OMNIBUS CODES

Policy Number: ADMINISTRATIVE 212.43 T2

Effective Date: May 1, 2018

Table of Contents

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTRUCTIONS FOR USE</td>
<td>1</td>
</tr>
<tr>
<td>APPLICABLE LINES OF BUSINESS/PRODUCTS</td>
<td>1</td>
</tr>
<tr>
<td>BENEFIT CONSIDERATIONS</td>
<td>1</td>
</tr>
<tr>
<td>COVERAGE RATIONALE AND CLINICAL EVIDENCE</td>
<td>8</td>
</tr>
<tr>
<td>POLICY HISTORY/REVISION INFORMATION</td>
<td>127</td>
</tr>
</tbody>
</table>

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

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

APPLICABLE LINES OF BUSINESS/PRODUCTS

This policy applies to Oxford Commercial plan membership.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE SUMMARY

All CPT/HCPCS codes/services addressed in this policy are noted in the table below. Precertification with a Medical Director review is required for the following services and devices except where otherwise noted. Click the CPT code to be directed to the full coverage rationale and clinical evidence applicable to each of the listed procedures.

Related Policies

- Clinical Trials
- Experimental/Investigational Treatment
- Experimental/Investigational Treatment for NJ Plans

CPT® is a registered trademark of the American Medical Association
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0054T</td>
<td>Computer-assisted musculoskeletal surgical navigational orthopedic procedure, with image-guidance based on fluoroscopic images (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0055T</td>
<td>Computer-assisted musculoskeletal surgical navigational orthopedic procedure, with image-guidance based on CT/MRI images (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0085T</td>
<td>Breath test for heart transplant rejection</td>
</tr>
<tr>
<td>0100T</td>
<td>Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy</td>
</tr>
<tr>
<td>0174T</td>
<td>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)</td>
</tr>
<tr>
<td>0175T</td>
<td>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</td>
</tr>
<tr>
<td>0205T</td>
<td>Intravascular catheter-based coronary vessel or graft spectroscopy (e.g., infrared) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation, and report, each vessel (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0206T</td>
<td>Computerized database analysis of multiple cycles of digitized cardiac electrical data from two or more ECG leads, including transmission to a remote center, application of multiple nonlinear mathematical transformations, with coronary artery obstruction severity assessment</td>
</tr>
<tr>
<td>0207T</td>
<td>Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral</td>
</tr>
<tr>
<td>0263T</td>
<td>Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest</td>
</tr>
<tr>
<td>0264T</td>
<td>Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest</td>
</tr>
<tr>
<td>0265T</td>
<td>Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy</td>
</tr>
<tr>
<td>0266T</td>
<td>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)</td>
</tr>
<tr>
<td>0267T</td>
<td>Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)</td>
</tr>
<tr>
<td>0268T</td>
<td>Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)</td>
</tr>
<tr>
<td>0272T</td>
<td>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)</td>
</tr>
<tr>
<td>0273T</td>
<td>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</td>
</tr>
<tr>
<td>0330T</td>
<td>Tear film imaging, unilateral or bilateral, with interpretation and report</td>
</tr>
<tr>
<td>0335T</td>
<td>Extra-osseous subtalar joint implant for talotarsal stabilization</td>
</tr>
<tr>
<td>0341T</td>
<td>Quantitative pupillometry with interpretation and report, unilateral or bilateral</td>
</tr>
<tr>
<td>0346T</td>
<td>Ultrasound, elastography (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0355T</td>
<td>Gastrointestinal tract imaging, intraluminal (e.g., capsule endoscopy), colon, with interpretation and report</td>
</tr>
<tr>
<td>0356T</td>
<td>Insertion of drug-eluting implant (including punctual dilation and implant removal when performed) into lacrimal canaliculus, each</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>0358T</td>
<td>Bioelectrical impedance analysis whole body composition assessment, with interpretation and report</td>
</tr>
<tr>
<td>0377T</td>
<td>Anoscopy with directed submucosal injection of bulking agent for fecal incontinence</td>
</tr>
<tr>
<td>0381T</td>
<td>External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
</tr>
<tr>
<td>0382T</td>
<td>External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only</td>
</tr>
<tr>
<td>0383T</td>
<td>External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
</tr>
<tr>
<td>0384T</td>
<td>External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only</td>
</tr>
<tr>
<td>0385T</td>
<td>External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
</tr>
<tr>
<td>0386T</td>
<td>External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only</td>
</tr>
<tr>
<td>0387T</td>
<td>Transcatheter insertion or replacement of permanent leadless pacemaker, ventricular</td>
</tr>
<tr>
<td>0388T</td>
<td>Transcatheter removal of permanent leadless pacemaker, ventricular</td>
</tr>
<tr>
<td>0389T</td>
<td>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, review and report, leadless pacemaker system</td>
</tr>
<tr>
<td>0390T</td>
<td>Peri-procedural device evaluation (in person) and programming of device system parameters before or after a surgery, procedure or test with analysis, review and report, leadless pacemaker system</td>
</tr>
<tr>
<td>0391T</td>
<td>Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, leadless pacemaker system</td>
</tr>
<tr>
<td>0394T</td>
<td>High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed</td>
</tr>
<tr>
<td>0395T</td>
<td>High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed</td>
</tr>
<tr>
<td>0396T</td>
<td>Intra-operative use of kinetic balance sensor for implant stability during knee replacement arthroplasty (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0398T</td>
<td>Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed</td>
</tr>
<tr>
<td>0400T</td>
<td>Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia; one to five lesions</td>
</tr>
<tr>
<td>0401T</td>
<td>Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia ;six or more lesions</td>
</tr>
<tr>
<td>0408T</td>
<td>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</td>
</tr>
<tr>
<td>0409T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only</td>
</tr>
<tr>
<td>0410T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>0411T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only</td>
</tr>
<tr>
<td>0412T</td>
<td>Removal of permanent cardiac contractility modulation system; pulse generator only</td>
</tr>
<tr>
<td>0413T</td>
<td>Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)</td>
</tr>
<tr>
<td>0414T</td>
<td>Removal and replacement of permanent cardiac contractility modulation system pulse generator only</td>
</tr>
<tr>
<td>0415T</td>
<td>Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)</td>
</tr>
<tr>
<td>0416T</td>
<td>Relocation of skin pocket for implanted cardiac contractility modulation pulse generator</td>
</tr>
<tr>
<td>0417T</td>
<td>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</td>
</tr>
<tr>
<td>0418T</td>
<td>Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system</td>
</tr>
<tr>
<td>0421T</td>
<td>Transurethral waterjet ablation of prostate, including control of post-operative bleeding, including ultrasound guidance, complete (vasectomy, meototomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included when performed)</td>
</tr>
<tr>
<td>0424T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)</td>
</tr>
<tr>
<td>0425T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
</tr>
<tr>
<td>0426T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; stimulation lead only</td>
</tr>
<tr>
<td>0427T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; pulse generator only</td>
</tr>
<tr>
<td>0428T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only</td>
</tr>
<tr>
<td>0429T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
</tr>
<tr>
<td>0430T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; stimulation lead only</td>
</tr>
<tr>
<td>0431T</td>
<td>Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only</td>
</tr>
<tr>
<td>0432T</td>
<td>Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only</td>
</tr>
<tr>
<td>0433T</td>
<td>Repositioning of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
</tr>
<tr>
<td>0434T</td>
<td>Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea</td>
</tr>
<tr>
<td>0435T</td>
<td>Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session</td>
</tr>
<tr>
<td>0436T</td>
<td>Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study</td>
</tr>
<tr>
<td>0440T</td>
<td>Ablation, percutaneous, cryoablation, includes imaging guidance; upper extremity distal/peripheral nerve</td>
</tr>
<tr>
<td>0441T</td>
<td>Ablation, percutaneous, cryoablation, includes imaging guidance; lower extremity distal/peripheral nerve</td>
</tr>
<tr>
<td>0442T</td>
<td>Ablation, percutaneous, cryoablation, includes imaging guidance; nerve plexus or other truncal nerve (e.g., brachial plexus, pudendal nerve)</td>
</tr>
<tr>
<td>0443T</td>
<td>Real time spectral analysis of prostate tissue by fluorescence spectroscopy, including imaging guidance (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0444T</td>
<td>Initial placement of a drug-eluting ocular insert under one or more eyelids, including fitting, training, and insertion, unilateral or bilateral</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>0445T</td>
<td>Subsequent placement of a drug-eluting ocular insert under one or more eyelids, including re-training, and removal of existing insert, unilateral or bilateral</td>
</tr>
<tr>
<td>0465T</td>
<td>Suprachoroidal delivery of pharmacologic agent (does not include supply of medication)</td>
</tr>
<tr>
<td>0469T</td>
<td>Retinal polarization scan, ocular screening with on-site automated results, bilateral</td>
</tr>
<tr>
<td>0470T</td>
<td>Optical coherence tomography (OCT) for microstructural and morphological imaging of skin, image acquisition, interpretation, and report; first lesion</td>
</tr>
<tr>
<td>0471T</td>
<td>Optical coherence tomography (OCT) for microstructural and morphological imaging of skin, image acquisition, interpretation, and report; each additional lesion (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0472T</td>
<td>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</td>
</tr>
<tr>
<td>0473T</td>
<td>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</td>
</tr>
<tr>
<td>0489T</td>
<td>Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; adipose tissue harvesting, isolation and preparation of harvested cells including incubation with cell dissociation enzymes, removal of non-viable cells and debris, determination of concentration and dilution of regenerative cells</td>
</tr>
<tr>
<td>0490T</td>
<td>Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; multiple injections in one or both hands</td>
</tr>
<tr>
<td>0493T</td>
<td>Near-infrared spectroscopy studies of lower extremity wounds (e.g., for oxyhemoglobin measurement)</td>
</tr>
<tr>
<td>20985</td>
<td>Computer-assisted surgical navigational procedure for musculoskeletal procedures, image-less</td>
</tr>
<tr>
<td>22899</td>
<td>Unlisted procedure, spine (cooled radiofrequency ablation)</td>
</tr>
<tr>
<td>27299</td>
<td>Unlisted procedure, pelvis or hip joint (cooled radiofrequency ablation)</td>
</tr>
<tr>
<td>27599</td>
<td>Unlisted procedure, femur or knee (cooled radiofrequency ablation)</td>
</tr>
<tr>
<td>29799</td>
<td>Unlisted procedure – Kinesio taping</td>
</tr>
<tr>
<td>30999</td>
<td>Unlisted procedure, nose (when used to report rhinophototherapy, intranasal application of ultraviolet and visible light, bilateral)</td>
</tr>
<tr>
<td>31634</td>
<td>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</td>
</tr>
<tr>
<td>31647</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), initial lobe</td>
</tr>
<tr>
<td>31648</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), initial lobe</td>
</tr>
<tr>
<td>31649</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), each additional lobe (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>31651</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), each additional lobe [List separately in addition to code for primary procedure]</td>
</tr>
<tr>
<td>32994</td>
<td>Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation</td>
</tr>
<tr>
<td>33340</td>
<td>Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation</td>
</tr>
<tr>
<td>43206</td>
<td>Esophagoscopy, flexible, transoral; with optical endomicroscopy</td>
</tr>
<tr>
<td>43252</td>
<td>Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy</td>
</tr>
<tr>
<td>48160</td>
<td>Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>48999</td>
<td>Unlisted procedure, pancreas</td>
</tr>
<tr>
<td>53855</td>
<td>Insertion of a temporary prostatic urethral stent, including urethral measurement</td>
</tr>
<tr>
<td>55874</td>
<td>Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed</td>
</tr>
<tr>
<td>60659</td>
<td>Unlisted laparoscopy procedure, endocrine system</td>
</tr>
<tr>
<td>64999</td>
<td>Unlisted procedure, nervous system</td>
</tr>
<tr>
<td>69799</td>
<td>Unlisted procedure, middle ear [when used to report balloon dilation]</td>
</tr>
<tr>
<td>76120</td>
<td>Cineradiography/videoradiography, except where specifically included</td>
</tr>
<tr>
<td>76125</td>
<td>Cineradiography/videoradiography to complement routine examination (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>77424</td>
<td>Intraoperative radiation treatment delivery, x-ray, single treatment session</td>
</tr>
<tr>
<td>77425</td>
<td>Intraoperative radiation treatment delivery, electrons, single treatment session</td>
</tr>
<tr>
<td>77469</td>
<td>Intraoperative radiation treatment management</td>
</tr>
<tr>
<td>86849</td>
<td>Unlisted immunology procedure</td>
</tr>
<tr>
<td>92499</td>
<td>Unlisted ophthalmological service or procedure Multifocal electroretinography (mERG) and Pattern Electroretinography (PERG)</td>
</tr>
<tr>
<td>93668</td>
<td>Peripheral arterial disease (PAD) rehabilitation, per session [when used to report Supervised Exercise Therapy (SET)]</td>
</tr>
<tr>
<td>93702</td>
<td>Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)</td>
</tr>
<tr>
<td>93799</td>
<td>Unlisted cardiovascular service or procedure</td>
</tr>
<tr>
<td>94011</td>
<td>Measurement of spirometric forced expiratory flows in an infant or child through 2 years of age</td>
</tr>
<tr>
<td>94012</td>
<td>Measurement of spirometric forced expiratory flows, before and after bronchodilator, in an infant or child through 2 years of age</td>
</tr>
<tr>
<td>94013</td>
<td>Measurement of lung volumes [i.e., functional residual capacity (FRC), forced vital capacity (FVC), and expiratory reserve volume (ERV)] in an infant or child through 2 years of age</td>
</tr>
<tr>
<td>94799</td>
<td>Unlisted pulmonary service or procedure</td>
</tr>
<tr>
<td>96902</td>
<td>Microscopic examination of hairs plucked or clipped by the examiner (excluding hair collected by the patient) to determine telogen and anagen counts, or structural hair shaft abnormality</td>
</tr>
<tr>
<td>97139</td>
<td>Unlisted therapeutic procedure (specify) (when used to report Kinesio Taping)</td>
</tr>
<tr>
<td>97799</td>
<td>Unlisted physical medicine/rehabilitation service or procedure (when used to report physical medicine/rehabilitation services and/or procedures performed utilizing the robotic lower body exoskeleton device)</td>
</tr>
<tr>
<td>99174</td>
<td>Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with remote analysis and report</td>
</tr>
<tr>
<td>99177</td>
<td>Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with onsite analysis</td>
</tr>
<tr>
<td>B4104</td>
<td>Additive for enteral formula (e.g., fiber)</td>
</tr>
<tr>
<td>B9998</td>
<td>NOC for enteral supplies</td>
</tr>
<tr>
<td>E1399</td>
<td>Durable medical equipment, miscellaneous (when used to report robotic lower body exoskeleton device)</td>
</tr>
<tr>
<td>G0341</td>
<td>Percutaneous islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>G0342</td>
<td>Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>G0343</td>
<td>Laparotomy for islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>L2999</td>
<td>Lower extremity orthoses, not otherwise specified (when used to report robotic lower body exoskeleton device)</td>
</tr>
<tr>
<td>L3999</td>
<td>Upper limb orthotic, not otherwise specified (when used to report MyoPro™)</td>
</tr>
<tr>
<td>L5781</td>
<td>Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system</td>
</tr>
<tr>
<td>L5782</td>
<td>Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system, heavy duty</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>L8605</td>
<td>Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, anal canal</td>
</tr>
<tr>
<td>L8607</td>
<td>Injectable bulking agent for vocal cord medialization, 0.1 ml, includes shipping and necessary supplies</td>
</tr>
<tr>
<td>L8699</td>
<td>Prosthetic implant, not otherwise specified [when used to report three-dimensional (3-D) printed cranial implants]</td>
</tr>
<tr>
<td>P2031</td>
<td>Hair analysis (excluding arsenic)</td>
</tr>
<tr>
<td>P2033</td>
<td>Thymol turbidity, blood</td>
</tr>
<tr>
<td>P2038</td>
<td>Mucoprotein, blood (seromucoid) (medical necessity procedure)</td>
</tr>
<tr>
<td>Q2026</td>
<td>Injection, Radiesse 0.1ML</td>
</tr>
<tr>
<td>Q2028</td>
<td>Injection, Sculptra 0.5 mg</td>
</tr>
<tr>
<td>Q4100</td>
<td>Skin substitute, not otherwise specified (when used to report Amniofix, CorMatrix, or Conexa)</td>
</tr>
<tr>
<td>Q4115</td>
<td>AlloSkin, per sq cm</td>
</tr>
<tr>
<td>Q4123</td>
<td>AlloSkin RT, per sq cm</td>
</tr>
<tr>
<td>Q4131</td>
<td>Epifix or Epicord, per sq cm</td>
</tr>
<tr>
<td>Q4132</td>
<td>Grafix Core and GrafixPL Core, per sq cm</td>
</tr>
<tr>
<td>Q4133</td>
<td>Grafix Prime and GrafixPL Prime, per sq cm</td>
</tr>
<tr>
<td>Q4134</td>
<td>HMatrix, per sq cm</td>
</tr>
<tr>
<td>Q4135</td>
<td>Mediskin, per square centimeter</td>
</tr>
<tr>
<td>Q4136</td>
<td>Ez-derm, per square centimeter</td>
</tr>
<tr>
<td>Q4137</td>
<td>AmnioExcel or BioDExCel, per sq cm</td>
</tr>
<tr>
<td>Q4138</td>
<td>BioDFence DryFlex, per sq cm</td>
</tr>
<tr>
<td>Q4139</td>
<td>AmnioMatrix or BioDMatrix, injectable, 1 cc</td>
</tr>
<tr>
<td>Q4140</td>
<td>BioDFence, per sq cm</td>
</tr>
<tr>
<td>Q4141</td>
<td>AlloSkin AC, per sq cm</td>
</tr>
<tr>
<td>Q4142</td>
<td>Xcm biologic tissue matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4143</td>
<td>Repriza, per square centimeter</td>
</tr>
<tr>
<td>Q4145</td>
<td>EpiFix, injectable, 1 mg</td>
</tr>
<tr>
<td>Q4146</td>
<td>Tensix, per square centimeter</td>
</tr>
<tr>
<td>Q4147</td>
<td>Architect, Architect PX, or Architect FX, extracellular matrix, per sq cm</td>
</tr>
<tr>
<td>Q4148</td>
<td>Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per sq cm</td>
</tr>
<tr>
<td>Q4149</td>
<td>Excellagen, 0.1 cc</td>
</tr>
<tr>
<td>Q4150</td>
<td>AlloWrap DS or dry, per sq cm</td>
</tr>
<tr>
<td>Q4151</td>
<td>AmnioBand or Guardian, per sq cm</td>
</tr>
<tr>
<td>Q4152</td>
<td>DermaPure, per sq cm</td>
</tr>
<tr>
<td>Q4153</td>
<td>Dermavest and Plurivest, per sq cm</td>
</tr>
<tr>
<td>Q4154</td>
<td>Biovance, per square centimeter</td>
</tr>
<tr>
<td>Q4155</td>
<td>Neox Flo or Clarix Flo 1 mg</td>
</tr>
<tr>
<td>Q4156</td>
<td>Neox 100 or Clarix 100, per sq cm</td>
</tr>
<tr>
<td>Q4157</td>
<td>Revitalon, per square centimeter</td>
</tr>
<tr>
<td>Q4158</td>
<td>Kerecis Omega3, per sq cm</td>
</tr>
<tr>
<td>Q4159</td>
<td>Affinity, per square centimeter</td>
</tr>
<tr>
<td>Q4160</td>
<td>Nushield, per sq cm</td>
</tr>
<tr>
<td>Q4161</td>
<td>Bio-connekt wound matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4162</td>
<td>WoundEx Flow, BioSkin Flow, 0.5 cc</td>
</tr>
<tr>
<td>Q4163</td>
<td>WoundEx, BioSkin, per sq cm</td>
</tr>
<tr>
<td>Q4164</td>
<td>Helicoll, per square centimeter</td>
</tr>
<tr>
<td>Q4165</td>
<td>Keramatrix, per square centimeter</td>
</tr>
<tr>
<td>Q4166</td>
<td>Cytal, per square centimeter</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Q4167</td>
<td>Truskin, per square centimeter</td>
</tr>
<tr>
<td>Q4168</td>
<td>Amnioband, 1 mg</td>
</tr>
<tr>
<td>Q4169</td>
<td>Artacent wound, per square centimeter</td>
</tr>
<tr>
<td>Q4170</td>
<td>Cygnus, per square centimeter</td>
</tr>
<tr>
<td>Q4171</td>
<td>Interfyl, 1 mg</td>
</tr>
<tr>
<td>Q4172</td>
<td>PuraPly or PuraPly AM, per sq cm</td>
</tr>
<tr>
<td>Q4173</td>
<td>Palingen or palingen xplus, per square centimeter</td>
</tr>
<tr>
<td>Q4174</td>
<td>Palingen or promatrix, 0.36 mg per 0.25 cc</td>
</tr>
<tr>
<td>Q4175</td>
<td>Miroderm, per square centimeter</td>
</tr>
<tr>
<td>Q4176</td>
<td>Neopatch, per square centimeter</td>
</tr>
<tr>
<td>Q4177</td>
<td>Floweramnionflo, 0.1 cc</td>
</tr>
<tr>
<td>Q4178</td>
<td>Floweramniopatch, per square centimeter</td>
</tr>
<tr>
<td>Q4179</td>
<td>Flowerderm, per square centimeter</td>
</tr>
<tr>
<td>Q4180</td>
<td>Revita, per square centimeter</td>
</tr>
<tr>
<td>Q4181</td>
<td>Amnio wound, per square centimeter</td>
</tr>
<tr>
<td>Q4182</td>
<td>Transcycyte, per square centimeter</td>
</tr>
<tr>
<td>S2102</td>
<td>Islet cell tissue transplant from pancreas; allogeneic</td>
</tr>
</tbody>
</table>

**Coverage Rationale and Clinical Evidence**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0054T</td>
<td>Computer-assisted musculoskeletal surgical navigational orthopedic procedure, with image-guidance based on fluoroscopic images (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0055T</td>
<td>Computer-assisted musculoskeletal surgical navigational orthopedic procedure, with image-guidance based on CT/MRI images (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>20985</td>
<td>Computer-assisted surgical navigational procedure for musculoskeletal procedures, image-less</td>
</tr>
</tbody>
</table>

**Computer-assisted musculoskeletal surgical navigational for orthopedic procedures (CAOS) is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

The term "computer-assisted musculoskeletal surgical navigational orthopedic procedure" describes navigation systems that provide additional information during a procedure in order to further integrate preoperative planning with intraoperative execution.

