○ CPT codes 33274 and 33275 no longer require clinical review<br>**Supporting Information**<br>• Updated *Clinical Evidence* and *References* sections to reflect the most current information<br>• Archived previous policy version CSNCT0535.05 |

# Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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