**Clinical Evidence**

Conventional fluoroscopic guidance provides imaging in only one plane. Standard surgical techniques for joint replacement currently utilize intramedullary or extramedullary guides; computer-assisted navigation is proposed as an adjunct to conventional arthroplasty or as an alternative to existing fluoroscopic image guidance.

Navigation involves 3 steps: data acquisition, registration, and tracking.

- **Data Acquisition**: Data can be acquired in three different ways, i.e., fluoroscopic, CT or MRI guided, or imageless systems. This data is then used for registration and tracking.
- **Registration**: Registration refers to the ability of relating images (i.e., x-rays, CT, MRI or patients’ 3-D anatomy) to the anatomical position in the surgical field. Registration techniques may require the placement of pins or "fiduciary markers" in the target bone. A surface-matching technique can be used in which the shapes of the bone surface model generated from preoperative images are matched to surface data points collected during surgery.
- **Tracking**: Tracking refers to the sensors and measurement devices that can provide feedback during surgery regarding the orientation and relative position of tools to bone anatomy. For example, optical or electromagnetic trackers can be attached to regular surgical tools, which can then provide real time information of the position and orientation of the tools’ alignment with respect to the bony anatomy of interest.

The published, peer-reviewed scientific literature reveals few clinical trials that have compared the outcomes of computer-assisted navigation to conventional surgery, and whether or not the accuracy of computer-assisted systems improves functional outcomes. Most of the evidence for computer-assisted orthopedic surgery is in the form of case series, consisting of small patient populations and lack of controls.
Because CAN is a surgical information system in which the surgeon is only acting on the information that is provided by the navigation system, surgical navigation systems generally are subject only to 510(k) clearance from FDA as Class II devices. As such, FDA does not require data documenting the intermediate or final health outcomes associated with CAN. (In contrast, robotic procedures, in which the actual surgery is robotically performed, are subject to the more rigorous requirement of the premarket approval application process.)

Ankle, Foot, Shoulder
There are limited studies in the literature that address the use of computer assisted surgery for these body areas.

Hip/Pelvis
The majority of studies within the literature are prospective studies, small in sample size, lack the long-term follow-up to determine the safety of applying CAOS and have produced conflicting data regarding the efficacy of these applications when compared to conventional techniques. Of the 4 studies reviewed (Najarian, 2008; Kalteis, 2006; Parratte, 2007; Hsieh, 2006), all concluded that the use of computer-assisted navigation is a feasible tool to provide real-time image guidance for hip/pelvis procedures; however, it offers little additional benefit when the surgery is done by an experienced surgeon and requires a learning curve in terms of accuracy of use.

A meta-analysis by Gandhi et al. (2009) found 3 relevant studies documenting the efficacy of computer assisted hip surgery however these all had small sample sizes. The authors found that while computer navigation appears promising for alignment of the acetabular cup, further studies are needed to evaluate the impact of this on clinical outcomes, survival and quality of life.

Reininga and colleagues (2013) conducted a randomized controlled trial that investigated the effectiveness of a minimally invasive computer-navigated anterior approach for THA compared to a conventional posterolateral THA technique on the restoration of physical functioning during recovery following surgery. A total of 75 participants were included in the study; 35 underwent minimally invasive computer-navigated THA via the anterior approach, and 40 of the participants underwent conventional THA using the conventional posterolateral approach. Gait analysis was performed preoperatively at intervals of 6 weeks, and 3 and 6 months using a body-fixed-sensor based gait analysis system. Cadence, walking speed, step length and frontal plane angular movements of the pelvis and thorax were evaluated. The same data were obtained from 30 healthy individuals. No differences were noted in the recovery of spatiotemporal parameters or in angular movements of the pelvis and thorax following the computer-navigated MIS anterior approach or the conventional posterolateral approach. The authors found that while there was an improvement in gait after surgery, small differences in several spatiotemporal parameters and angular movements of the trunk remained at 6 months postoperatively between both the participants and the healthy subjects.

Knee
Aoude et al. (2016) reported computer-assisted surgery (CAS) has gained popularity in orthopedics for both TKA and total hip arthroplasty (THA) in the past decades. The American College of Surgeons National Surgical Quality Improvement Program database was used to identify patients who underwent a primary, unilateral THA and TKA from 2011 to 2013. Multivariate analysis was conducted to compare the postoperative complications in patients whose surgery involved the use of CAS with those by conventional techniques. The authors identified 103,855 patients who had THA and TKA in the database between 2011 and 2013. The rate of reoperation was higher in the CAS group for TKA. The results also showed higher overall adverse events, minor events and requirements for blood transfusion in the conventional group than compared to CAS for THA. Nevertheless, superficial wound infections were shown to be higher in the CAS group undergoing THA. The authors concluded the use of CAS in THA and TKA reduced the number of minor adverse events in the first 30 days postoperatively. However, CAS was associated with an increased number of reoperations and superficial infections. The clinical benefits and disadvantages of CAS should be considered when determining the potential benefit-cost ratio of this technology.

Rebal and colleagues (2014) conducted a meta-analysis of level I randomized trials comparing TKA using imageless computer navigation to conventional instrumentation. Based on radiographic and functional outcomes analysis, TKA performed with computer navigation was more likely to be within 3° of ideal mechanical alignment (87.1% vs. 73.7%). Navigated TKAs had a higher increase in Knee Society Score at 3 month follow-up (68.5 vs. 58.1) and at 12-32 month follow-up (53.1 vs. 45.8). Although the authors found that computer navigation in TKA provides more accurate alignment and superior functional outcomes at short-term follow-up, the impact on functional outcomes has yet to be firmly demonstrated.

Yaffe and colleagues (2013) reported the results of a study that explored whether differences in clinical, functional, or radiographic outcomes existed at 5-year follow-up between subjects who underwent computer-assisted or manual TKA. At the five-year follow-up, 63 participants (34 from the manual group and 29 from the computer-assisted group) were evaluated. No statistically significant differences were found in the Knee Society knee, function score, range of motion pain score or UCLA activity score between the 2 groups.
In another study, Harvie and colleagues (2012) reported on 71 subjects who were randomly allocated to undergo either computer-navigated or conventional arthroplasty. A statistically significant improvement in alignment was seen in the computer-navigated group. Five-year functional outcome was assessed using the Knee Society, Short Form-36, Western Ontario and McMaster Universities Osteoarthritis Index, and a patient satisfaction score. At 5 years, 46 of the study participants were available for assessment (24 navigated and 22 conventional knees). None of the participants had undergone revision. No statistically significant difference was observed in any component of any measure of outcome between navigated and conventional groups. Longitudinal data showed function to be well maintained with no difference in functional score between 2 and 5 years in either group. The authors concluded that despite achieving better alignment, at the time of the 5-year postoperative review, the functional outcome with computer-navigated knee arthroplasty appears to be no different than those seen using a conventional jig-based technique.

In 2011, Barrett and colleagues, in a multicenter, prospectively randomized trial, compared the radiographic alignment of imageless computer-assisted surgery with conventional instrumentation in individuals undergoing TKA. A total of 208 subjects were enrolled in the study. The preoperative surgical plan was compared to postoperative 2-dimensional radiographic alignment measured by a blinded reviewer. The authors found that the use of computer assisted surgery did not offer a clinically meaningful improvement in postoperative alignment, clinical, functional, or safety outcomes compared with conventional TKA.

In an archived Hayes report searched the peer-reviewed medical literature to evaluate imageless computer-assisted surgical navigation for total knee replacement surgery. They concluded that results of some studies suggest computer-assisted navigation of knee surgery leads to statistically significant improvements in the placement and alignment of implanted components. However, these improvements were usually small, and only three studies assessed functional outcomes to determine if the improvements in accuracy of implantation provided improved clinical outcomes. Further studies with prolonged follow-up and measurement of functional outcomes are needed to determine if this navigation provides clinically significant benefits for patients.

A meta-analysis by Bauwens et al. (2007), of 33 studies (11 randomized trials) involving 3423 patients were reviewed comparing navigated and conventional knee arthroplasty and concluded that the navigated knee replacement provided few advantages over conventional surgery based on radiographic evidence; therefore, its clinical benefits are unclear and remain to be defined on a larger scale.

These findings were confirmed by Brin et al. (2011) in a meta-analysis of 23 papers. The authors found that while imageless navigation improves component orientation and postoperative limb alignment, further studies are needed to evaluate the clinical benefits.

Cheng et al. (2010) conducted a meta-analysis of 40 studies (29 quasi-randomized/ randomized controlled trials and 11 prospective studies) and found that imageless computer-assisted navigation systems improve lower limb axis and component orientation in the coronal and sagittal planes, but not the rotational alignment in total knee arthroplasty. Further multiple-center clinical trials with long-term follow-up are needed to determine differences in the clinical and functional outcomes of knee arthroplasties performed using computer-assisted techniques.

A study by Hasegawa et al. (2010) compared standard approach (jig-based) total knee arthroplasty (TKA) with computer-assisted navigation in 100 equally divided patients. The authors found no significant differences between the procedures in the frontal and sagittal planes as well as rotational alignment of the femoral or tibial components.

Professional Societies
The American Association of Hip and Knee Surgeons (AAHKS) Position Statement (2008) states that longer and more comprehensive follow-up CAOS studies are needed to better understand the indications, limitations and complications of this surgical technology. Future studies will also determine if the short term improvements reported from CAOS can increase joint implant longevity and improve overall outcomes for patients undergoing total hip and knee replacement surgery.

Spine
There are limited studies in the literature that address the use of computer assisted surgery on the spine. Specific patient selection criteria have not been determined. While the literature suggests that the additional radiographic assistance may improve intra-operative realignment for the insertion of instrumentation or other surgical corrective measures, the long-term impact of utilizing these radiation enhanced techniques has not been determined in relation to clinical outcomes.

In summary, computer-assisted surgery is a complex process that is currently being introduced into the field of orthopedic surgery. Some of the proposed benefits of this emerging technology include intraoperative flexibility, accurate alignment of components and soft tissue balancing. Obstacles to computer-assisted surgery include
increased operating time, additional exposure to ionizing radiation, and extensive training of the surgical team. At present, there is insufficient evidence to allow strong scientific conclusions regarding the superiority or added value of computer assisted technologies for orthopedic surgery compared to conventional methods. Researchers have assessed only short-term outcomes; long-term effectiveness has not been demonstrated. Further studies are needed to determine if computer-assisted navigational systems for orthopedic procedures improve functional outcomes such as decreased pain and disability, and improve range of motion, joint function, and flexibility.

While results of controlled trials suggest improvements in the intermediate biomechanical outcomes, there is inadequate data on final health outcomes, as assessed by improvements in functional outcomes or surgical revision rates. Computer-assisted musculoskeletal navigation has been primarily investigated as an adjunct to surgery of the appendicular skeletal system. Most of the research has focused on its use in the knee and hip.

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>008ST</td>
<td>Breath test for heart transplant rejection</td>
</tr>
</tbody>
</table>

Breath testing for a measure of heart transplant rejection is unproven and not medically necessary. There is insufficient evidence in the peer-reviewed clinical literature to support the use of a breath test measuring methylated alkanes to predict organ rejection in heart transplant patients.

Clinical Evidence
In a manufacturer-sponsored, multicenter case-series study, Phillips et al. (2004) evaluated 1061 breath volatile organic compounds (VOC) samples collected from 539 heart transplant recipients before scheduled endomyocardial biopsy. The results of the breath methylated alkane contour (BMAC) tests were compared to the results of endomyocardial biopsies to calculate test sensitivity and specificity. The study concluded that a breath test for markers of oxidative stress was more sensitive (sensitivity 78.6%) and less specific (specificity 62.4%) for grade three heart transplant rejections than a biopsy reading by a site pathologist. A screening breath test could potentially identify transplant recipients at low risk of Grade 3 rejection and reduce the number of endomyocardial biopsies.
The Centers for Medicare and Medicaid Services (CMS) issued a National Coverage Determination (NCD) for the Heartsbreath test (Menssana Research Inc.) concluding that the available clinical evidence did not demonstrate that the test, which is intended to predict heart transplant rejection, actually improved health outcomes in Medicare beneficiaries. CMS also found that the evidence failed to adequately define the technical characteristics of the test. Heartsbreath is a noninvasive test that was granted a Humanitarian Device Exemption (HDE) by the Food and Drug Administration (FDA) in 2004. The FDA approved the test for use as an adjunct to, and not as a substitute for, endomyocardial biopsy. Specifically, Heartsbreath is indicated to assist in the diagnosis of grade 3 heart transplant rejection in patients who have received a heart transplant within the preceding year and an endomyocardial biopsy within the prior month. (CMS, 2008)

The Heartsbreath test received FDA approval under the Humanitarian Device Exemption (HDE) program on February 24, 2004 (H030004). Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=h030004. (Accessed April 20, 2017)

No professional society guidelines addressing this technology were identified.

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0100T</td>
<td>Placement of a subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy</td>
</tr>
<tr>
<td>0472T</td>
<td>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</td>
</tr>
<tr>
<td>0473T</td>
<td>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</td>
</tr>
</tbody>
</table>

The use of retinal prosthetic devices is unproven and not medically necessary for treating retinal disease due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
The Argus® II Retinal Prosthesis System (Second Sight Medical Products, Inc.) is a retinal implant that requires use of an external device to provide electrical stimulation to the retina to induce some visual perception in blind individuals with severe to profound retinitis pigmentosa (RP).

The Argus II Retinal Prosthesis System received a Humanitarian Device Exemption (HDE) from the U.S. Food and Drug Administration (FDA) in February 2013. According to FDA documentation, the device is indicated for use in individuals with severe to profound retinitis pigmentosa who meet the following criteria: age 25 or older; with bare light or no light perception in both eyes; a previous history of useful form vision; aphakic or pseudophakic eyes; and who are willing and able to receive the recommended post implant clinical follow-up, device fitting, and visual rehabilitation. Eligibility determination requires that patients with no residual light perception undergo testing for evidence of intact inner-layer retinal function. The procedure description indicates that patients with phakic eyes have their natural lens removed during the implant procedure. The device is intended for use in one eye—the worse-seeing eye. The HDE approval required the company to conduct 2 post-approval studies, including an extended (10-year) follow-up of patients receiving the implant and a 5-year, prospective, multicenter study of the visual function, device reliability, and adverse events in patients receiving the implant. See the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H110002. (Accessed May 16, 2017)

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 adverse events were typically mild but some serious adverse events 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-VL), 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 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 quality of life. (Fontanarosa et al., 2016)

Health Quality Ontario (2016) performed a systematic search of the literature for studies examining the effects of the Argus II retinal prosthesis system in patients with advanced retinitis pigmentosa, and appraised the evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. The focus of the review included visual function, functional outcomes, quality of life, and adverse events. One multicentre international study and one single-center study were included in the clinical review. In both studies, patients showed improved visual function with the Argus II system. However, the sight-threatening surgical complication rate was substantial. Retinitis pigmentosa significantly affects people's ability to navigate physical and virtual environments. Argus II was described as enabling the fundamental elements of sight. As such, it had a positive impact on quality of life for people with retinitis pigmentosa. The authors concluded that based on evidence of moderate quality, patients with advanced retinitis pigmentosa who were implanted with the Argus II retinal prosthesis system showed significant improvement in visual function, real-life functional outcomes, and quality of life, but there were complications associated with the surgery that could be managed through standard ophthalmologic treatments.

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

da Cruz et al. (2016) reported the clinical trial results at 5 years after Argus II implantation in 30 subjects. Twenty-four of 30 patients remained implanted with functioning Argus II Systems at 5 years after implantation. Only 1 additional serious adverse event was experienced after the 3-year time point. Patients performed significantly better with the Argus II on than off on all visual function tests and functional vision tasks. According to the authors, the 5-year results of the Argus II trial support the long-term safety profile and benefit of the Argus II System for patients blind as a result of retinitis pigmentosa (RP). This study is limited by a small study population which makes it difficult to complete a robust statistical analysis of the safety results because of limited power.

Geruschat et al. (2016) compared observer-rated tasks in patients implanted with the Argus II Retinal Prosthesis System, when the device is ON versus OFF. The Functional Low-Vision Observer Rated Assessment (FLORA) instrument was administered to 26 blind patients implanted with the Argus II Retinal Prosthesis System at a mean follow-up of 36 months. The tasks are evaluated individually and organized into four discrete domains, including 'Visual orientation', 'Visual mobility', 'Daily life' and 'Interaction with others'. Twenty-six patients completed each of the 35 tasks. Overall, 24 out of 35 tasks (69 percent) were statistically significantly easier to achieve with the device ON versus OFF. In each of the four domains, patients' performances were significantly better with the device ON versus OFF, ranging from 19 to 38 per cent improvement. The authors concluded that patients with an Argus II Retinal Prosthesis implanted for 18 to 44 months, demonstrated significantly improved completion of vision-related tasks with the device ON versus OFF. These findings require confirmation in a larger study.

Dagnelie et al. (2017) conducted a study to test Argus II subjects on three real-world functional vision tasks. Testing was conducted in a hospital/research laboratory setting at the various participating centers. Twenty-eight Argus II subjects, all profoundly blind, were included in the study. Subjects were tested on the three real-world functional vision tasks: Sock Sorting, Sidewalk Tracking and Walking Direction Discrimination task For the Sock Sorting task, percentage correct was computed based on how accurately subjects sorted the piles on a cloth-covered table and on a bare table. In the Sidewalk Tracking task, an 'out of bounds' count was recorded, signifying how often the subject...
veered away from the test course. During the Walking Direction Discrimination task, subjects were tested on the number of times they correctly identified the direction of testers walking across their field of view. The mean percentage correct OFF versus ON for the Sock Sorting task was found to be significantly different for both testing conditions. On the Sidewalk Tracking task, subjects performed significantly better with the system ON than they did with the system OFF. Eighteen (18) of 27 subjects (67%) performed above chance with the system ON, and 6 (22%) did so with system OFF on the Walking Direction Discrimination task. The authors concluded that the Argus II subjects performed better on all three tasks with their systems ON than they did with their systems OFF. These findings require confirmation in a larger study.

Published peer-reviewed medical literature is limited regarding the use of retinal prosthetic devices. While the results of available studies are promising, more research is needed regarding adverse events and improvement of visual functions with this device.

Clinical trials of artificial retinal devices are currently ongoing including a 3-year observational study of a larger group of patients implanted with the Argus II Retinal Prosthesis System than was available in the premarket approval study. This study will gather information on the nature and rate of adverse events and, secondarily, visual function. See the following website for more information: http://www.clinicaltrials.gov/ct2/show/NCT01490827. (Accessed April 16, 2017)

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0174T</td>
<td>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)</td>
</tr>
<tr>
<td>0175T</td>
<td>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</td>
</tr>
</tbody>
</table>

Computer aided detection (CAD) of chest x-rays is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
A computer-aided detection (CAD) system is used as an adjunctive tool in assessing chest radiographs. The basic function of CAD is to provide radiologists with a computer algorithm that assists with interpreting radiological images. Computer-aided detection (CAD) has become one of the principal research areas in medical imaging and diagnostic radiology. It can be defined as diagnoses rendered by radiologists who utilize the output from computerized algorithm analyses of medical images as a second opinion in detecting lesions and in making diagnostic decisions. Computer-aided detection (CAD) or technology may increase the sensitivity of CXRs. Early published literature regarding CAD for CXRs consists primarily of technical capabilities of CAD systems as reported by Freedman (2002 and 2004) and Kadeda (2004).

In a small retrospective study, Dellios et al. (2017) applied two computer-aided detection (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.

de Hoop et al. (2010) assessed how computer-aided detection (CAD) affects reader performance in detecting early lung cancer on chest radiographs. A total of 46 individuals with 49 computed tomographically (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.

The diagnostic utility of using computer-aided detection (CAD) systems with chest radiographs has not been demonstrated in the published peer-reviewed scientific literature. Large, well-designed, controlled clinical trials comparing radiograph CAD results to additional manual radiologist review (i.e., second opinion) results or computed tomography (CT) results (with and without CT CAD) are needed to determine whether the addition of CAD improves the interpretation of chest radiographs and ultimately, has an impact on meaningful health outcomes. Furthermore, additional studies are needed to determine if early detection of lung cancer, by CAD of chest radiographs in comparison with other methods of detection, will lead to an improvement in life expectancy.

**Professional Societies**

**American College of Radiology (ACR)**

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

**American College of Chest Physicians (AACP)**

The AACP does not address the use of computer-aided detection of chest x-rays for detection of lung cancer and/or lung cancer screenings in their guidelines on the diagnosis and management of lung cancer (AACP, 2013).

In summary, while CAD for chest radiographs may be potentially useful in screening lung cancer, its clinical value needs to be established by Randomized Controlled Trials.

**Reference(s)**


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0205T</td>
<td>Intravascular catheter-based coronary vessel or graft spectroscopy (e.g., infrared) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation, and report, each vessel (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

The use of intravascular catheter-based spectroscopy to assess coronary artery plaque vulnerability is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.
**Clinical Evidence**

Intravascular imaging techniques are used to guide treatment decision-making by enhancing visualization of coronary lesions. Near infrared spectroscopy (NIRS) is an imaging technique for visualizing coronary anatomy that is still evolving. NIRS uses a catheter containing an optic fiber that is used to measure diffuse reflectance signals with NIR light as an energy source. NIRS yields information about the plaque chemical composition via the pattern of absorption of the light in relation to the wavelength. This pattern is unique for lipid and each of the other plaque elements. The major limitation of NIRS is that it provides compositional but not structural information. (Raman et al., 2013)

Danek et al. (2017) analyzed the outcomes of 239 patients who underwent NIRS coronary imaging. The following variables were associated with major adverse cardiovascular events (MACE): diabetes mellitus, prior percutaneous coronary intervention and non-target vessel lipid core burden index (LCBI). The 5-year MACE rate was 37.5% (cardiac mortality was 15.0%). The authors concluded that non-target vessel lipid burden measured using NIRS appears to be a predictor of MACE during long-term follow-up. This study is limited by a retrospective design and potential for selection bias.

In a prospective, observational study, Oemrawsingh et al. (2014) evaluated the long-term prognostic value of intracoronary NIRS in patients with coronary artery disease (CAD). NIRS was performed on a nonculprit coronary artery in 203 patients referred for angiography due to stable angina or acute coronary syndrome. The primary endpoint was the composite of all-cause mortality, nonfatal ACS, stroke and unplanned coronary revascularization. The 1-year cumulative incidence of the primary endpoint was 10.4%. Patients with an LCBI equal to or above the median of 43.0 had a four-fold risk of adverse cardiovascular events during one-year follow-up. The authors noted that this observation warrants confirmation by larger studies with extended follow-up.

Waxman et al. (2009) reported on a diagnostic, nonrandomized, open label, uncontrolled trial designed to determine whether catheter-based NIRS signals obtained with a catheter-based system from coronary arteries of living individuals are similar to those from autopsy specimens. The authors concluded that this intravascular NIRS system safely obtained spectral data in patients that were similar to those from autopsy specimens. These results demonstrate the feasibility of invasive detection of coronary lipid core-containing plaques with this novel system, yet do not establish the clinical utility of testing.

No professional society guidelines addressing this technology were identified.

**Reference(s)**


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0206T</td>
<td>Computerized database analysis of multiple cycles of digitized cardiac electrical data from two or more ECG leads, including transmission to a remote center, application of multiple nonlinear mathematical transformations, with coronary artery obstruction severity assessment.</td>
</tr>
</tbody>
</table>

The use of a two-lead, computerized, resting electrocardiography (ECG) analysis to diagnose heart disease is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

**Clinical Evidence**

Synonyms: MultiFunction Cardiogram (MCG), 3DMP, multiphase resting ECG analysis.

The MCG uses a mathematical approach to diagnose heart disease. Practices using the technology provide an in-office test similar to a resting ECG and then send the information to an MCG datacenter for analysis, which includes scoring the cardiac disease severity and listing differential diagnoses. The MCG system uses two leads. (Premier Heart website)
ECG signal analysis technologies are enhanced versions of the standard resting or exercise ECG that utilize special software to analyze the ECG signals. The 3DMP™, mfEMT™ (sometimes referred to as mfEMT™) or Multifunction Cardiogram (MCG™) system (Premier Heart) rely on mathematical models derived from a very large clinical database. Only data from two of the standard 12 ECG leads are used. Evidence to date from several small studies shows this technology is sufficiently sensitive to have a possible role in ruling out coronary artery disease (CAD); specificity has been shown to be moderately high. However, no studies were designed to measure the effect on treatment plans or health outcomes. In addition, there has been no systematic attempt to determine whether these technologies are good alternatives to other noninvasive tests or how they might best be combined with other tests. (Hayes, 2011; updated 2015; archived 2017)

In a single-center, prospective study (MED-FIT), Kawaji et al. (2015) validated MCG using fractional flow reserve (FFR) as the reference standard. Of 100 stable patients with suspected CAD scheduled for coronary angiography, data from 91 patients was included in the analysis. The primary and secondary analyses evaluated the diagnostic performance of the MCG severity score to detect functional myocardial ischemia and angiographically significant coronary stenosis (percent diameter stenosis ≥50%). The prevalence of functional myocardial ischemia and angiographically significant stenosis was 42.7% and 41.8%, respectively. Sensitivity and specificity of the MCG severity score for functional myocardial ischemia and angiographically significant stenosis was also low (32%/67% and 37%/72%) using a cutoff value of 4.0. The authors concluded that the diagnostic performance of the MCG severity score was poor for both functional myocardial ischemia and angiographically significant stenosis.

An Agency for Healthcare Research and Quality (AHRQ) technology assessment concluded that the evidence regarding the clinical utility of ECG-based signal analysis technologies is insufficient. Further research is needed to better describe the performance characteristics of these devices to determine in what circumstances, if any, they would replace or add to the standard ECG in testing patients with CAD. (Coeytaux et al., 2012)

A meta-analysis by Leisy et al. (2013) concluded that the evidence is insufficient to confidently inform the appropriate use of ECG-based signal analysis technologies for detecting ischemia or infarct in acute coronary syndrome. Further research is needed to determine in what circumstances, if any, these devices might precede, replace or add to the standard ECG.

Strobeck et al. (2009) conducted a meta-analysis of three published prospective trials performed in the US to assess sensitivity and specificity of a computerized, multiphase, resting electrocardiogram analysis device (MCG) for the detection of relevant coronary stenosis. A total of 1076 patients were included in the analysis. The authors concluded that MCG safely and accurately identified patients with relevant coronary stenosis (>70%) with high sensitivity and specificity and high negative predictive value. The three trials used in the analysis were all authored by Joseph Shen, MD, founder and co-developer of the MCG technology.

No professional society guidelines addressing this technology were identified.

Reference(s)


Strobeck JE, et al. Comparison of a two-lead, computerized, resting ECG signal analysis device, the MultiFunction-CardioGram or MCG (a.k.a. 3DMP), to quantitative coronary angiography for the detection of relevant coronary artery stenosis (>70%) – a meta-analysis of all published trials performed and analyzed in the US. Int J Med Sci. 2009; 6(4):143-55.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0207T</td>
<td>Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral</td>
</tr>
</tbody>
</table>

The use of automated evacuation of meibomian glands using heat and intermittent pressure is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.
Clinical Evidence

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

Blackie et al. (2015) investigated the published peer-reviewed results of the novel vectored thermal pulsation therapy for patients with meibomian gland dysfunction (MGD). The PubMed and meeting abstract search revealed a total of 31 peer-reviewed reports on vectored thermal pulsation therapy at the time of the search (eight manuscripts and 23 meeting abstracts). All manuscripts evidence a significant increase in meibomian gland function (~3×) and symptom improvement post a single 12-min treatment. Additional reported objective measures such as osmolarity, tear breakup-time, or lipid layer thickness also increased as a result of the therapy; however, not all findings were statistically significant. The randomized controlled studies evidence sustained gland function and symptom relief lasting out to 12 months. The uncontrolled case series evidence significantly longer duration of effect. According to the investigators, a single 12 minute vectored thermal pulsation treatment allows for reducing dry eye symptoms, improving meibomian gland function and other correlates of the ocular surface health. According to the authors, the duration of efficacy of the therapy is still under investigation. The review included a systematic review of five clinical trials, three case reports, and 23 meeting abstract. This review was funded by the manufacturer, TearScience, which has the potential for introducing bias in the reporting of outcomes.

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

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

In a prospective, randomized, crossover, observer-masked clinical trial, Finis et al. (2014a) compared the effectiveness of a single LipiFlow treatment with combined lid warming and massage in patients with meibomian gland dysfunction (MGD). Study participants were randomized to receive either a single 12-min LipiFlow Thermal Pulsation (LTP) system treatment or to perform combined twice-daily lid warming and massage for 3 months. All subjects were examined before, and 1 and 3 months after initiation of treatments. A total of 31 subjects completed the 3-month follow-up. At 1 and 3 months, patients in the LipiFlow treatment group had a significant reduction in Ocular Surface Disease Index (OSDI) scores compared with those in the lid-margin hygiene group. Both treatments produced a significant improvement in expressible meibomian glands compared to the baseline parameters, but no significant difference was noted between the two groups. The other investigated objective parameters did not show a significant difference. The authors concluded that a single LipiFlow treatment is as least as effective as a 3-month, twice-daily lid margin hygiene regimen for MGD. According to the authors, a limitation of the present study was that it was observer-masked only, i.e., patients were aware of the fact that they received either an established or a new and modern treatment for MGD. Thus, a placebo effect may have confounded any improvements in subjective symptoms and other parameters in both groups. The authors also stated that additional studies using a sham LipiFlow treatment in a double-masked design with larger cohorts and longer follow-up times are warranted.

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


Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0263T</td>
<td>Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest</td>
</tr>
</tbody>
</table>
Intramuscular autologous bone marrow cell therapy is unproven and not medically necessary for treating peripheral arterial disease.

Clinical Evidence

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

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

MOBILE is a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of intramuscular injections of concentrated bone marrow aspirate (cBMA) in promoting amputation-free survival in patients with critical limb ischemia (CLI) due to severe peripheral arterial disease (PAD). Patients with critical limb ischemia were randomized to intramuscular injection of autologous bone marrow derived stem cells (n = 119) versus placebo injection (n = 36). Patients with rest pain or tissue loss resulting from advanced peripheral arterial disease, as characterized by anklebrachial index (<0.6), toe-brachial index (<0.4), or transcutaneous pressure of oxygen (<50 mm Hg), were eligible for inclusion if surgical revascularization was not possible secondary to advanced disease. Treatment and 1-year follow-up of 155 patients enrolled in MOBILE are completed. Long-term follow-up is ongoing. (Clinical Trial- NCT02474121) Wang et al. (2017)

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

Roohi et al. (2014) conducted a systematic review to evaluate the effectiveness and safety of local intramuscular autologous mononuclear cells to treat lower limb ischemia. Study results of two randomized controlled trials (total n=57) indicated positive treatment effects in terms of significantly reduced number of amputations and significantly increased in pain-free walking distance when compared with controls. However, study authors concluded that the evidence base is currently insufficient to support the use of this treatment and larger randomized controlled trials with sufficient power are needed to assess the role of intramuscular mononuclear cell implantation in patients with lower limb ischemia.
A European Society of Cardiology (ESC) guideline addresses novel therapies to stimulate neovascularization, known as therapeutic angiogenesis. These therapies promote revascularization and remodelling of collateral vessels to reduce the symptoms of peripheral vascular disease and prevent amputation. For autologous cell transplantation in humans, bone marrow and peripheral blood are rich sources of stem and progenitor cells. Bone marrow is currently the most frequent source of cells used for clinical repair trials, because it is easy to obtain and no complex purification steps are required. Another advantage is that it contains a variety of stem and progenitor cells. At present angiogenic gene and stem cell therapy are still being investigated, and it is too early to give firm recommendations. (Tendera et al., 2011)

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

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

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

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0266T</td>
<td>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)</td>
</tr>
<tr>
<td>0267T</td>
<td>Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)</td>
</tr>
<tr>
<td>0268T</td>
<td>Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)</td>
</tr>
<tr>
<td>0272T</td>
<td>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)</td>
</tr>
<tr>
<td>0273T</td>
<td>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</td>
</tr>
</tbody>
</table>

**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 clinical evidence of safety and/or efficacy in the published peer-reviewed medical literature.**

In December 2014, the FDA granted a unique and limited Humanitarian Device Exemption (HDE) for use of the Barostim neo legacy device for treatment of hypertension. The HDE applies to U.S. clinical trial patients who were implanted with the Rheos Baroreflex Hypertension device, who achieved a significant decrease in blood pressure during their trial participation, and who now require a procedure to replace the device battery and/or repair the electrode lead. The FDA will allow the obsolete Rheos Baroreflex Hypertension device to be replaced by the current Barostim neo legacy device. The HDE does not apply for treatment of heart failure. Additional information available at: https://www.accessdata.fda.gov/cdrh_docs/pdf13/h130007c.pdf. (Accessed May 30, 2017)

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

**Note:** The Barostim neo™ is a second generation device that replaces the Rheos® System. (CVRx website)

**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 2017)

**Hypertension**

A Hayes report concluded that published evidence to date on BAT for drug-resistant hypertension does not adequately demonstrate definitive safety or efficacy. The report also noted that evidence is insufficient to determine whether Barostim neo offers superior clinical or safety benefits over predecessor Rheos in patients with drug-resistant hypertension. (Hayes, 2016)

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

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

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

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

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

Heart Failure
A Hayes report concluded that no firm conclusions can be drawn regarding the safety and efficacy of Barostim neo for the treatment of heart failure (HF) until further randomized controlled trial data are available. (Hayes, 2015)

ECRI states that reported clinical trial data suggests BAT for HF may modestly improve New York Heart Association (NYHA) functional class, exercise capacity and quality of life through six months and slightly reduce medication use. Data from larger trials that measure outcomes such as mortality, hospitalizations and device longevity are needed to better estimate the technology’s potential health impact, especially compared with potential competing technologies and drug therapy alone. (ECRI, 2013; updated 2017)

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, quality-of-life 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. (Barostim Neo System in the Treatment of Heart Failure; NCT01471860; Barostim HOPE4HF (Hope for Heart Failure) Study; NCT01720160).

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 CRT device. The goal was to determine differences in treatment effect produced by BAT in the two 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. (Barostim Neo System in the Treatment of Heart Failure; NCT01471860; Barostim HOPE4HF (Hope for Heart Failure) Study; NCT01720160).

Gronda et al. (2014) assessed the effects of BAT in clinical HF. In a single-center, open-label pilot study, eleven patients with NYHA class III HF, ejection fraction <40%, optimized medical therapy and not eligible for cardiac resynchronization therapy received BAT for 6 months. Efficacy was assessed with serial measurement of muscle sympathetic nerve activity (MSNA) and clinical measures of quality of life 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 quality of life. 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 and American Heart Association joint guidelines on the management of heart failure do not include recommendations for BAT. (Yancy et al., 2013)

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0330T</td>
<td>Tear film imaging, unilateral or bilateral, with interpretation and report</td>
</tr>
</tbody>
</table>
Tear film imaging to monitor or assess tear film disorders is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

**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.

Arita et al. (2016) investigated whether the tear interferometric pattern was able to identify differences in tear film kinetics among clinical subtypes of dry eye. A total of 138 eyes of 76 subjects (38 men and 38 women; mean age ± SD, 61.6 ± 16.2 years) with or without dry eye were enrolled in a cross-sectional study. Clinical diagnosis of dry eye subtype was based on tear film parameters. The pattern of tear film kinetics determined by interferometry was classified as 0 [monotonous gray or multicolor interferometric fringe with a noninvasive breakup time (NIBUT) of ≥5 seconds], 1 (multicolor interferometric fringe with a NIBUT of <5 seconds), or 2 (grayish amorphous interferometric fringe with a NIBUT of <5 seconds), and reliability of classification was evaluated. Lipid layer thickness (LLT) for the tear film was also determined by interferometry. Intrarater κ values for evaluation of interferometric patterns ranged from 0.57 to 0.94 for both physicians and nonphysicians with reference to a dry eye expert, the latter of whom showed an intrarater reliability of 0.90. The distribution of eyes among interferometric patterns 0, 1, and 2 coincided well with the clinical subgroups of normal tear condition, non-Sjögren syndrome aqueous-deficient dry eye, and meibomian gland dysfunction, respectively. A multicolor interferometric fringe was essentially observed only at an LLT of >70 nm. The authors concluded that tear interferometry was able to reliably distinguish clinical subtypes of dry eye by reflecting the balance between the lipid and aqueous layers of the tear film. The study did not confirm the utility of such findings in improving care and outcome of patients.

In a prospective case-control study, Hosaka et al. (2011) compared tear film thickness between normal subjects and aqueous tear deficiency dry eye patients by tear interferometry. Central precorneal tear film thickness was measured noninvasively using an interference thin-film thickness measurement device. (Quore MSPA1100; Mamiya-OP) Tear film thickness of 14 eyes from 14 normal subjects and of 28 eyes from 28 aqueous tear deficiency dry eye patients were compared along with noninvasively measured tear meniscus height, DR-1 (Kowa) dry eye severity grading, fluorescein and rose bengal staining scores, tear film break-up time, and Schirmer test results. Among dry eye patients, 13 eyes underwent punctual occlusion, and tear film thickness was compared before and after the surgery. Tear film was significantly thinner in dry eye patients than normal subjects. Tear film thickness showed good correlation with other dry eye examinations. After punctal occlusion, tear film thickness increased significantly from 1.7 ± 1.5 μm to 4.9 ± 2.8 μm with the improvement of tear meniscus height, fluorescein and rose bengal staining scores, tear film break-up time, and Schirmer test values. The authors concluded that interferometric tear film thickness measurement revealed impaired precorneal tear film formation in aqueous tear deficiency dry eyes and was useful for showing the reconstruction of tear film after punctal occlusion surgery. According to the authors, interferometry of precorneal tear film may be helpful for the evaluation of aqueous tear deficiency in conjunction with other dry eye examinations. These findings require confirmation in a larger study.

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


**Reference(s)**

The use of extra-osseous subtalar joint implant for talotarsal stabilization is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

**Clinical Evidence**

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

Subtalar arthroereisis (SA) is a surgical procedure designed to correct the excessive talar displacement and calcaneal eversion by placing an implant in the sinus tarsi, a canal located between the talus and the calcaneus. The body of literature evaluating SA consists mainly of retrospective case series and case reports and presents low-quality, limited evidence regarding efficacy and safety. All of the studies consistently found positive effects for the majority of patients. SA consistently improved pain, functionality, and radiographic findings associated with flatfoot in children, and these effects were observed for 12 years following the procedure. However, all of these studies used a retrospective uncontrolled design, and biased results cannot be ruled out. The evidence regarding adults, while positive, is too limited in quantity to support conclusions regarding efficacy and safety. No randomized controlled studies are available to compare SA with other established surgical techniques for SA such as arthrodesis or osteotomy. (Hayes, 2012; updated 2016)

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

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

There is currently no published evidence from randomized controlled trials on SA. Numerous implant systems have received approval through the FDA's 510(k) process. A complete listing of subtalar implant devices that have received FDA approval are posted on the FDA's Center for Devices and Radiologic Health (CDRH) website.

**Professional Studies**

**American Association of Orthopaedic Surgeons (AAOS)**

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

The evidence in the peer-reviewed published literature is currently insufficient to draw conclusions as to the safety and effectiveness of extraosseous subtalar implants for talotarsal stabilization and subtalar arthroereisis. Further research is required in the form of prospective controlled studies with long-term follow-up of functional improvement.

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0341T</td>
<td>Quantitative pupillometry with interpretation and report, unilateral or bilateral</td>
</tr>
</tbody>
</table>

Pupillometry is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

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

Suys et al. (2015) evaluated the accuracy of quantitative pupillary light reactivity to predict health outcomes of patients who experienced a coma following cardiac arrest (n=50). Results showed that prognostic accuracy of pupillometry was comparable to conventional measures using EEG and SSEP. Tatham et al. (2014) evaluated the ability of pupillometry to differentiate between healthy subjects and patients with glaucoma (n=116; 66 glaucoma patients; 50 healthy patients). Study results indicate that pupillometry performed poorly in patients with symmetric glaucoma, although results were acceptable in asymmetric disease. Pupillometry has been used in a research setting to evaluate the autonomic function, pain response, psychological processes, sleep disorders, and drug metabolism.

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

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

**Reference(s)**


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0346T</td>
<td>Ultrasound, elastography (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

The use of ultrasound elastography is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

**Clinical Evidence**

Sonoelastography (SE) is a newly introduced ultrasound technique that evaluates tissue elasticity and thus provides additional information to that offered by conventional ultrasound images. In the musculoskeletal field, sonoelastography can help improve estimation of tendon stiffness. The technique employs external compression in order to induce strain inside the tissue that is scanned. Tissue compression produces strain or displacement within the tissue; therefore, the strain is smaller and harder in the malignant tissue than in the benign tissue. By measuring the tissue strain, tissue hardness can be estimated differentiating between malignant and benign masses.

Sonoelastography (SE): Evaluates reproducible differences in backscattered ultrasound signals that result from compression of tissues and uses color doppler to generate an image of tissue movement in response to the external vibrations.

Ultrasound elastography (EUS) has been investigated in a variety of clinical applications, including, but not limited to, breast imaging, assessment of liver fibrosis, endoscopic, vascular and prostate imaging as well as thyroid, skin and brain tumors.

There was no information found in MCG™, ECRI or Hayes for this treatment.

The US Food and Drug Administration (FDA) approved the diagnostic ultrasound system (Elastography combined B/M-mode) under 510(K) (K132341) on May 22, 2013. This elastography device employs an array of probes that include linear array, convex array, and phased array with a frequency range of approximately 3-10.0MHz.

**Professional Societies**

The Association for Medical Ultrasound does not make a recommendation on elastography in their clinical practice guidelines.

The National Comprehensive Cancer Network (NCCN) practice guidelines for colon cancer, and lobular carcinoma in Situ, does not indicate elastography as a diagnostic modality in their clinical guidelines.
The evidence in the published medical literature for ultrasound elastography is inadequate to permit scientific conclusions. The main limitation is the lack of controlled studies as well as the lack of long-term outcomes. Further long-term research is needed to establish the role of ultrasound elastography.

**Reference(s)**


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0355T</td>
<td>Gastrointestinal tract imaging, intraluminal (e.g., capsule endoscopy), colon, with interpretation and report</td>
</tr>
</tbody>
</table>

**Pillcam Colon2 is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

Studies are needed that compare Pillcam Colon2 to available methods of colorectal cancer screening in order to determine whether Pillcam Colon2 is an effective screening tool to reduce the risk of death from colorectal cancer.

**Clinical Evidence**

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

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

- [www.accessdata.fda.gov/cdrh_docs/reviews/k123666.pdf](http://www.accessdata.fda.gov/cdrh_docs/reviews/k123666.pdf)
- [www.accessdata.fda.gov/cdrh_docs/pdf15/k153466.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf15/k153466.pdf)

(Accessed April 21, 2017)

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

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

In a case controlled study Rondonotti et al. (2014) assessed the accuracy of the colon capsule [Pillcam2 (cc2)] and a computed tomographic colonography (CTC) in those patients who are unable or unwilling to undergo optical colonoscopy (OC). 50 individuals who had been prior identified to have at least one polyp 6mm or larger. The combination of OC, CTC, and CC2 identified 16 cases with at least 1 polyp 6 mm or larger (reference standard). CTC identified the polyps with 88.2% sensitivity, 84.8% specificity, a 3.0 positive likelihood ratio, and a 0.07 negative likelihood ratio. CC2 identified the polyps with 88.2% sensitivity, 87.8% specificity, a 3.75 positive likelihood ratio, and a 0.06 negative likelihood ratio. Thirty-nine subjects (78%) said they preferred CC2 to CTC. The authors concluded that CC2 and CTC detect polyps 6 mm and larger with high levels of accuracy; these techniques are effective in selecting iFOBT-positive individuals who do not need to be referred for optical colonoscopy. CC2 seems to be better tolerated than CTC, and could be a reliable alternative to CTC for iFOBT-positive individuals who are unable or unwilling to undergo OC. Limitations of this study are the small sample size and study methodology, i.e., case controlled.

In a prospective single center study, Negreanu et al. (2013) assessed the feasibility, accuracy and acceptability of PillCam Colon2 in detection of significant lesions in colorectal cancer risk patients, unable or unwilling to perform colonoscopy. A total of 70 patients at risk of colorectal cancer were enrolled in the study. In three patients the procedure failed because the capsule was not functioning when entered the colon. PillCam Colon2 showed positive findings in 23 (34%, 95%CI: 21.6%-44.1%) of the remaining 67 patients. Six patients were diagnosed with tumors: 4 with colon cancers, 1 with gastric cancer and 1 with a small bowel cancer. The capsule findings were confirmed after surgery in all these patients. The capsule excretion rate in twelve hours was 77% with 54 patients having a complete examination. The rectum was not explored during CCE procedure, in 16 patients (23%, 95%CI: 13.7%-34.4%). Every patient accepted CCE as an alternative exploration tool and 65/70 (93%) agreed to have another future control by CCE. No complications were reported during or after CCE examination. The authors concluded that the PillCam Colon 2 capsule was effective in detecting significant lesions and might be considered an adequate alternative diagnostic tool in patients unable or unwilling to undergo colonoscopy. Interpretation of the findings is limited due to the small sample size studied in this uncontrolled prospective single center study.

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

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

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

Yung et al. (2016) reviewed the current clinical evidence of colon capsule endoscopy (CCE) in comparison with a complete colonoscopy for detection of polyps. In the authors’ opinion, further software and hardware development is required to enable CCE to fulfill its potential as a minimally-invasive and reliable method of colonoscopy. Significant limitations noted in their review include the need for aggressive bowel preparation and the labor-intensiveness of CCE reading.

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

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

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

In 2013, the American Society for Gastrointestinal Endoscopy (ASGE) published a Technology Status Evaluation Report for Wireless Capsule Endoscopy (WCE). The report states that WCE applications still remain limited within the colon. (Wang et al., 2013)

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

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

Reference(s)
Han YM, Im JP. Colon capsule endoscopy: where are we and where are we going. Clin Endosc 2016;49: 449-453.


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0356T</td>
<td>Insertion of drug-eluting implant (including punctal dilation and implant removal when performed) into lacrimal canaliculus, each</td>
</tr>
</tbody>
</table>

The use of drug eluting punctal plugs or implants into the lacrimal canaliculus is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence

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

There are few published studies addressing the use of drug eluting implants into the lacrimal canaliculus. Therefore, it is not possible to conclude whether these implants have a beneficial effect on health outcomes.

Torkildsen et al. (2017) conducted a randomized, double-masked, vehicle-controlled, Phase 2 study evaluate the efficacy and safety of a sustained-release dexamethasone intracanalicular insert (Dextenza™) for treating allergic conjunctivitis. The subjects included in the study had to have a positive conjunctival allergen challenge (CAC) reaction to allergen at Visit 1, and for 2 of 3 time points on subsequent visits. Subjects who met entry criteria were randomized to receive Dextenza or PV (vehicle insert). Challenges occurred over 42 days, with efficacy assessed at 14 (primary endpoint visit), 28, and 40 days postinsertion. Outcome measures included the evaluation of ocular itching, redness, tearing, chemosis, eyelid swelling, rhinorrhea, and congestion. Twenty-eight subjects completed the study in the Dextenza group and 31 in the vehicle group. At 14 days postinsertion, Dextenza was statistically superior to PV. Clinical significance, defined as a 1-U decrease from PV, was not met for primary efficacy. Secondary endpoints, including number of subjects reporting itching and conjunctival redness, indicated superior performance of Dextenza compared with vehicle. Eleven Dextenza-treated (35.5%) and 10 vehicle-treated (30.3%) subjects each experienced a single adverse event. The authors concluded that this Phase 2 study demonstrated preliminary efficacy and safety data of Dextenza for treatment of allergic conjunctivitis. Well-designed randomized clinical trials with extended follow-up are necessary to evaluate the long-term efficacy and late complications of these intracanalicular inserts.

Walters et al. (2016) evaluated the safety and efficacy of OTXDP, a sustained-release dexamethasone punctum plug when placed in the canaliculus of the eyelid for the treatment of post-surgical pain and inflammation in patients who had undergone cataract surgery. Two prospective, Phase 3, multicenter, randomized, parallel-arm, double-masked, vehicle-controlled studies (referred to as Study 1 and Study 2) were conducted across 32 private practice sites in the United States. Patients were randomized (2:1) on Day 1 to receive a sustained release dexamethasone depot, (0.4 mg; Study 1, n=164; Study 2, n=161) or placebo vehicle depot (Study 1, n=83; Study 2, n=80) in the inferior canaliculus. The primary endpoint for ocular pain was met in both studies; statistically higher proportions of patients

Omnibus Codes
UnitedHealthcare Oxford Clinical Policy ©1996-2018, Oxford Health Plans, LLC Effective 05/01/2018
in OTX-DP groups, compared with placebo groups, had no ocular pain at day 8. However the inflammation endpoint was met only in Study 1. The authors suggest that this endpoint failed to reach statistical significance in Study 2 because of an unusually high percentage of placebo group patients without anterior chamber cells at day 14. Significantly fewer OTX-DP group than placebo group patients required rescue medications on study days 8 and 14; this endpoint did not statistically differ on study days 1, 2, and 4. No treatment-related adverse events were reported. OXTDP is currently undergoing US Food and Drug Administration (FDA) review.

Chee (2012) assessed the safety and feasibility of a moxifloxacin-loaded punctum plug (MP) in 2 groups of cataract patients. Two prospective, single-arm, Phase I studies were conducted with 20 cataract patients (10 per study) at the Singapore National Eye Center. After cataract surgery, the MP was inserted into the punctum, and follow-up assessments were conducted at 1 h, 24 h, and on days 3, 7, 10, 20, and 30. Study endpoints included MP retention, ease of placement, and moxifloxacin concentrations in the tear fluid. After the course of therapy, the plug would resorb and be absent from the punctum by day 30. MP retention in the punctum was 95% (19/20) through day 10, and all plugs were absent at day 30. Average moxifloxacin concentrations in the tear film ranged from 155 to 785 ng/mL for Study 1 and 2,465 to 3,236 ng/mL for Study 2 through day 7. These values were above the target of 250 ng/mL for all time points except for day 1 of Study 1. The authors concluded that the MP delivered and maintained moxifloxacin tear fluid concentrations at therapeutic levels above the MIC(90) values for common susceptible conjunctivitis pathogens for 7 days (Study 2). The MP also exhibited a favorable safety and tolerability profile and, hence, may be a viable alternative to topical antibiotic drops for the treatment of bacterial conjunctivitis. Limitations of this study include non-randomization and a small sample size.

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0358T</td>
<td>Bioelectrical impedance analysis whole body composition assessment, with interpretation and report</td>
</tr>
</tbody>
</table>

Bioelectrical impedance analysis whole body composition assessment is unproven and not medically necessary due to insufficient clinical evidence of safety/efficacy in published peer-reviewed medical literature.

Clinical Evidence

Bioelectrical impedance analysis (BIA) is a commonly used method for estimating body composition, and in particular body fat. Since the advent of the first commercially available devices in the mid-1980s the method has become popular owing to its ease of use, portability of the equipment and it’s relatively low cost compared to some of the other methods of body composition analysis. It is familiar in the consumer market as a simple instrument for estimating body fat. BIA actually determines the electrical impedance, or opposition to the flow of an electric current through body tissues which can then be used to calculate an estimate of total body water (TBW). TBW can be used to estimate fat-free body mass and, by difference with body weight, body fat. Research studies have shown that BIA was quite variable and that some users did not regard it as providing an accurate measure of body composition. In recent years technological improvements have made BIA a more reliable and therefore more acceptable way of measuring body composition.

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

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

In this study, Widen et al. (2014) was attempting to provide validation of bioelectric impedance analysis. The purpose of the study was to measure the total body water and percent body fat before and 12 months after bariatric surgery. The findings showed that the T0 to T12 median (IQR) change in deuterium TBW and 3C%fat was -6.4 L (6.4 L) and -14.8% (13.4%), respectively. There were no statistically significant differences between deuterium and BIA determined TBW [median (IQR) difference: T0-0.1 L (7.1 L), p = 0.75; T12 0.2 L (5.7 L), p = 0.35; Δ 0.35 L (6.3 L), p = 1.0]. Compared with 3C, BIA underestimated % fat at T0 and T12 [T0 -3.3 (5.6), p < 0.001; T12 -1.7 (5.2), p = 0.04] but not change [0.7 (8.2), p = 0.38]. Except for %fat at 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.

No professional society guidelines addressing this technology were identified.

Reference(s)


<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0381T</td>
<td>External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
</tr>
<tr>
<td>0382T</td>
<td>External heart rate and 3-axis accelerometer data recording up to 14 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only</td>
</tr>
<tr>
<td>0383T</td>
<td>External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
</tr>
<tr>
<td>0384T</td>
<td>External heart rate and 3-axis accelerometer data recording from 15 to 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only</td>
</tr>
<tr>
<td>0385T</td>
<td>External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; includes report, scanning analysis with report, review and interpretation by a physician or other qualified health care professional</td>
</tr>
<tr>
<td>0386T</td>
<td>External heart rate and 3-axis accelerometer data recording more than 30 days to assess changes in heart rate and to monitor motion analysis for the purposes of diagnosing nocturnal epilepsy seizure events; review and interpretation only</td>
</tr>
</tbody>
</table>

A nocturnal epilepsy monitoring system that records external heart rate and accelerometer motion data is investigational, unproven and not medically necessary due to lack of U.S. Food and Drug Administration approval.
(FDA) approval and insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
The ProGuardianREST™ (Cyberonics, Inc.) monitoring system is designed to sense changes in heart rate or movement during sleep in people with epilepsy. The device includes an adhesive patch connected to a sensor that continuously detects and records heart rate and movement which communicates with a base hub device. (ProGuardian website) This device has not yet received FDA approval.

No studies evaluating a device with these features were identified in the clinical literature.

Reference

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0387T</td>
<td>Transcatheter insertion or replacement of permanent leadless pacemaker, ventricular</td>
</tr>
<tr>
<td>0388T</td>
<td>Transcatheter removal of permanent leadless pacemaker, ventricular</td>
</tr>
<tr>
<td>0389T</td>
<td>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, review and report, leadless pacemaker system</td>
</tr>
<tr>
<td>0390T</td>
<td>Peri-procedural device evaluation (in person) and programming of device system parameters before or after a surgery, procedure or test with analysis, review and report, leadless pacemaker system</td>
</tr>
<tr>
<td>0391T</td>
<td>Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, leadless pacemaker system</td>
</tr>
</tbody>
</table>

Leadless pacemakers are unproven and not medically necessary for treating cardiac arrhythmias due to insufficient clinical evidence of safety and/or efficacy in the published peer-reviewed medical literature.

Clinical Evidence
Leadless pacemakers are much smaller than traditional pacemakers and do not require surgery to implant. They are delivered directly into the ventricle of the heart through the femoral vein using a steerable catheter that eliminates the need to surgically create a pocket for the pacemaker and leads. The devices are designed to be retrievable so they can be repositioned during implantation and later retrieved if necessary. Potential advantages are fewer adverse events, fewer lead complications and improved quality of life.


An ECRI report concluded that very preliminary evidence suggests that the Nanostim™ leadless pacemaker might be effective for treating bradycardia. Available information is insufficient to determine whether it is as safe and effective as, or more safe and effective than, traditional pacemakers. No clinical trial data directly comparing the two types of pacemakers is available. (ECRI, 2014)

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

Using historical comparisons, Reynolds et al. (2016) performed an interim analysis of the primary end points when 300 patients reached 6 months of follow-up. The primary safety end point was freedom from system- or procedure-related major complications. The primary efficacy end point was the percentage of patients with low and stable pacing capture thresholds at 6 months. The safety and efficacy end points were evaluated against performance goals (based on historical data) of 83% and 80%, respectively. The authors also compared the rates of major complications with those in a control cohort of 2,667 patients with transvenous pacemakers from six previously published studies. The device was successfully implanted in 719 of 725 patients (99.2%). Ninety-six percent (696 of 725) of patients receiving the device achieved freedom from device- or procedure-related major complications through 6 months. The primary efficacy end point rate was 98.3% among 292 of 297 patients with paired 6-month data. Although there were 28 major complications in 25 patients, patients with transcatheter pacemakers had significantly fewer major complications than control patients. The authors concluded that the transcatheter pacemaker met the prespecified safety and efficacy goals. The device had a safety profile similar to that of a transvenous system while providing low
and stable pacing thresholds. Duray et al. (2017) reported 12-month safety data and 24-month electrical performance. The long-term safety objective was achieved with a freedom from major complication rate of 96.0% at 12 months. The risk of major complications for patients with Micra (n=726) was 48% lower than that for patients with transvenous systems through 12 months postimplant. Across subgroups of age, sex and comorbidities, Micra reduced the risk of major complications compared to transvenous systems. The authors reported that long-term performance of the Micra transcatheter pacemaker remains consistent with previously reported data. This study is limited by lack of comparison with a randomized control group and short-term follow-up. Further studies are needed to assess long-term efficacy, observed longevity and ease of removal.

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

A Hayes report concluded that available published evidence is insufficient to draw firm conclusions about health outcomes for the Micra device or to determine the procedural and safety risks associated with the device. The benefits and risks of the Micra device relative to a standard VVIR pacemaker or another leadless pacemaker are unknown; no randomized trials to date have directly compared these devices. (Hayes, 2016)

**LEADLESS II Trial**

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

Reddy et al. (2015) reported on the first 300 patients (primary cohort) who had reached the 6-month primary endpoint. Data from these patients was analyzed for the primary efficacy and safety endpoints at 6 months. The primary efficacy endpoint was acceptable pacing threshold and sensing amplitude. The primary safety endpoint was freedom from device-related serious adverse events. The primary efficacy endpoint was met in 270 of the 300 patients (90%), and the primary safety endpoint was met in 280 of the 300 patients (93.3%). At 6 months, device-related serious adverse events were observed in 6.7% of the patients. Events included device dislodgement with percutaneous retrieval (1.7%), cardiac perforation (1.3%), and pacing-threshold elevation requiring percutaneous retrieval and device replacement (1.3%). An additional 226 patients were enrolled as part of the ongoing trial. The total cohort of 526 patients was assessed for device-related and non-device-related serious adverse events. The device was successfully implanted in 504 of the 526 patients (95.8%). Data from these patients was analyzed together with data from the primary cohort that had extended follow-up beyond 6 months. In the total cohort, the mean sensing and pacing threshold values improved significantly over time. In the total cohort of 526 patients, the rate of device-related serious adverse events was 6.5%, including cardiac perforation in 1.5% of the patients, device dislodgement in 1.1% and device retrieval due to elevated pacing thresholds in 0.8%. In the total cohort, there were 28 deaths (5.3%) during follow-up. The authors reported that the leadless pacemaker met prespecified pacing and sensing requirements in the large majority of patients. This study is limited by observational design and short-term follow-up. Further studies that directly compare leadless pacemakers with conventional devices are needed to determine the safety and efficacy of these devices.

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

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

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

A Hayes report concluded that available published evidence is insufficient to draw firm conclusions about health outcomes for the Nanostim device or to determine the procedural and safety risks associated with the device. The benefits and risks of the Nanostim device relative to a standard VVIR pacemaker or another leadless pacemaker are unknown; no randomized trials to date have directly compared these devices. (Hayes, 2016)

No professional society guidelines addressing this technology were identified.

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0394T</td>
<td>High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed</td>
</tr>
<tr>
<td>0395T</td>
<td>High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed</td>
</tr>
</tbody>
</table>

High dose rate electronic brachytherapy is unproven and not medically necessary for treating all indications due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

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

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

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

The American Society for Radiation Oncology (ASTRO) model policy for brachytherapy states that commercially available electronic brachytherapy (EBT) devices closely resemble the size and shape of commercially available high dose rate (HDR) brachytherapy devices and replicate the radiation dose distribution administered with HDR brachytherapy devices. The published literature establishing the clinical equivalence of electronic brachytherapy to HDR is evolving. (ASTRO, 2012)

**Breast Cancer**

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

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

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

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer do not specifically address electronic brachytherapy. The guidelines state that boost treatment in the setting of breast conservation can be delivered using enface electrons, photons or brachytherapy. When addressing APBI, the guidelines indicate that preliminary studies suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast radiation therapy. However, follow-up is limited and studies are ongoing. Patients are encouraged to participate in clinical trials. (NCCN, 2017)

**Skin Cancer**

Ballester-Sánchez et al. (2016) assessed outcomes from two consecutive prospective, single-center, non-randomized, pilot studies using different radiation doses of electronic brachytherapy with the Esteya® system for treating superficial and nodular basal cell carcinoma. Twenty patients were treated in each study. Group 1 was treated with 36.6 Gy in 6 fractions of 6.1 Gy, and Group 2 with 42 Gy in 6 fractions of 7 Gy. Cure rate, acute toxicity and late toxicity related to cosmesis were analyzed. Group 1 achieved a 90% clinical cure rate at 1 year. Group 2 achieved a 95% clinical cure rate at 1 year. The differences in acute toxicity and cosmetic results between the two treatment groups were not statistically significant. The authors noted that the role of electronic brachytherapy in the treatment of basal cell carcinoma is still to be defined. Both studies were limited by small numbers, short-term follow-up and lack of randomization or comparison of outcomes to established surgical treatment (e.g., Mohs surgery).
Bhatnagar (2013) reported clinical outcomes at 1 year or more after high-dose-rate (HDR) electronic brachytherapy (EBT) using surface applicators for the treatment of nonmelanoma skin cancer (NMSC). A total of 122 patients with 171 NMSC lesions were treated with EBT to a dose of 40Gy in eight fractions, delivered twice weekly. At followup, patients were assessed for acute and late toxicities, cosmesis and local control. No recurrences were reported with a mean follow-up of 10 months. Follow-up data at 1 year or more were available for 46 lesions in 42 patients. Hypopigmentation (all Grade 1) was present in 5 (10.9%) of 46 lesions at 1 year. Other late effects at 1 year included dry desquamation, alopecia and rash dermatitis, which occurred in 1 (2.2%), 1 (2.2%) and 3 (6.5%) of 46 lesions, respectively. Cosmesis was excellent for 39 (92.9%) and good for 3 (7.1%) of the 42 evaluable lesions. This study is limited by lack of randomization and control and short-term follow-up.

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

Delishaj et al. (2015) retrospectively evaluated 57 lesions in 39 elderly patients affected with NMSC treated with HDR-BT 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.

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, 2017a; NCCN 2017b)

Several clinical trials are ongoing.

An American Academy of Dermatology position statement on electronic surface brachytherapy (2014) presents several guiding principles, including the following:

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

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

Reference(s)

©1996-2018, Oxford Health Plans, LLC

Page 39 of 127
Effective 05/01/2018


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0396T</td>
<td>Intra-operative use of kinetic balance sensor for implant stability during knee replacement arthroplasty (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

The use of intra-operative kinetic balance sensor for implant stability during knee replacement arthroplasty is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
The surgeon temporarily inserts the sensor between the components of a knee implant during surgery. It allows the surgeon to capture data about the knee in order to customize implant positioning. Once the implant position is stabilized, the sensor is removed and replaced with a permanent implant.

The US Food and Drug Administration (FDA) approved the Verasense Knee System under 510(K) (K130380) on June 18, 2013. VERASENSE is the first intraoperative instrument system to combine quantifiable data on limb alignment, implant position and soft tissue balancing for surgeons during total knee replacement surgery.

Hayes (2016) Technology at a Glance conducted a literature review of Verasense sensor. They concluded that the quality of evidence does not allow for definitive conclusions to be drawn regarding the efficacy, comparative effectiveness, or safety of Verasense-assisted TKA. Currently, there is no evidence to support the use of kinetic balance sensor implants over other soft-tissue balancing procedures. The limitations of the individual studies were extensive, including: limited follow-up, lack of active comparators, lack of randomization, and the evaluation of the sensor-embedded device after manual balancing had occurred. The overall quality of the evidence was assessed taking into consideration the quality of individual studies; the precision, directness, and consistency of data; and the applicability of the data to general practice. Additional randomized controlled trials (RCTs) are ongoing and are necessary in order to adequately assess the clinical effectiveness and utility of VSA-TKA compared with manual intraoperative soft-tissue balancing.

One multicenter evaluation of intraoperative sensors was conducted by Gustke et al. (2014). There were limitations to this study. Firstly, the study did not have a control group. The primary design of the multicenter evaluation was intended to be observational. Secondly, the number of unbalanced patients was much smaller than balanced patients. While power analyses did confirm that comparisons could be reasonably made, an equal proportion of patients in each group would have been more favorable. Controlled trials with longer follow-up are needed to demonstrate that use of intra-operative kinetic balance sensors for implant stability during knee replacement arthroplasty results in improved clinical outcomes.

There are currently two clinical trials for the Verasense in TKA were found on the ClinicalTrials.gov database. One is a randomized and blinded and one is prospective clinical study evaluating intraoperative sensing during TKA. (NCT02290119, NCT02286739)

There was no information found in MCG™ or ECRI for this treatment. No formal position statements issued by any societies at this time.

Reference(s)


**Clinical Evidence**

Magnetic resonance guided focused ultrasound therapy (MRgFUS) (ExAblate®; InSightec Ltd.) is a noninvasive treatment that integrates magnetic resonance imaging (MRI) with high-intensity focused ultrasound for the precise planning and control of the localized delivery of high-frequency sound waves to destroy lesions in tissue or bone. The ExAblate Neuro system is being evaluated for tremor dominant Parkinson's disease and essential tremor. On July 11, 2016, the Food and Drug Administration (FDA) approved ExAblate Neuro for use in patients with essential tremor who have not responded to medication. Despite FDA approval, findings from ongoing clinical trials will need to be completed to determine whether any patient populations may benefit from this therapy. A double-blind randomized controlled trial of transcranial ExAblate and sham transcranial ExAblate evaluating patients with severe, medication refractory essential tremor is scheduled to be completed in December 2017. For more information, see ClinicalTrials.gov Identifier NCT01827904.

Elias et al. (2016) enrolled 76 patients with moderate-to-severe essential tremor that had not responded to at least two trials of medical therapy and randomly assigned them in a 3:1 ratio to undergo unilateral focused ultrasound thalamotomy with magnetic resonance imaging (MRI) guidance or a sham procedure. The Clinical Rating Scale for Tremor and the Quality of Life in Essential Tremor Questionnaire were administered at baseline and at 1, 3, 6, and 12 months. Tremor assessments were videotaped and rated by an independent group of neurologists who were unaware of the treatment assignments. The primary outcome was the between-group difference in the change from baseline to 3 months in hand tremor, rated on a 32-point scale (with higher scores indicating more severe tremor). After 3 months, patients in the sham-procedure group could cross over to active treatment (the open-label extension cohort). 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. The improvement in the thalamotomy group was maintained at 12 months (change from baseline, 7.2 points). Secondary outcome measures assessing disability and quality of life also improved with active treatment (the blinded thalamotomy cohort) as compared with the sham procedure. Adverse events in the thalamotomy group included gait disturbance in 36% of patients and paresthesias or numbness in 38%; these adverse events persisted at 12 months in 9% and 14% of patients, respectively. The authors concluded that MRI-guided focused ultrasound thalamotomy reduced hand tremor in patients with essential tremor. Permanent neurological deficits such as sensory and gait disturbances can occur. The limitations of this study include small study population and limited follow-up which was 12 months. Studies with longer followup are needed to determine the sustained benefit of this treatment.

Zaaroor et al. (2017) evaluated patients with severe medication-resistant tremor who underwent unilateral ventral intermediate nucleus (VIM) thalamotomy using MR-guided focused ultrasound (MRgFUS). Thirty patients underwent MRgFUS, including 18 with essential tremor (ET), 9 with Parkinson's disease (PD), and 3 with ET-PD. The mean age of the study population was 68.9 ± 8.3 years. MRgFUS created a lesion at the planned target in all patients, resulting in cessation of tremor in the treated hand immediately following treatment. At 1 month posttreatment, the mean Clinical Rating Scale for Tremor (CRST) score of the patients with ET decreased from 40.7 ± 11.6 to 9.3 ± 7.1 and was 8.2 ± 5.0 six months after treatment. During follow-up of 6-24 months (mean 11.5 ± 7.2 months), tremor reappeared in 6 of the patients (2 with ET, 2 with PD, and 2 with ET-PD), to a lesser degree than before the procedure in 5. Adverse events that transiently occurred during sonication included headache (n = 11), short-lasting vertigo (n = 14) and dizziness (n = 4), nausea (n = 3), burning scalp sensation (n = 3), vomiting (n = 2) and lip paresthesia (n = 2). Adverse events that lasted after the procedure included gait ataxia (n = 5), unsteady feeling (n = 4), taste disturbances (n = 4), asthenia (n = 4), and hand ataxia (n = 3). No adverse event lasted beyond 3 months. Patients underwent on average 21.0 ± 6.9 sonications with an average maximal sonication time of 16.0 ± 3.0 seconds. The authors concluded that MRgFUS VIM thalamotomy to relieve medication-resistant tremor was safe and effective in patients with ET, PD, and ET-PD. Current results emphasize the superior adverse events profile of MRgFUS over other surgical approaches for treating tremor with similar efficacy. According to the authors, large randomized studies are needed to assess prolonged efficacy and safety.

In a retrospective study, Huss et al. (2015) compared functional outcomes and quality of life in essential tremor patients treated with either bilateral Vim deep brain stimulation (DBS) or unilateral procedures (focused ultrasound or DBS). The authors hypothesized that all three would effectively treat the dominant hand and positively impact functional outcomes and quality of life. The study included medication-refractory essential tremor patients with...
bilateral Vim DBS (n = 57), unilateral Vim DBS (n = 13), or unilateral focused ultrasound Vim thalamotomy (n = 15). Tremor was rated for all patients before and after treatment, using the Clinical Rating Scale for Tremor and Quality of Life in Essential Tremor Questionnaire. Patients undergoing bilateral DBS treatment had more baseline tremor and worse quality of life scores. Patients had significant improvements in tremor symptoms and quality of life with all three treatments. Both DBS procedures improved axial tremor. No difference was seen in the degree of improvement in upper extremity tremor score, disability, or overall quality of life between bilateral and either unilateral procedure. The authors concluded that bilateral thalamic DBS improves overall tremor more than unilateral DBS or focused ultrasound treatment; however, unilateral treatments are equally effective in treating contralateral hand tremor. The authors stated that despite the greater overall tremor reduction with bilateral DBS, there is no difference in disability or quality of life comparing bilateral versus unilateral treatments. Further research with randomized controlled trials is needed to validate these findings.

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

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0400T</td>
<td>Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia; one to five lesions</td>
</tr>
<tr>
<td>0401T</td>
<td>Multi-spectral digital skin lesion analysis of clinically atypical cutaneous pigmented lesions for detection of melanomas and high risk melanocytic atypia; six or more lesions</td>
</tr>
</tbody>
</table>

Multi-spectral digital skin lesion analysis is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature. Too few studies are available to evaluate the consistency of patient-oriented outcomes of interest among different studies.

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

Monheit et al. (2011) conducted a prospective, multicenter, blinded study to demonstrate the safety and effectiveness of MelaFind, a noninvasive and objective computer-vision system designed to aid in detection of early pigmented cutaneous melanoma. The diagnostic performance of MelaFind and of study clinicians was evaluated using the histologic reference standard. Standard images and patient information for a subset of 50 randomly selected lesions (25 melanomas) were used in a reader study of 39 independent dermatologists to estimate biopsy sensitivity to melanoma, participating clinicians representing 3 academic and 4 community practices in the United States with expertise in management of pigmented skin lesions. A total of 1383 patients with 1831 lesions enrolled from January
2007 to July 2008; 1632 lesions (including 127 melanomas-45% in situ-with median Breslow thickness of invasive lesions, 0.36 mm) were eligible and evaluable for the study end points sensitivity of MelaFind; specificities and biopsy ratios for MelaFind and the study investigators; and biopsy sensitivities of independent dermatologists in the reader study. The measured sensitivity of MelaFind was 98.4% (125/127 melanomas) with a 95% lower confidence bound at 95.6% and a biopsy ratio of 10.8:1; the average biopsy sensitivity of dermatologists was 78% in the reader study. Including borderline lesions (high-grade dysplastic nevi, atypical melanocytic proliferations, or hyperplasias), MelaFind’s sensitivity was 98.3% (172/175), with a biopsy ratio of 7.6:1. On lesions biopsied mostly to rule out melanoma, MelaFind’s average specificity (9.9%) was superior to that of clinicians (3.7%). The author concluded that MelaFind is a safe and effective tool to assist in the evaluation of pigmented skin lesions.

In May 2015, FDA issued a Class II device recall of the MelaFind system. According to FDA, "the probability and histogram data within the Melafind's device displayed user interface is not included in the PMA supplement."

NCCN guidelines on melanoma do not address multi-spectral digital skin lesion analysis. (NCCN, 2016)

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0408T</td>
<td>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</td>
</tr>
<tr>
<td>0409T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator only</td>
</tr>
<tr>
<td>0410T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; atrial electrode only</td>
</tr>
<tr>
<td>0411T</td>
<td>Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; ventricular electrode only</td>
</tr>
<tr>
<td>0412T</td>
<td>Removal of permanent cardiac contractility modulation system; pulse generator only</td>
</tr>
<tr>
<td>0413T</td>
<td>Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)</td>
</tr>
<tr>
<td>0414T</td>
<td>Removal and replacement of permanent cardiac contractility modulation system pulse generator only</td>
</tr>
<tr>
<td>0415T</td>
<td>Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)</td>
</tr>
<tr>
<td>0416T</td>
<td>Relocation of skin pocket for implanted cardiac contractility modulation pulse generator</td>
</tr>
<tr>
<td>0417T</td>
<td>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</td>
</tr>
<tr>
<td>0418T</td>
<td>Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording and disconnection per patient encounter, implantable cardiac contractility modulation system</td>
</tr>
</tbody>
</table>

**Cardiac contractility modulation, using an implantable device, is investigational, unproven and not medically necessary for treating chronic heart failure due to lack of U.S. Food and Drug Administration (FDA) approval and insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

However, depending on the member specific benefit plan document, coverage may be available through participation in an eligible clinical trial.
Clinical Evidence
Cardiac contractility modulation (CCM) signals are nonexcitatory electrical signals delivered during the cardiac absolute refractory period (between beats) that enhance the strength of cardiac muscular contraction. CCM signals are provided by a pacemaker-like device that is connected to three standard pacemaker leads threaded through veins into the right ventricle. One lead is used to sense atrial activity, and the other two are used to sense ventricular activity and deliver the CCM signals. In contrast to a pacemaker or a defibrillator, the system is designed to modulate the strength of contraction of the heart muscle rather than the rhythm.

The Optimizer™ implantable CCM system has not yet received FDA approval and is limited to investigational use in the United States. The device is intended for patients who are unable to achieve desired optimal medical therapy goals and are not candidates for cardiac resynchronization therapy. Several clinical trials are ongoing.

Klopp et al. (2016) conducted a single center pilot evaluation study involving 19 medically refractory symptomatic patients with heart failure and reduced left ventricular function who underwent implantation of an Optimizer system. Patients were randomized into one of two treatment groups; 5 h/day CCM treatment or 12 h/day CCM treatment. Subjects and evaluating physicians were blinded to the study group. Subjects returned to the hospital after 12 and 24 weeks. Efficacy evaluations included changes from baseline to 24 weeks in Minnesota Living With Heart Failure Questionnaire score (MLWHFQ), maximal oxygen consumption in the cardio-pulmonary stress test (peak VO2), NYHA classification, 6-min walk distance (6MWD), and ejection fraction (EF). At the end of 24 weeks, clinical improvement was observed in the entire cohort in all efficacy measures. There were no significant differences, either clinically or statistically, between the groups receiving CCM for 5 h/day vs. 12 h/day. Given the small sample size, further studies are warranted.

In a prospective, multicenter, randomized controlled trial (FIX-HF-5), Kadish et al. (2011) evaluated the safety and efficacy of CCM in patients with heart failure. A total of 428 NYHA class III or IV, narrow QRS patients with EF ≤35% were randomized to optimal medical therapy (OMT) plus CCM (n=215) or OMT alone (n=213). Efficacy was assessed by ventilatory anaerobic threshold (VAT), peak oxygen consumption and quality of life measures at 6 months. The primary safety end point was a test of noninferiority between groups at 12 months for the composite of all-cause mortality and hospitalizations. While VAT (primary end point) did not improve at 6 months, CCM significantly improved peak oxygen consumption and quality of life measures over OMT. Forty-eight percent of OMT and 52% of CCM patients experienced a safety end point. Limitations include short-term follow-up and the inability to blind participants to therapy being used. The authors concluded that further study is required to clarify the role of CCM as a treatment for medically refractory heart failure.

Borggrefe et al. (2008) conducted a multicenter, randomized, double blind, crossover study of CCM signals in patients with heart failure. One hundred and sixty-four patients with EF <35% and NYHA Class II (24%) or III (76%) symptoms received a CCM pulse generator. Patients were randomly assigned to Group 1 (n 80, CCM treatment 3 months, sham treatment second 3 months) or Group 2 (n=84, sham treatment 3 months, CCM treatment second 3 months). Baseline EF, peak oxygen consumption (VO2, peak) and quality of life measures were similar between the groups. VO2, peak increased similarly in both groups during the first 3 months (placebo effect). During the next 3 months, VO2, peak decreased in the group switched to sham and increased in patients switched to active treatment. Quality of life measures trended better with treatment during the first 3 months, increased during the second 3 months in the group switched to sham and decreased further in patients switched to active treatment. The authors concluded that, overall, in patients with chronic heart failure and left ventricular dysfunction, CCM signals were safe and improved exercise tolerance and quality of life with as little as 3-months of treatment. Limitations include short-term follow-up and a noted placebo effect. Larger scale studies of safety and effectiveness of CCM signals are needed to confirm these findings.

Neelagaru et al. (2006) conducted a randomized, double-blind, pilot study to determine the feasibility of safely and effectively delivering CCM signals in patients with heart failure. Forty-nine patients with ejection fraction <35%, normal QRS duration (105 +/- 15 ms) and NYHA class III or IV heart failure despite medical therapy received a CCM pulse generator. Patients were randomized to have their devices programmed to deliver CCM signals (n=25) or to remain off (n=24). After 6 months, there were no statistically significant differences in NYHA class, 6-minute walk, cardiopulmonary stress test and quality of life measures. More patients in the treatment group were free of hospitalization for any cause at 6 months (84% vs 62%). The authors concluded that despite a sicker population in the treatment group, no specific safety concerns emerged with chronic CCM signal administration. This study is limited by small sample size and short-term follow-up. Further study is required to definitively define the safety and efficacy of CCM signals.

European Society of Cardiology guidelines for the diagnosis and treatment of heart failure state that the clinical evidence is insufficient to support specific recommendations for cardiac contractility modulation. (Ponikowski et al., 2016)
**Reference(s)**


---

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0421T</td>
<td>Transurethral waterjet ablation of prostate, including control of post-operative bleeding, including ultrasound guidance, complete (vasectomy, meatomny, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included when performed)</td>
</tr>
</tbody>
</table>

**Transurethral waterjet ablation of the prostate, also known as aquablation, is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

A small published study and only a handful of abstracts were found addressing the use of transurethral waterjet ablation to treat BPH. Therefore, it is not possible to conclude whether this new technology has a beneficial effect on health outcomes. Robust studies with larger numbers of patients and longer follow-up are needed to confirm preliminary results.

**Clinical Evidence**

Benign prostatic hyperplasia (BPH) is a condition that occurs in men when the prostate gland becomes enlarged due to noncancerous proliferation of smooth muscle and epithelial cells of the prostate. Initial treatment for BPH is usually medical therapy, but this often provides only modest relief. Up to 30% of patients require surgical intervention. Aquablation is a medical device that allows rapid removal of prostate tissue without leaving a zone of thermal damage on the treated tissue. It utilizes a waterjet for automated tissue resection as well as for optical energy delivery for cauterization in the treatment of BPH. (Hayes, 2016)

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

An abstract from The Journal of Urology reported on nine patients treated with Aquablation (the AquaBeam®, PROCEPT BioRobotics), stating that all procedures were technically successful, and there were no peri-operative complications. The limitations of this study are the small patient sample, and the fact that the study was funded by the device manufacturer.
Another abstract from Research and Reports in Urology addressing minimally invasive devices for treating PBH, including aquablation concludes: "More systematic laboratory research and currently ongoing clinical trials need to be completed to elucidate the potential role of these newer devices for the treatment of LUTS/BPH."

In 2015, the device's manufacturer received an Investigation Device Exemption (IDE) from the FDA to collect data on safety and effectiveness in the U.S. Currently, there's an on-going prospective multi-center randomized blinded study comparing outcomes observed with aquablation to those observed with transurethral resection of the prostate. In this study, the primary endpoints for safety and efficacy will be assessed at 3 and 6 months, respectively, and subjects will be followed out to 3 years to collect long-term clinical data. (ClinicalTrials.gov Identifier:NCT02505919)

The American Urological Association (AUA) guidelines for management of BPH do not contain any recommendations for waterjet excision of the prostate. AUA notes that surgical intervention should be reserved for patients with moderate to severe symptoms of BPH, and that transurethral resection of the prostate (TURP) is still the gold standard of interventional treatment.

Reference(s)
Waterjet Ablation Therapy for Endoscopic Resection of Prostate Tissue (WATER).

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0424T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; complete system (transvenous placement of right of left stimulation lead, sensing lead, implantable pulse generator)</td>
</tr>
<tr>
<td>0425T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
</tr>
<tr>
<td>0426T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; stimulation lead only</td>
</tr>
<tr>
<td>0427T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; pulse generator only</td>
</tr>
<tr>
<td>0428T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only</td>
</tr>
<tr>
<td>0429T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
</tr>
<tr>
<td>0430T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; stimulation lead only</td>
</tr>
<tr>
<td>0431T</td>
<td>Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only</td>
</tr>
<tr>
<td>0432T</td>
<td>Repositioning of neurostimulator system for treatment of central sleep apnea; stimulation lead only</td>
</tr>
<tr>
<td>0433T</td>
<td>Repositioning of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
</tr>
<tr>
<td>0434T</td>
<td>Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea</td>
</tr>
<tr>
<td>0435T</td>
<td>Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session</td>
</tr>
<tr>
<td>0436T</td>
<td>Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study</td>
</tr>
</tbody>
</table>

Implantable neurostimulation devices for the treatment of central sleep apnea are investigational, unproven and not medically necessary due to lack of U.S. Food and Drug Administration (FDA) approval and insufficient clinical evidence of safety and/or efficacy in the published peer-reviewed medical literature. However, depending on the member specific benefit plan document, coverage may be available through participation in an eligible clinical trial. Implantable neurostimulation devices have not yet received FDA approval and are limited to investigational use.
Clinical Evidence

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

An expert analysis on the basics of sleep apnea for the American College of Cardiology recommends treating the underlying cause of CSA first (e.g., heart failure in Cheyne-Stokes respirations, reduction of respiratory depressant dosing). Most patients are managed medically with diuretics, digoxin, angiotensin-converting enzyme (ACE) inhibitors, and beta blockers. Research has shown that once heart failure is clinically improved, CSA often improves as well. Both continuous positive airway pressure (CPAP) and nocturnal oxygen supplementation have been shown to reduce episodes of CSA, improve cardiac function and exercise capacity, and reduce sympathetic activity. However, neither therapy has been shown to reduce mortality, and adherence to CPAP therapy remains a significant problem (Singh, 2013).

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

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

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

A pivotal clinical trial of the Respicardia remedē® System is currently ongoing, with an estimated study completion date of late 2017. The primary purpose of this prospective, multicenter, randomized trial is to evaluate the safety and effectiveness of therapy delivered by the remedē® System in subjects with moderate to severe central sleep apnea and optimal medical management, compared to outcomes in randomized control subjects receiving optimal medical management and implanted but inactive remedē® systems.
No professional society guidelines addressing implantable neurostimulators for treatment of central sleep apnea were identified.

**Reference(s)**


ClinicalTrials.gov. Respicaedra, Inc. Pivotal Trial of the remedē System. (NCT01816776)


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

**Percutaneous cryoablation of upper/lower extremity distal/peripheral nerve(s), of nerve plexuses or of other truncal nerves is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

**Clinical Evidence**

Cryoablation of nerves is a procedure used to temporarily block nerve conduction along nerve pathways by inserting a small probe which freezes the targeted nerve, permitting regeneration of that nerve’s structure and function. No meaningful published literature was identified on treatment of peripheral neuromas or lesions other than studies treating Morton neuroma. Due to the lack of high-quality, controlled trials comparing ablative techniques to alternatives, the evidence is insufficient to conclude if the use of cryoablation of peripheral nerves has a beneficial effect on health outcomes.

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

No formal position statements have been issued by any societies at this time.

There is one clinical trial in progress studying the use of cryoablation with Intermetatarsal Neuroma. For more information, please see [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

**Reference(s)**

Real time spectral analysis of prostate tissue by fluorescence spectroscopy is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in the published peer-reviewed medical literature.

Clinical Evidence
Sharma et al. (2014) conducted a study to evaluate the capability of detecting prostate cancer (PCa) using a dual-modal optical device (dMOD), which incorporates dual measurements from auto-fluorescence lifetime spectroscopy (AFLS) and light reflectance spectroscopy (LRS). Patients were selected with an intermediate-to-high grade of disease and a moderate-to-high volume of prostate cancer. Both AFLS and LRS were taken on n = 724 distinct locations from both prostate capsular (nc = 185) and parenchymal (np = 539) tissues, including PCa tissue, benign peripheral zone tissue and benign prostatic hyperplasia of fresh ex vivo radical prostatectomy specimens from 37 patients. The study reported accuracy above 90% in differentiating benign from malignant tissue and a sensitivity and specificity of 75% and 87.3%, respectively, for PCa detection. The authors concluded that the dMOD approach is able to discriminate prostatic tissue types of ex vivo prostate specimens with excellent classification sensitivity, specificity and accuracy. They did acknowledge that re-evaluation of their methodology under in vivo setting may yield different spectral outputs; the sample size was relatively small, and limited to patients with high grade PCa.

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

No professional society guidelines addressing this technology were identified.

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0443T</td>
<td>Real time spectral analysis of prostate tissue by fluorescence spectroscopy, including imaging guidance (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

The placement of drug eluting ocular inserts under the eyelid(s) is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

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

Brandt et al. (2016) conducted a parallel-arm, multicenter, double-masked, randomized, controlled trial of 130 patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). Eligible patients were randomized 1:1 to receive a bimatoprost ocular insert plus artificial tears twice daily or a placebo insert plus timolol (0.5% solution) twice daily for 6 months after a screening washout period. Diurnal IOP measurements (at 0, 2, and 8 hours) were obtained at baseline; weeks 2, 6, and 12; and months 4, 5, and 6. A mean reduction from baseline IOP of -3.2 to -6.4 mmHg
was observed for the bimatoprost group compared with -4.2 to -6.4 mmHg for the timolol group over 6 months. The study met the non-inferiority definition at 2 of 9 time points but was underpowered for the observed treatment effect. Adverse events (AEs) were consistent with bimatoprost or timolol exposure; no unexpected ocular AEs were observed. Primary retention rate of the insert was 88.5% of patients at 6 months. The authors concluded that clinically relevant reduction in mean intraocular pressure (IOP) was observed over 6 months with a bimatoprost ocular insert and seems to be safe and well tolerated. According to the authors, longer-term studies of a high-risk (low-adherence) population will be required to demonstrate the full usefulness of this ocular drug-delivery system in preserving visual fields, but such studies will require several years of follow-up and currently are not feasible at this stage of development.

Torrón et al. (2013) compared the efficacy and safety of an ocular insert versus conventional mydriasis in cataract surgery. Seventy patients who were undergoing cataract surgery were included in the study. Thirty five patients (Group 1) received instillation of mydriatic drops (tropicamide 1%, phenylephrine 10%, and cyclopentolate 1%) prior to surgery, and 35 patients (Group 2) had a Mydriasert insert (Théa Pharma) (0.28 mg of tropicamide and 5.4 mg of phenylephrine hydrochloride) placed in the inferior fornix of the eye. Pupil size before and after surgery, blood pressure, and heart rate were measured. Before surgery, pupil diameter was 9.44 ± 1.17 mm in Group 1 and 9.05 ± 1.54 in Group 2. Twenty four hours after surgery, pupil diameter was 5.20 ± 1.54 mm in Group 1 and 3.33 ± 1.15 in Group 2. The authors concluded that the effect of the Mydriasert insert was similar to conventional mydriatic agents. The authors indicated that pupil size was restored to normal faster when using the Mydriasert insert compared with conventional mydriatic agents for pupil dilation. Study limitations included a small study population and the investigators used an additional topical drug (cyclopentolate) in Group 1.

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0465T</td>
<td>Suprachoroidal delivery of pharmacologic agent (does not include supply of medication)</td>
</tr>
</tbody>
</table>

The use of suprachoroidal delivery of pharmacologic agents is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence

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

Drug delivery by injection into the suprachoroidal space is another technique that has recently been proposed in the treatment of posterior segment disease. The suprachoroidal space provides a potential route of access from the anterior region of the eye to the posterior region.

Several nonrandomized studies have been published on the use of suprachoroidal drug delivery for various posterior segment eye disorders. However, the results of these studies have many limitations.

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

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

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

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

There is inadequate evidence regarding the clinical utility of suprachoroidal injection of pharmacologic agents for the treatment of any ophthalmologic condition. Clinical outcome studies published in the peer-reviewed medical literature are needed to determine the value of this drug delivery method in the management of patients with diseases of the posterior segment of the eye.

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0469T</td>
<td>Retinal polarization scan, ocular screening with on-site automated results, bilateral</td>
</tr>
</tbody>
</table>

Retinal birefringence scanning/retinal polarization scanning is unproven and not medically necessary for the detection of eye misalignment or strabismus due to insufficient clinical evidence of safety and/or efficacy in the published peer-reviewed medical literature.

While the results of some studies show promising results for the detection of strabismus and amblyopia, current clinical literature is insufficient to substantiate the safety and efficacy of these devices. More well conducted studies with larger sample sizes including the general population are needed.

Clinical Evidence
Retinal birefringence scanners (RBS), such as the Pediatric Vision Scanner (PVS) by RebiScan, are hand held devices that measure the changes in the polarization of light returning from the eye to detect eye misalignment or strabismus during a brief scan of the eye.

The U.S. Food and Drug Administration (FDA) approved PVS on December 13, 2013 under the de novo classification utilized for devices with low to moderate risk as a strabismus detection device. Use of this device is limited. For more information, please refer to the following website:


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

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

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

A 3 year, prospective clinical trial evaluating the PVS is currently underway (NCT02536963).

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0470T</td>
<td>Optical coherence tomography (OCT) for microstructural and morphological imaging of skin, image acquisition, interpretation, and report; first lesion</td>
</tr>
<tr>
<td>0471T</td>
<td>Optical coherence tomography (OCT) for microstructural and morphological imaging of skin, image acquisition, interpretation, and report; each additional lesion (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

Optical coherence tomography (OCT) is unproven and not medically necessary for diagnosing and treating skin conditions due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
OCT is an emerging noninvasive imaging technology that produces cross-sectional images using light waves. Although a number of smaller observational studies have shown promising results, the clinical evidence supporting OCT in dermatological applications is limited at this time. Further studies, with larger sample sizes, are required to validate the applications of OCT in dermatology and compare it to the gold standard biopsy.

Cheng et al. (2015) conducted a systematic review to assess the accuracy of OCT in the diagnosis and management of basal cell carcinoma (BCC). Twenty-two studies with 556 histologically proven BCCs were included. While some studies have shown OCT to be useful in the diagnosis, treatment planning and treatment monitoring of BCC, further studies with good methodological quality are needed to implement OCT into daily practice.

Gambichler et al. (2015) performed a systematic review of the clinical application of OCT in dermatology. Twenty-five papers were selected and described OCT of epidermal thickness, skin appendages, wound healing, extracellular matrix and skin fibrosis, vascular malformations and skin tumors such as BCC, actinic keratosis and malignant melanoma. The authors noted that although it is possible to characterize normal and pathologic skin morphology by providing high-resolution images, more systematic clinical studies on reasonable sample sizes are required to validate the applications of OCT in dermatology.
Mogensen et al. (2009) assessed the diagnostic accuracy of OCT in differentiating nonmelanoma skin cancer from benign lesions and normal skin. The authors performed an observer-blinded evaluation by dermatologists and a pathologist in 104 patients with 176 lesions. Depending on the observers, sensitivity and specificity varied from 57 to 94 % and 43 to 96 %, respectively. Experienced observers reached a sensitivity of 79 to 94 % and a specificity of 85 to 96 %. Discrimination of actinic keratosis from BCC had an error rate of 50% to 52%.

**American Academy of Dermatology (AAD)**

AAD guidelines for the management of primary cutaneous melanoma do not address noninvasive technologies and state that biopsy is the first step for a definitive diagnosis of cancer. (Bichakjian et al., 2011)

**Reference(s)**


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

**Autologous adipose-derived regenerative cell therapy for scleroderma of the hands is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

**Clinical Evidence**

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

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

Del Papa et al. (2015) treated systemic sclerosis (SSc)-related digital ulcers (DUs) by implantation of autologous adipose tissue-derived cell (ATDC) fractions. Fifteen patients with SSc having a long-lasting DU in one fingertip who were unresponsive to intensive systemic and local treatment were enrolled in the study. The grafting procedure
consisted of the injection, at the base of the corresponding finger, of 0.5-1 ml of autologous ATDC fractions, separated by centrifugation of adipose tissue collected through liposuction from subcutaneous abdominal fat. Time to heal after the procedure was the primary end point of the study, while reduction of pain intensity and of analgesic use represented a secondary end point. Healing of the DUs was reached in all of the enrolled patients (mean time to healing 4.23 weeks; range 2-7 weeks). A significant reduction of pain intensity was observed after a few weeks, while the number of capillaries was significantly increased at the 3- and 6-month half video capillaroscopy (NVC) assessment. Finally, a significant after-treatment reduction of digit artery resistivity was also observed. Even with the limitations related to the small number of patients included and to the open-label design of the study, the observed strongly favorable outcome suggests that local grafting with ATDCs could represent a promising option for the treatment of SSC-related DUs. According to the authors, the positive outcome reported in this trial requires confirmation in larger, controlled studies.

Two ongoing clinical trials for autologous adipose-derived regenerative cell therapy for scleroderma were found on the www.clinicaltrials.gov website (NCT02396238 and NCT02558543).

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0493T</td>
<td>Near-infrared spectroscopy studies of lower extremity wounds (e.g., for oxyhemoglobin measurement)</td>
</tr>
</tbody>
</table>

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

Clinical Evidence
In a prospective single-center observational study, Laroche et al. (2017) evaluated near-infrared spectroscopy (NIRS) versus transcutaneous oxygen tension (TcPO2) for microcirculatory assessment of vascular transistibial stumps at the stabilized period of prosthesis fitting, as a preliminary step before exploring its ability to predict stump healing. Thirty individuals with unilateral transistibial amputation for peripheral artery disease, at the definitive stage of prosthesis fitting, able to perform a 2-minute walk test were included in the trial. Test-retest, with the stump being evaluated in supine and inclined positions, first by NIRS (tissue saturation index [TSI], oxyhemoglobin, deoxyhemoglobin, and total hemoglobin) and second by TcPO2. Subjects carried out a 2-minute walk test and visual analog scales (wound healing and pain). Feasibility and tolerance of NIRS were satisfactory. The reliability of NIRS and TcPO2 values was good. No significant relation was found between NIRS and TcPO2. No responsiveness (inclined vs supine) was reported. A significant relation between TSI and the 2-minute walk test was found. The authors concluded that NIRS is painless, complication-free, and feasible, with good reliability. Further studies with larger patient populations are necessary to determine the long-term safety and efficacy of this technology.

Roskosky et al. (2014) conducted a study to measure the thickness of the subcutaneous tissue overlaying the posterior muscle compartment in subjects with tibia fractures to determine if it might compromise rSO2 measurement in the muscle. Acute compartment syndrome is a rare but serious consequence of traumatic leg injury. Near-infrared spectroscopy (NIRS) is able to measure oxygenation to a depth of 2 cm to 3 cm below the skin, raising concerns over the ability of NIRS to accurately determine oxygenation of injured leg compartments in the presence of swelling and in the obese. Data was analyzed on 50 patients with severe leg injuries. Distance from the skin to the fascia in the superficial posterior compartment of both legs was measured on each patient using a portable ultrasound device. Subject age ranged from 18 years to 65 years (mean, 39 years), with 43 male and 7 female patients. The mean (SD) subcutaneous adipose tissue thickness (ATT) was 6.98 (3.17) mm for the injured leg and 7.06 (3.37) mm for the uninjured leg, and the mean body mass index for the group was 27.08 kg/m. No significant correlation was found between the ATT of the injured or uninjured legs and body mass index. Mean comparison testing revealed no difference in ATT between the injured and uninjured legs (null hypothesis: equal means, p > 0.05). Of the 50 subjects analyzed, no subject had a subcutaneous depth of more than 2 cm on the injured or uninjured leg. The data suggest that, within this traumatically injured population, symptoms associated with leg injury (such as swelling and edema) do not significantly affect the distance from the skin to the fascia. It is also notable that subcutaneous depth beyond the 2-cm mark (validated in previous studies) is a rare occurrence in this population. The author concluded the results further support the use of continuous NIRS monitoring for diagnosis of acute compartment syndrome. Further studies with larger patient populations are necessary to determine the long-term safety and efficacy of this technology.
Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>22899</td>
<td>Unlisted procedure, spine</td>
</tr>
<tr>
<td>27299</td>
<td>Unlisted procedure, pelvis or hip joint</td>
</tr>
<tr>
<td>27599</td>
<td>Unlisted procedure, femur or knee</td>
</tr>
<tr>
<td>64999</td>
<td>Unlisted procedure, nervous system</td>
</tr>
</tbody>
</table>

Cooled radiofrequency ablation (RFA) is unproven and not medically necessary for the treatment of pain of any etiology due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Cooled RFA is a minimally-invasive treatment using radiofrequency energy to heat and cool the tissue at the site of pain, e.g., back, hip, knee, to create a treatment area that is larger than with conventional radiofrequency ablation procedures. The purported advantages of cooled-tip probes are the larger heating distance (up to 3 cm from the active tip) and greater depth of lesion creation; also, because needle placement is perpendicular rather than parallel, this technique is considered to be technically easier to perform and less likely to cause tissue trauma. The larger lesion diameter may also ablate more pain nerves (ECRI, 2014).

The FDA has cleared, under 510(k) premarket notifications, cooled RFA products including the Baylis Pain Management Cooled Probe in 2005, the Coolief Transdiscal Cooled RF Probe in 2007 (Baylis Medical, now Halyard Health), and the Coolief RF probe for the management of osteoarthritis of the knee in April 2017.

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

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

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

Omnibus Codes
UnitedHealthcare Oxford Clinical Policy
©1996-2018, Oxford Health Plans, LLC
Page 55 of 127
Effective 05/01/2018
In an observational study, Karaman et al. (2011) investigated the efficacy and safety of cooled RFA for sacral lateral-branch denervation (n=15). At the final control, while 80% of the patients reported at least a 50% decline in pain scores, 86.7% of those reported at least a ten-point reduction in Oswestry Disability Index (ODI) scores.

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

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

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

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

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

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

Cooled RFA of the knee or hip joints is a relatively new treatment for chronic knee or hip pain in patients that are not candidates for arthroplasty.

McCormick et al. (2017) reported 6 month outcomes from thirty-three patients (52 discrete knees) who met inclusion criteria for genicular nerve cooled radiofrequency ablation (C-RFA). Patients were surveyed 6 or more months after C-RFA and numeric rating scale (NRS), Medication Quantification Scale III (MQSIII), Patient Global Impression of Change (PGIC), and total knee arthroplasty (TKA) data were collected. Logistic regression was used to identify factors that predicted treatment success. Thirty-five percent [95% confidence interval (CI) = 22-48] of procedures resulted in the combined outcome of 50% or greater reduction in NRS score, reduction of 3.4 or more points in MQSIII score, and PGIC score consistent with “very much improved/improved.” Nineteen percent (95% CI = 10-33) of procedures resulted in complete pain relief. Greater duration of pain and greater than 80% pain relief from diagnostic blocks were identified as predictors of treatment success. The accuracy of the model was 0.88 (95% CI = 0.78-0.97, P < .0001). The authors concluded that genicular C-RFA demonstrated a success rate of 35% based on a robust combination of outcome measures, and 19% of procedures resulted in complete relief of pain at a minimum of six months of follow-
up. Further prospective well-designed studies are needed to optimize the patient selection protocol and success rate of this procedure.

In a systematic review of published studies investigating conventional, pulsed, or cooled radiofrequency ablation in the setting of chronic knee pain, Gupta et al. (2017) provided an overview of the current knowledge regarding variations in procedures, nerve targets, adverse events, and temporal extent of clinical benefit. The authors reported that while the wide search strategy included a variety of articles, broad conclusions and pooled data could not be obtained based on the studies analyzed. These included small randomized controlled trials, retrospective reviews or case studies. The authors reported that there is a low level of certainty in supporting the superiority of any specific RFA procedure modality. The majority of the studies report positive patient outcomes, but the inconsistent procedural methodology, inconsistent patient assessment measures, and small study sizes limit the applicability of any specific study to clinical practice.

**Reference(s)**


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>29799</td>
<td>Unlisted procedure, casting or strapping (when used to report Kinesio Taping)</td>
</tr>
</tbody>
</table>

See [97139](#) for additional information.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>30999</td>
<td>Unlisted procedure, nose (when used to report rhinophototherapy, intranasal application of ultraviolet and visible light, bilateral)</td>
</tr>
</tbody>
</table>

**Rhinophototherapy is unproven and not medically necessary for treating allergies due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**
Clinical Evidence

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

In a prospective, randomized study, Tatar et al. (2013) investigated the effect of rhinophototherapy with medical therapy on quality of life in persistent allergic rhinitis. The study included 65 patients with dust mite allergies. The patients were divided into two groups. The first group (n=33) was given topical mometasone furoate 200 mcg/day and levocetirizine 5 mg/day for a month. Rhinophototherapy was applied with the same medical therapy to the second group (n=32), twice a week for three weeks continuously. The patients were evaluated before the treatment, at the first month and at the third month after treatment. Improvements of all variables of the quality of life questionnaire, nasal symptom scores and visual analogue scale (VAS) were statistically significant in the second group both on the first and the third months when compared with the first group. The authors concluded that rhinophototherapy plus medical therapy was better than purely medical therapy in patients with persistent and moderate/severe allergic rhinitis with respect to quality of life and symptoms improvement. The study showed that the permanent effect of phototherapy at the third month decreased when compared with the first month. According to the authors, long-term assessments of rhinophototherapy are necessary to evaluate the impact of this treatment in patients with allergic rhinitis.

Albu and Baschir (2013) compared the efficacy of intranasal phototherapy with that of azelastine in patients with seasonal allergic rhinitis (SAR). Seventy seven patients were randomly assigned to the two treatment groups: Group A (phototherapy) and Group B (azelastine). The study demonstrated that both azelastine and intranasal phototherapy are able to significantly improve Total Nasal Symptom Score (TNSS), including individual nasal symptoms. Phototherapy reduced nasal obstruction better than azelastine. Both treatments were highly effective in improving Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores overall and in seven separate domains. The small study population limits the validity of the conclusion of this study. The authors state that phototherapy should be evaluated in future studies and clinical trials.

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>31634</td>
<td>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</td>
</tr>
</tbody>
</table>

Bronchoscopic treatment of bronchopleural fistulas with an occlusive substance, such as fibrin glue, is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence

Prolonged air leak and presence of bronchopleural fistulae (BPF) are often encountered in clinical practice. Tsilimigras and colleagues (2017) conducted a systematic review to investigate the role and the efficacy of BioGlue® in these scenarios. Twelve studies with a total number of 194 patients were included. One hundred seventy-eight patients were treated for alveolar air leaks (AAL), 14 for bronchopleural fistulae (BPF) and 2 for lymphatic leaks. BioGlue® was utilized at the time of initial operation in 172 (96.7%) patients for AAL, while at secondary intervention in 13 (92.9%) for BPF and 1 (50%) for lymphatic leak. In the AAL cases, only 2 out of 4 studies showed statistically significant
Cardillo et al. (2015) retrospectively reviewed the records of 3,832 patients who underwent pulmonary anatomic resections. The overall incidence of bronchopleural fistulas was 1.4%. Primary bronchoscopic treatment was performed in 35 of 52 patients with a fistula of less than 1 cm and with a viable stump. The remaining 17 patients underwent primary operation. The fistula was cured with endoscopic treatment in 80% and with operative repair in 88.2%. Cure rates were 62.5% after pneumonectomy and 86.4% after lobectomy. The cure rate with endoscopic treatment was 92.3% in very small fistulas, 71.4% in small fistulas, and 80% in intermediate fistulas. The cure rate after surgical treatment was 100% in small fistulas, 75% in intermediate fistulas, and 100% in very large fistulas. The authors concluded that bronchoscopic approach shows promising results in all but the largest bronchopleural fistulas. Very small, small, and intermediate fistulas with a viable bronchial stump can be managed endoscopically, using mechanical abrasion, polidocanol sclerosing agent, and cyanoacrylate glue. Bronchoscopic treatment can be repeated, and if it fails, does not preclude subsequent successful surgical treatment. The study is limited by its retrospective observations.

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

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

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

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

No professional society current guidelines addressing this technology were identified.

Reference(s)
The use of implantable bronchial valves, as an alternative to lung volume reduction surgery (LVRS) in patients with emphysema, is investigational, unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in the published peer-reviewed medical literature.

Patient selection criteria to identify optimal candidates for the procedure are lacking. In addition, there is no long-term data on the durability of the treatment or long-term complications. However, benefit coverage for this less invasive alternative to LVRS may be available in the context of eligible clinical trials or for persons with life-threatening illness when certain conditions are met.

Clinical Evidence

This minimally invasive alternative to lung volume reduction surgery uses bronchoscopy to place small one-way valves into the airways of emphysema patients. These implantable valves close during inspiration to block air from reaching lung segments that have lost their elasticity, and open during expiration to permit usual escape of air and secretions.

Liberator et al. (2016) performed a retrospective analysis to determine the role of lobe selection and identify preprocedure predictors of response to endobronchial valve (EBV) therapy. A total of 492 patients were randomized to EBV or control therapy. Spirometry and functional measurements were taken at baseline and 12 months later. Patients undergoing EBV therapy showed improvement in forced expiratory volume (FEV1) change compared to control regardless of treatment to upper or lower lobe. There was no difference in forced expiratory volume in the first second (FEV1) outcomes between upper and lower lobe treatment groups. The authors concluded that complete fissure status preprocedure has the greatest influence on FEV1 outcome improvement. Interpretation of these findings is limited due to the retrospective design of the study.

A meta-analysis was undertaken by Liu et al. (2015) to evaluate the efficacy and safety of bronchoscopic lung volume reduction with endobronchial valves (EBV) for advanced emphysema. Randomized control clinical trials on treatment of emphysema for 3-12 months with the EBV compared with standard medications and sham EBV were reviewed. The primary outcome was the percentage of the forced expiratory volume in the first second (FEV1). Secondary outcomes included St George’s Respiratory Questionnaire (SGRQ) score, the distance of the 6-minute walk (6MWD) test, the Modified Medical Research Council (MMRC) dyspnea score, cycle ergometry workload at 3 or 12 months. Three trials (565 patients) were considered in the meta-analysis. EBV patients yielded greater increases in FEV1 than standard medications, EBV patients also demonstrated a significant change for SGRQ score, MMRC dyspnea score, and cycle ergometry workload. A similar level was evident for 6MWD. EBV may increase the rate of hemoptysis, but didn't increase the adverse events including mortality, respiratory failure, empyema, pneumonia, and pneumothorax. The overall rates for complications compared EBV with standard medications and sham EBV was not significant. The authors concluded that EBV lung volume reduction for advanced emphysema showed superior efficacy and a good safety and tolerability compared with standard medications and sham EBV. More randomized controlled trial (RCT) studies are needed to pay more attention to the long-term efficacy and safety of bronchoscopic lung volume reduction with EBV in advanced emphysema.

Giddings et al. (2014) reported a systematic review of the literature including studies of endobronchial valve placement for the treatment of bronchopleural fistulas. They describe a number of case series and reports on the use of one-way endobronchial valves for the treatment of bronchopleural fistula, after spontaneous pneumothorax, lung resection and complication of suppurative lung disease. In the largest series (40 patients), 93% of patients experienced improvement in air leak, with 48% experiencing full resolution. Complications include pneumonia, expectoration or migration of valves, and bacterial colonization. The use of endobronchial valves for the treatment of bronchopleural fistula is well tolerated and effective. However, additional well-designed controlled clinical trials are needed to further evaluate their efficacy and identify patient selection criteria.

Study authors of a comprehensive systematic review and meta-analysis (Choi et al., 2015) evaluated bronchoscopic lung volume reduction surgery for severe emphysema. Review authors included 15 studies. Overall, results of forced expiratory volume in 1 second (FEV1) improved in the treatment group compared with the control group [mean difference (MD)=6.71, 95% confidence interval (CI): 3.31-10.11]. Six-minute walking distance (MD=15.66, 95% CI: 1.69-29.64) and cycle workload (MD=4.43, 95% CI: 1.80-7.07) also improved. In addition, St George's Respiratory Questionnaire score decreased (MD=4.29, 95% CI: -6.87 to -1.71) in the intervention group. Complications of

---

### Omnibus Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>31648</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), initial lobe</td>
</tr>
<tr>
<td>31649</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with removal of bronchial valve(s), each additional lobe</td>
</tr>
<tr>
<td>31651</td>
<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak,</td>
</tr>
<tr>
<td></td>
<td>airway sizing, and insertion of bronchial valve(s), each additional lobe [List separately in addition to code for primary procedure(s)]</td>
</tr>
</tbody>
</table>

©1996-2018, Oxford Health Plans, LLC

Effective 05/01/2018
respiratory failure and pneumothorax incidence rates were relatively higher in the BLVR group, but the difference was not statistically significant. Study authors concluded that BLVR may be an effective and safe procedure for the treatment of severe COPD patients with emphysema, based on existing studies.

In a multicenter 91-patient pilot trial of the Spiration IBV Valve, Sterman et al. (2010) evaluated the safety and effectiveness of the IBV Valve for the treatment of severe emphysema. 609 bronchial valves were placed bilaterally into the upper lobes (UL). There were no procedure-related deaths and 30-day morbidity and mortality were 5.5 and 1.1%, respectively. Pneumothorax was the most frequent serious device-related complication and primarily occurred when all segments of a lobe, especially the left UL, were occluded. Highly significant health-related quality of life (HRQL) improvement was observed. HRQL improvement was associated with a decreased volume in the treated lobes without visible atelectasis. FEV₁, exercise tests, and total lung volume were not changed but there was a proportional shift, a redirection of inspired volume to the untreated lobes. Combined with perfusion scan changes, this suggests that there is improved ventilation and perfusion matching in non-UL lung parenchyma. Bronchial valve treatment of emphysema has multiple mechanisms of action and acceptable safety, and significantly improves quality of life for the majority of patients.

In the international Endobronchial Valve for Emphysema Palliation Trial (VENT), Sciurba et al. (2010) evaluated endobronchial valves in patients with pulmonary hyperinflation related to advanced emphysema. The randomized, controlled trial compared the safety and efficacy of endobronchial valve therapy in patients with heterogeneous emphysema (n=220) versus standard medical care (n=101). Endobronchial valve treatment for advanced heterogeneous emphysema induced modest improvements in lung function, exercise tolerance and symptoms at the cost of more frequent exacerbations of COPD, pneumonia and hemoptysis after implantation.

Emphysema patients who have been treated with endobronchial valves (EBV) in the STELVIO trial (independent, randomized, controlled trial which compared the Zephyr EBV with standard medical care) were invited for a voluntary 1-year follow-up visit. Both the original treatment group and the control group who crossed over to treatment were included. Klooster et al. (2017) performed an uncontrolled study to investigate the efficacy and safety of EBV treatment. Sixty-four patients received EBV treatment. At 1 year, 40 patients visited the hospital and underwent pulmonary function measurements, a 6-min walk test, chest x-ray and completed questionnaires. The authors noted improvements between baseline and 1 year follow-up for FEV₁ (+17%, 95% CI, 11 to 24), RV (−687 mL, 95% CI, −918 to −456), 6MWD (+61 m, 95% CI, 42 to 80), and SGRQ (−11 points, 95% CI, −17 to −6). Seventeen percent of the patients underwent valve replacement and 22% of the initially treated patients had permanent valve removal. The authors concluded that EBV treatment results in clinically relevant benefits at 1 year of follow-up and that the study supports the use of EBV treatment in carefully selected patients with severe emphysema without collateral ventilation. Further research with randomized controlled trials with a larger number of patients is needed to validate these findings.

National Institute for Health and Care Excellence (NICE) guidelines state that the current evidence on the efficacy and safety of endobronchial valves for persistent air leaks is limited in both quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. (NICE, 2013)

National Institute for Health and Care Excellence (NICE) guideline update (NICE, 2013) states current evidence on the efficacy of insertion of endobronchial valves for lung volume reduction in emphysema shows some clinical and quality-of-life benefits. However, this evidence includes data from patients who have and those who have not had assessment of collateral ventilation, which specialists now advise as fundamental to selection for treatment. Evidence of safety in the short term is adequate but the evidence of safety in the longer term is inadequate in quantity. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

The following clinical trials are underway:
- Long Term Follow up Investigation of Endobronchial Valves in Emphysema. This is an observational prospective single arm multicenter study to observe the effect over 5 years of Zephyr endobronchial valve therapy for emphysema. ClinicalTrials.gov identifier: NCT01580215.
- Pulmonx Endobronchial Valves Used in Treatment of Emphysema (LIBERATE Study). The purpose of this research is to study an investigational medical device that is designed to produce lung volume reduction in diseased areas of the lungs in patients with severe emphysema. ClinicalTrials.gov identifier: NCT01796392.

Reference(s)
Omnibus Codes

measures included complications, local tumor control, and pain response. Mean pain scores decreased from 7.0 ± 1.9 under went cr
metastases control tumor progression and reduce pain (12 patients; 12 tumors). A total of 7 patients (58%) in another retrospective analysis, Hegg et al. (2014) evaluated the safety and effectiveness of cryoablation of sternal
56.6% ± 16.5; and the 5-year survival rate was 67.8% ± 15.3; the cancer-specific survival rate was 56.6% ± 16.5; and the 5-year progression-free survival rate was 87.9% ± 9. The combined local and regional recurrence rate was about 36%. Major complications occurred in roughly 6% of patients, including 2 cases of hemoptysis and a prolonged placement of a chest tube requiring mechanical sclerosis in one patient. There were no deaths in the first 30 days after treatment.

In another retrospective analysis, Hegg et al. (2014) evaluated the safety and effectiveness of cryoablation of sternal metastases control tumor progression and reduce pain (12 patients; 12 tumors). A total of 7 patients (58%) underwent cryoablation for pain palliation, and five (42%) underwent cryoablation for local tumor control. Outcome measures included complications, local tumor control, and pain response. Mean pain scores decreased from 7.0 ± 1.9.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>32994</td>
<td>Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; cryoablation</td>
</tr>
</tbody>
</table>

**Percutaneous cryoablative therapy of pulmonary tumors, including the pleura or chest wall when involved by tumor extension, is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy in the published peer-reviewed medical literature.**

**Clinical Evidence**

Percutaneous cryoablation of pulmonary tumors, including the pleura or chest wall when involved by tumor extension, is unproven due to the lack of high quality evidence regarding its safety and efficacy. With one exception, majority of the available evidence pertains primarily to early feasibility and safety evaluations. Although preliminary results are positive, the overall evidence base in the peer-reviewed medical literature is small and low quality. Additional well-designed studies are needed to confirm the safety and efficacy of this treatment approach.

A Hayes report (2016) on cryoablation for treatment of non-small cell lung cancer (NSCLC) examined 1 RCT, 6 nonrandomized comparative studies, and 1 uncontrolled study published between 1998-2013. Results of the available studies provide preliminary evidence that cryoablation of NSCLC provides benefits that outweigh the potential risks of this procedure. In studies that provided direct assessments of the effect of cryoablation versus other treatments for NSCLC, cryoablation had approximately the same or somewhat better efficacy than other common therapies for NSCLC. However, almost all of these findings were obtained in retrospective nonrandomized comparative studies, most of which were small or had small treatment groups, and there were substantial variations between the studies in stage of NSCLC treated and treatments provided as adjuncts to or for comparison with cryoablation. Additional well-designed studies with long-term follow-up are needed to define the clinical role of cryoablation relative to other common therapies for NSCLC such as surgery, radiofrequency ablation (RFA), chemotherapy, radiation therapy, and immunotherapy.

Chou et al. (2015) conducted a retrospective analysis to evaluate the efficacy and rate of survival following percutaneous CT-guided cryoablation for malignant lung tumors (n=26; 45 tumors). Follow up CT-scans were used to assess local tumor progression. Complications included pneumothorax (15%), pleural effusion (20%), pulmonary hemorrhage (24%), pneumonitis (15%), hemothorax (15%), hemoptysis (10%), and pain (20%). No patients died following cryoablation. The overall survival (OS) rate of 1, 2, and 3 years, respectively. Study authors suggested that cryoablation for malignant lung tumors is relatively safe and effective as a means of local control of tumor growth.

Moore et al. (2015) conducted a retrospective analysis to evaluate long-term survival in patients with early stage NSCLC after cryoablation treatment. The 5-year survival rate was 67.8% ± 15.3; the cancer-specific survival rate was 56.6% ± 16.5; and the 5-year progression-free survival rate was 87.9% ± 9. The combined local and regional recurrence rate was about 36%. Major complications occurred in roughly 6% of patients, including 2 cases of hemoptysis and a prolonged placement of a chest tube requiring mechanical sclerosis in one patient. There were no deaths in the first 30 days after treatment.

In another retrospective analysis, Hegg et al. (2014) evaluated the safety and effectiveness of cryoablation of sternal metastases control tumor progression and reduce pain (12 patients; 12 tumors). A total of 7 patients (58%) underwent cryoablation for pain palliation, and five (42%) underwent cryoablation for local tumor control. Outcome measures included complications, local tumor control, and pain response. Mean pain scores decreased from 7.0 ± 1.9.
(median, 7; range, 4-10) at baseline to 1.8 ± 1.2 (median, 1.5; range, 0-4) following cryoablation (P = 0.00049). A total of 2 patients had durable pain palliation, and four had greater than 1 month of pain relief, with a median duration of 5.7 months (range, 1.5-14.7 mo). Local tumor control was achieved in 4 of 5 patients (80%) with median follow-up of 8.4 months (range, 2.6 to 13.6).

In a nonrandomized uncontrolled feasibility study, Inoue et al. (2012) evaluated 117 consecutive patients with lung tumors. Pneumothorax, pleural effusion, and hemoptysis occurred after 119 (61.7%), 136 (70.5%), and 71 (36.8%) sessions, respectively. Phrenic nerve palsy, frostbite, and empyema occurred after one session each (0.52%). Proximal tumor implantation was observed in one of 471 punctures (0.20%). Of 119 sessions with pneumothorax, 21 (17.6%) required chest tube insertion and two (1.7%) required pleurodesis. Delayed and recurrent pneumothorax occurred in 15 of 193 sessions each (7.8%). A greater number of cryoprobes was a significant (P = 0.001) predictor of pneumothorax. Being male (P = 0.047) and no history of ipsilateral surgery (P = 0.012) were predictors for the need for chest tube insertion, and no history of ipsilateral surgery (P = 0.021) was a predictor for delayed or recurrent pneumothorax. Greater number of cryoprobes (P = .001) and no history of ipsilateral surgery (P = 0.004) were predictors for pleural effusion. Greater number of cryoprobes (P < 0.001) and younger age (P = 0.034) were predictors for hemoptysis. Study authors concluded that percutaneous cryoablation could be performed minimally invasively with acceptable rates of complications.

Yashiro et al. (2013) evaluated risk factors for local tumor progression following percutaneous cryoablation of lung tumors. Seventy-one consecutive patients with 210 tumors were treated with 102 sessions of PCLT. Rates of local tumor progression and technique effectiveness were estimated by Kaplan-Meier method. The median follow-up period was 454 days (range, 79-2467). Local tumor progression occurred in 50 tumors (23.8%). Local progression-free survival rates were approximately 80%, (at one year), 69% (at two years) and 68% (at three years), respectively. Technique effectiveness rates were 91%, 83%, and 83%, respectively. Existence of a thick vessel (diameter ≥ 3 mm) no more than 3 mm from the edge of the tumor was assessed as an independent factor [hazard ratio (HR), 3.84; 95% CI, 1.59-9.30; P = 0.003] associated with local progression by multivariate analysis.

Pusceddu et al. (2013) reported their initial experience with CT-guided thin cryoprobes for percutaneous cryoablation in patients with primary and secondary lung tumors. CT-guided cryoablation was performed on 34 lung masses in 32 consecutive patients. All cryoablation sessions were successfully completed. All primary and metastatic lung tumors were ablated. No procedure-related deaths occurred. Morbidity consisted of 21% (7 of 34) pneumothorax and 3% (1 of 34) cases asymptomatic small pulmonary hemorrhage, respectively, all of CTCAE grade 1 (Common Terminology Criteria for Adverse Events). Low density of entire lesion, central necrosis and solid mass appearance were identify in 21 (62%), 7 (21%) and 6 (17%) of cryoablated tumors, respectively. No lymphadenopathy developed in the region of treated lesions. Technical success (complete lack of enhancement) was achieved in 4 of 5 patients (80%) with median follow-up period of 8.4 months (range, 79-2467). Local tumor progression occurred in 50 tumors (23.8%). Local progression-free survival rates were approximately 80%, (at one year), 69% (at two years) and 68% (at three years), respectively. Existence of a thick vessel (diameter ≥ 3 mm) no more than 3 mm from the edge of the tumor was assessed as an independent factor [hazard ratio (HR), 3.84; 95% CI, 1.59-9.30; P = 0.003] associated with local progression by multivariate analysis.

NCCN guidelines on non-small cell and small cell lung cancers do not address percutaneous cryoablation (2017).

**References**


Implantable cardiac devices for percutaneous closure (occlusion) of the left atrial appendage (LAA) are unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in the published peer-reviewed medical literature.

**Clinical Evidence**


A Hayes report concluded that the evidence supports the use of the Watchman device in LAA closure to reduce the risk of stroke in adult patients with nonvalvular atrial fibrillation (AF) who are deemed eligible but have a valid rationale for not using warfarin oral anticoagulation therapy. Since following implantation of the Watchman device patients must continue on warfarin therapy for approximately 45 days, there is very limited data on if and how to use the device in patients with absolute contraindications to warfarin. Further randomized studies are needed to compare the safety and efficacy of the Watchman device with newer oral anticoagulants. (Hayes, 2015; updated 2016)

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

A NICE guideline states that current evidence suggests that percutaneous occlusion of the LAA is efficacious in reducing the risk of thromboembolic complications associated with non-valvular AF. With regard to safety, there is a risk of life-threatening complications from the procedure, but the incidence of these is low. Therefore, this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit. (NICE, 2010)

In a separate report on the management of AF, NICE states that LAA occlusion should not be recommended as an alternative to anticoagulation unless anticoagulation is contraindicated or not well tolerated. (NICE, 2014)

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

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

**PROTECT AF**

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

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

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

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

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

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

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

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

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

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

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

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

Additional Product Information

- Amplatz® Cardiac Plug (St. Jude Medical) – not FDA approved at this time
- Amplatz™ Amulet™ Left Atrial Appendage Occluder (St. Jude Medical) - not FDA approved at this time
- PLAATO – no longer on the market
- Watchman FLX – not FDA approved at this time

Reference(s)


Optical endomicroscopy is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
Optical endomicroscopy also referred to as confocal endomicroscopy (CEM) or optical biopsy is a new 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 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, and Barrett’s esophagus (BE) and for the identification of Helicobacter pylori infection.

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

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>43206</td>
<td>Esophagoscopy, flexible, transoral; with optical endomicroscopy</td>
</tr>
<tr>
<td>43252</td>
<td>Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy</td>
</tr>
</tbody>
</table>


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

In a prospective, multicenter, randomized clinical trial, Wallace et al. (2012) assessed if use of probe-based confocal laser endomicroscopy (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 two groups. The authors concluded that this study yields no evidence that the addition of pCLE to HDWL imaging for detection of residual BE or neoplasia can provide improved treatment.

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

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

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

Despite promising findings, the overall quality of the evidence on probe-based endoscopic confocal laser endomicroscopy (eCLE) for diagnosis of esophageal neoplasia in patients with BE is low. There is a paucity of data, and some studies have shortcomings such as small sample sizes. None of the studies systematically evaluated the impact of eCLE on treatment decision making and long-term health outcomes such as esophage cancer-related morbidity and mortality. There is no proof that eCLE can be used as a stand-alone test; it must be used as an adjunct to existing tests for esophageal neoplasia. There is also no evidence that its use would avoid biopsy and histopathological confirmation of esophageal lesions or whether its findings could reliably allow for endoscopic therapy of suspicious lesions detected in real time in the general clinical setting. There is a need for additional RCTs that use standardized protocols for eCLE, that compare the clinical performance of eCLE-directed biopsies with HD-WLE and 4-quadrant biopsies, and that have adequate follow-up time to determine the long-term outcomes of BE patients who undergo this test. Head-to-head comparisons are also needed between eCLE, probe-based CLE, and other novel tests for surveillance of patients with BE. (Hayes, 2016)

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>48160</td>
<td>Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells</td>
</tr>
<tr>
<td>48999</td>
<td>Unlisted procedure, pancreas</td>
</tr>
<tr>
<td>60659</td>
<td>Unlisted laparoscopy procedure, endocrine system</td>
</tr>
<tr>
<td>G0341</td>
<td>Percutaneous islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>G0342</td>
<td>Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>G0343</td>
<td>Laparotomy for islet cell transplant, includes portal vein catheterization and infusion</td>
</tr>
<tr>
<td>S2102</td>
<td>Islet cell tissue transplant from pancreas; allogeneic</td>
</tr>
</tbody>
</table>

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

### Allogeneic islet cell transplantation is unproven and not medically necessary for the treatment of diabetes due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

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

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

### Clinical Evidence

At the present time, there is some limited evidence to suggest that islet cell transplantation can provide at least several years of insulin independence and improvement in glycemic control for some patients with severe type 1 diabetes whose serum glucose level was uncontrolled despite intensive insulin therapy.

Results of a Hayes (2016) report of reviewed studies suggest that of islet autotransplantation after total pancreatectomy (TP/IAT) may provide durable improvements in patient-reported pain reductions in narcotic use, adequate glycemic control and insulin independence in many patients, and may improve quality of life in patients with intractable and debilitating symptoms from chronic pancreatitis. It may also improve survival with an acceptable level of mortality. Higher-quality evidence is needed to fully assess the effectiveness of TP/IAT.

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

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

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

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

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

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

Studies supporting the use of allogeneic islet transplantation are limited by small numbers of recipients and significant adverse events.

**Reference(s)**


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>53855</td>
<td>Insertion of a temporary prostatic urethral stent, including urethral measurement</td>
</tr>
</tbody>
</table>

The insertion of a temporary prostatic urethral stent is unproven and not medically necessary due to insufficient clinical evidence and/or efficacy in the published peer-review medical literature.

**Clinical Evidence**

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

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

The U.S. Food and Drug Administration (FDA) approved the Spanner Temporary Prostatic Stent on December 14, 2006. Refer to the following website for additional information:  
(Accessed April 21, 2017)

The Memokath has not yet received FDA approval.

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

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

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

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

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

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

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

The American Urological Association’s clinical guideline for the management of benign prostatic hyperplasia does not make a specific recommendation for or against temporary stents. (McVary et al., 2010)

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>55874</td>
<td>Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed</td>
</tr>
</tbody>
</table>

The transperineal placement of biodegradable material, peri-prostatic (via needle) is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in the published peer-reviewed medical literature.

**Clinical Evidence**

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

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


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

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

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

Yeh et al. (2016) studied rectal toxicity rates in 326 patients administered a polyethylene glycol (PEG) hydrogel rectal spacer in conjunction with combination high-dose-rate brachytherapy at 16 Gy [average dose 15.5 Gy; standard deviation (SD) = 1.6 Gy] and external beam radiotherapy of 59.4 Gy (average dose 60.2 Gy; SD = 2.9 Gy). Clinical efficacy was determined by measuring acute and chronic rectal toxicity using the National Cancer Center Institute Common Terminology Criteria for Adverse Events v4.0 grading scheme. Median followup was 16 months. The mean anterior-posterior separation achieved was 1.6 cm (SD = 0.4 cm). Rates of acute Grade 1 and 2 rectal toxicity were 37.4% and 2.8%, respectively. There were no acute Grade 3/4 toxicities. Rates of late Grade 1, 2, and 3 rectal toxicity were 12.7%, 1.4%, and 0.7%, respectively. There were no late Grade 4 toxicities. The authors concluded that acute and chronic rectal toxicities are low despite aggressive dose escalation. Longer term outcomes are needed to evaluate impact.

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

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>64999</td>
<td>Unlisted procedure, nervous system</td>
</tr>
</tbody>
</table>
Surgical treatment (that may include laminectomy and sacral reconstruction) of a Tarlov cyst from the sacrum is proven and medically necessary for patients who experience pain or neurologic symptoms attributed to the Tarlov cyst.

Information Pertaining to Medical Necessity Review (When Applicable)
Because most Tarlov cysts are asymptomatic, surgery is rarely required. Surgery for a Tarlov cyst is proven based on a correlation among symptoms, physical examination and radiographic findings:

- Where the cyst causes neurological symptoms.
- Where pain is attributable to the cyst. In general, larger cysts (greater than 1.5 cm) with corresponding radicular symptoms are most likely to benefit from surgery.
- Where the patient has failed an appropriate course of non-operative treatment.

Clinical Evidence
Tarlov cysts are fluid-filled sacs that affect the nerve roots of the spine, especially near the base of the spine (sacral region). Individuals may be affected by multiple cysts of varying size.

Tarlov cysts are difficult to diagnose because of the limited knowledge about the condition, and because many of the symptoms can mimic other disorders. Most perineural cysts (Tarlov's cysts) are asymptomatic. They are usually diagnosed incidentally, and a specific treatment is not necessary. They should be operated on, only if they produce or have disabling symptoms clearly attributable to them.

There was no information found in MCG™, ECRI or Hayes for this diagnosis with this treatment.

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

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

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

National Institute of Neurological Disorders and Stroke (NINDS)
Tarlov cysts are sacs filled with cerebrospinal fluid that most often affect nerve roots in the sacrum, the group of bones at the base of the spine. These cysts (also known as meningeal or perineural cysts) can compress nerve roots, causing lower back pain, sciatica (shock-like or burning pain in the lower back, buttocks, and down one leg to below the knee), urinary incontinence, headaches (due to changes in cerebrospinal fluid pressure), constipation, sexual dysfunction, and some loss of feeling or control of movement in the leg and/or foot. Pressure on the nerves next to the cysts can also cause pain and deterioration of surrounding bone.
Tarlov cysts may be drained and shunted to relieve pressure and pain, but relief is often only temporary and fluid build-up in the cysts will recur. Corticosteroid injections may also temporarily relieve pain. Other drugs may be prescribed to treat chronic pain and depression. Injecting the cysts with fibrin glue (a combination of naturally occurring substances based on the clotting factor in blood) may provide temporary relief of pain. Some scientists believe the herpes simplex virus, which thrives in an alkaline environment, can cause Tarlov cysts to become symptomatic. Making the body less alkaline, through diet or supplements, may lessen symptoms. Microsurgical removal of the cyst may be an option in selected individuals who do not respond to conservative treatments and who continue to experience pain or progressive neurological damage. (NINDS, 2012)

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>69799</td>
<td>Unlisted procedure, middle ear [when used to report balloon dilation]</td>
</tr>
</tbody>
</table>

Balloon dilation is unproven and not medically necessary for treating eustachian tube dysfunction (ETD) due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
Eustachian tube dysfunction (ETD) is a condition where the tubes do not open up properly causing pressure, pain or a muffled sensation that occur in the ear. Balloon dilation is a new procedure to treat ETD. A Hayes report (2017) concluded there was sufficient evidence to evaluate the technology however did state the findings presented were conflicting.

The Acclarent Aera™ Eustachian balloon dilation system is intended for treatment of persistent Eustachian tube (ET) dysfunction. Limited evidence is insufficient to determine how well the Aera Eustachian balloon dilation system works to correct protracted otitis media with effusion or atelectasis of the tympanic membrane (ECRI, 2017).

In a prospective, multicenter, randomized, controlled trial, Poe et al. (2017) assessed balloon dilation of the Eustachian tube with Eustachian tube balloon catheter in conjunction with medical management as treatment for Eustachian tube dilatory dysfunction. Patients aged 22 years and older were assigned in a ratio of 2:1 and underwent balloon dilation of the Eustachian tube with balloon catheter in conjunction with medical management or medical management alone. The conclusions demonstrated superiority of balloon dilation of the Eustachian tube with balloon catheter plus medical management compared to medical management alone. However, a limitation of the study was the small sample size utilized.

Huisman et al. (2017) conducted a systematic review to evaluate the success of balloon dilation in adult patients with Eustachian tube dysfunction. The systematic literature search was conducted independently by two authors which resulted in 36 articles with 15 of them for inclusion in the study. A total of 1,155 patients were treated with balloon dilation with follow up ranging from just after therapy to 50 months later. Conclusions suggested that balloon dilation of the Eustachian tube can be a helpful treatment in patients with Eustachian tube dysfunction, however placebo controlled trials are still warranted.

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

Randtrup and Ovesen (2015) conducted a systematic review and meta-analysis of the evidence for balloon eustachian tuboplasty as a treatment modality for ETD. Twelve databases were searched and included a total of 443 patients. All studies were of poor quality with a high risk of bias. No firm conclusions were made other than more RCTs or case controlled trials were needed.

A National Institute for Health and Care Excellence (NICE) guideline concluded that current evidence on the safety and efficacy of balloon dilation of the Eustachian tube is inadequate in quantity and quality (NICE, 2015).
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/pmncf.cfm?ID=K163509. (Accessed December 6, 2017)


Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>76120</td>
<td>Cineradiography/videoradiography, except where specifically included</td>
</tr>
<tr>
<td>76125</td>
<td>Cineradiography/videoradiography to complement routine examination (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

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

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

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

The current literature evaluating the clinical utility of dynamic spinal visualization techniques, including but not limited to digital motion x-ray and cineradiography (videofluoroscopy), for the evaluation and assessment of the spine is extremely limited to a few studies (Lee, et al., 2002; Teyhen, et al., 2007) involving small numbers of participants. While these studies do indicate that there may be some benefit from the use of these technologies, further evidence from large controlled trials is needed to demonstrate that the results have significant impact on clinical care and are superior to currently available alternatives.

Several clinical trials are ongoing.

Reference(s)
Intraoperative radiation therapy, using low-energy x-rays or electrons, is unproven and not medically necessary for treating all indications due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

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

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

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

**ELIOT**
Veronese et al. (2013) conducted ELIOT, a single-institution trial, included patients with early breast cancer, aged 48 years or older, with a tumor size no larger than 2.5 cm. After undergoing standard breast-conserving surgery, patients were randomly assigned to receive a single dose of intraoperative radiotherapy of 21 Gy to the tumour bed during surgery (n=651) or conventional radiation therapy consisting of a 50-Gy postoperative external-beam dose to the whole breast with conventional fractionation plus a 10-Gy boost (n=654). The prespecified equivalence margin was local recurrence of 7.5% in the intraoperative radiotherapy group. The primary endpoint was occurrence of ipsilateral breast tumour recurrences (IBTR); overall survival was a secondary outcome. After a medium follow-up of 5.8 years, 35 patients in the intraoperative radiotherapy group and four patients in the external radiotherapy group had a recurrence. The 5-year recurrence risk was 4.4% in the IORT group and 0.4% in the EBRT group. 5-year overall survival was 96.8% in the IORT group and 96.9% in the EBRT. The authors noted that although the rate of recurrence in the IORT group was within the prespecified equivalence margin, the rate was significantly greater than with EBRT. Overall survival did not differ between groups. Improved selection of patients could reduce the rate of recurrence with IORT with electrons.

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

National Comprehensive Cancer Network (NCCN) guidelines on breast cancer do not specifically address IORT using low-energy x-rays or electrons. The guidelines state that boost treatment in the setting of breast conservation can be delivered using enface electrons, photons or brachytherapy. When addressing APBI, the guidelines indicate that...
preliminary studies suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast radiation therapy. However, follow-up is limited and studies are ongoing. Patients are encouraged to participate in clinical trials. (NCCN, 2017)

References


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>86849</td>
<td>Unlisted immunology procedure</td>
</tr>
</tbody>
</table>

The following information applies to the use of this unlisted code for antiprothrombin antibody testing.

**Antiprothrombin antibody testing for antiphospholipid syndrome is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

**Clinical Evidence**

Anti-phospholipid syndrome (APS) is an autoimmune condition characterized by moderate-to-high levels of circulating anti-phospholipid antibodies. Antiphospholipid antibodies have been associated with a variety of medical problems, including arterial thrombosis, venous thrombosis, autoimmune thrombocytopenia and recurrent fetal loss. Research shows variable sensitivity and a lack of standardization with available tests.

Prothrombin (PT) is a target for antibodies with lupus anticoagulant (LA) activity, suggesting the possible application of anti-prothrombin antibody (aPT) assays in patients with antiphospholipid syndrome (APS). Different methods - both homemade and commercial - for the detection of aPT are available, but they seem to produce conflicting results.

Tincani et al. (2007) compared the performance of different assays on a set of well-characterized serum samples. Sera were gathered from 4 Forum Interdisciplinare per la Ricerca nelle Malattie Autoimmuni (FIRMA) institutions, and distributed to 15 participating centers. Forty-five samples were from patients positive for LA and/or anticardiolipin antibodies (aCL) with or without APS, and 15 were from rheumatoid arthritis (RA) patients negative for antiphospholipid antibodies. The samples were evaluated for IgG and IgM antibodies using a homemade direct aPT assay (method 1), a homemade phosphatidylserine-dependent aPT assay (aPS/PT, method 2), and two different commercial kits (methods 3 and 4). In addition, a commercial kit for the detection of IgG-A-M aPT (method 5) was used. Inter-laboratory results for the 5 methods were not always comparable when different methods were used. Good inter-assay concordance was found for IgG antibodies evaluated using methods 1, 3, and 4 (Cohen k > 0.4), while the IgM results were discordant between assays. In patients with thrombosis and pregnancy losses, method 5 performed better than the others. While aPT and aPS/PT assays could be of interest from a clinical perspective, their routine performance cannot yet be recommended because of problems connected with the reproducibility and interpretation of the results.

Zigon et al. (2013) stated that anti-prothrombin antibodies, measured with phosphatidylserine/prothrombin complex (aPS/PT) ELISA, have been reported to be associated with APS. They are currently being evaluated as a potential classification criterion for this autoimmune disease, characterized by thromboses and obstetric complications. Given the present lack of clinically useful tests for the accurate diagnosis of APS, these researchers evaluated in-house and commercial assays for determination of aPS/PT as a potential serological marker for APS. They screened 156 patients with systemic autoimmune diseases for antibodies against PS/PT, β2-glycoprotein I, cardiolipin and for lupus anticoagulant activity. These investigators demonstrated a high degree of concordance between the concentrations of aPS/PT measured with the in-house and commercial assays. Both assays performed comparably relating to the clinical manifestations of APS, such as arterial and venous thromboses and obstetric complications. IgG aPS/PT represented the strongest independent risk factor for the presence of obstetric complications, among all tested aPL. Both IgG and IgM aPS/PT were associated with venous thrombosis, but not with arterial thrombosis. Most importantly, the association between the presence of IgG/IgM aPS/PT and lupus anticoagulant activity was highly significant. The authors concluded that aPS/PT antibodies detected with the in-house or commercial ELISA represent a promising serological marker for APS and its subsets.
ECRI (2017) conducted a review of the literature to assess antiprothrombin antibody testing for diagnosing APS. After reviewing the literature the authors concluded that the available evidence on aPT testing for diagnosing APS does not support its use as a substitute for the current 3 antibody criteria (anticardiolipin, anti-beta-2 glycoprotein I, and lupus anticoagulant).

ECRI (2017) also conducted a search of clinical guidelines associated with APS. The authors noted the following relevant guidelines:
- American College of Chest Physicians (2012) guideline on venous thromboembolism and pregnancy recommends screening for antiphospholipid antibodies in “women with recurrent early pregnancy loss (three or more miscarriages before 10 weeks of gestation).” The guideline did not mention testing for aPT.
- American College of Obstetricians and Gynecologists (2012) guideline on APS does not recommend testing for antibodies other than the lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein I.
- British Society for Hematology (2012) guideline on APS does not mention testing for aPT.
- European League Against Rheumatism (2017) guideline on APS does not mention testing for aPT.

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

The antiprothrombin antibody test is a diagnostic test that falls under FDA regulation as either an “in-house” test with a hospital or proprietary laboratory, or as a marketed and distributed test kit or device. In-house testing falls under the rule of the Centers for Medicare & Medicaid Services (CMS) Clinical Laboratory Improvement Amendments (CLIA) of 1988. Premarket approval from the FDA is not required for this type of laboratory test. However, tests that are marketed, distributed, and sold as kits or devices do fall under the FDA 510(k) and/or premarket approval (PMA) processes.

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>92499</td>
<td>Unlisted ophthalmological service or procedure</td>
</tr>
<tr>
<td></td>
<td>Multifocal Electoretinography (mfERG) and Pattern Electoretinography (PERG)</td>
</tr>
</tbody>
</table>

Multifocal electoretinogram (mfERG) is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Pattern electoretinogram (PERG) or pattern electoretinogram optimized for glaucoma screening (PERGLA) is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
Multifocal electoretinogram (mfERG) is a noninvasive test used to detect the regional functional changes of the central retina by measuring the electrophysiological response. The available studies of multifocal electoretinography do not provide convincing evidence that multifocal electoretinography provide objective information regarding changes in retinal function. Pattern ERG (PERG) is being studied as a tool to diagnose glaucoma and retinal disorders and monitor success of surgical procedures. Pattern electoretinogram optimized for glaucoma screening (PERGLA) is a non-invasive, fully automatic version of the pattern ERG. Clinical evidence regarding the PERG test is limited. Well-designed controlled trials with larger patient populations are required to determine if these tests are effective for diagnosing retinal conditions.

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

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

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

A report by the American Academy of Ophthalmology reviewed the published literature to summarize and evaluate the effectiveness of visual function tests in diagnosing glaucoma and in monitoring progression. The report indicated that technologies, such as multifocal visual-evoked potential and electroretinography, which were designed as objective measures of visual function, provide testing free of patient input, but issues prevent their adoption for glaucoma management. The authors also state that objective visual field tests that do not depend on patient responses, such as multifocal electroretinography (mfERG), are under development. (Jampel et al. 2011)

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

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

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

In a prospective study, Ambrosio et al. (2015) examined the role of mERG for predicting visual acuity (VA) decline in early age-related macular degeneration (ARMD) with time. A total of 26 early ARMD patients (12 males and 14 females, mean age of 66.9 ± 9.8; range of 46 to 82 years) were included in the study. A complete ophthalmic examination and mERG (Retiscan, Roland Germany, ISCEV standard protocol) were performed at the study entry (baseline), after 20 and 24 months. The first-order kernel mERG responses were analyzed by ring analysis. The amplitude density (AD) of the first positive peak (P1, nV/deg²), the P1 amplitude (µV) and P1 implicit time (ms) for Rings 1 (central) to 6 (most peripheral) were evaluated. Data were statistically analyzed by analysis of variance and receiver operating characteristic (ROC) curves. The loss in the mERG Ring 1 AD from normal control values, recorded at baseline, was correlated with the decrease in ETDRS VA with time (p = 0.004); ROC analysis showed that, after 24 months, the average decline in VA was greater (3 letters versus 0.4 letters, p = 0.0021) in patients whose Ring 1 P1 AD at baseline was equal to or less than 65.9 nV/deg², compared to those with higher AD values. Both P1 amplitude and AD of Ring 1 had an area under the curve of 0.702 (95% CI: 0.50 to 0.92) with a sensitivity of 64.3% (35.14 to 87.24%) and a specificity of 91.7% (61.52 to 99.79%). The authors concluded that these results indicate that mERG P1 amplitude and AD of Ring 1 may be highly specific to predict visual acuity decline in early AMD. This was a nonrandomized study design without a control group, and small patient sample size.

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

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

Preiser et al. (2013) compared photopic negative response (PhNR) and pattern electroretinogram (PERG) in different stages of the disease. Eleven eyes with preperimetric glaucoma (glaucomatous optic disc with normal field); 18 with manifest glaucoma; and 26 normals were included in the study. Based on the results of the study, the authors concluded that both PhNR and PERG performed similarly to detect glaucoma; for both, ratios performed better than amplitudes. The authors stated that the PhNR has the advantage of not requiring clear optics and refractive correction; the PERG has the advantage of being recorded with natural pupils. This study is limited by a small study population.
Sehi et al. (2009) examined retinal ganglion cell function measured using pattern electroretinogram optimized for glaucoma screening (PERGLA) in 29 normal individuals, 28 glaucoma patients, and 37 glaucoma suspect volunteers. According to the authors, retinal ganglion cell function measured using pattern electroretinogram optimized for glaucoma screening (PERGLA) is reduced in glaucoma but only demonstrates modest correlations with central SAP sensitivity values and structural measures of optic nerve topography and retinal nerve fiber layer thickness.

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

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

In another study of 71 patients, Bowd et al. (2009) reported that pattern electroretinograms recorded using the PERGLA paradigm can discriminate between healthy and glaucomatous eyes, although this technique performed no better than SAP at this task.

**Reference(s)**


Peripheral arterial disease rehabilitation / Supervised Exercise Therapy (SET) is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence

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

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

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

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

Omnibus Codes

UnitedHealthcare Oxford Clinical Policy

©1996-2018, Oxford Health Plans, LLC

Page 84 of 127
Effective 05/01/2018
Another randomized controlled trial by Niccoli et al. (2010) compared exercise therapy in the form of "go home and walk" advice (WA) (n=102), SET (n=109), or SET with feedback (n=93). Walking distance was measured between baseline and 12 months. Walking distance for the WA group was 110 (0-300) meters, 310 (145-995) meters in the SET group, and 360 (173-697) meters in the SET with feedback group. While these results are promising, outcomes were subjective and walking distance was approximately ¼ mile which remains in a nonfunctional range.

A Cochrane systematic evidence review (Bendermacher et al., 2006) found that supervised exercise therapy has not been proven to be better than non-supervised exercise therapy in managing patients with intermittent claudication. Randomized and controlled clinical trials comparing supervised exercise programs with non-supervised exercise programs for people with intermittent claudication were selected. Two authors independently selected trials and extracted data. One author assessed trial quality and this was confirmed by a second author. For all continuous outcomes the authors extracted the number of participants, the mean differences, and the standard deviation. If data were available, the standardized mean difference was calculated using a fixed-effect model. These researchers identified 27 trials, of which 19 had to be excluded because the control group received no exercise therapy at all. The remaining 8 trials involved a total of 319 male and female participants with intermittent claudication. The follow-up ranged from 12 weeks to 12 months. In general, the supervised exercise regimens consisted of 3 exercise sessions per week. All trials used a treadmill walking test as one of the outcome measures. The overall quality of the included trials was good, though the trials were all small with respect to the number of participants, ranging from 20 to 59.

Supervised exercise therapy showed statistically significant and clinically relevant differences in improvement of maximal treadmill walking distance compared with non-supervised exercise therapy regimens in the short-term, with an overall effect size of 0.58 at 3 months. This translated to a difference of approximately 150 meters increase in walking distance in favor of the supervised group. However, there is a high possibility of a training effect as the supervised exercise therapy groups were trained primarily on treadmills (and the home based were not) and the outcome measures were treadmill based. The authors concluded that supervised exercise therapy is suggested to have clinically relevant benefits compared with non-supervised regimens in the short-term, which is the main prescribed exercise therapy for people with intermittent claudication. However, the clinical relevance has not been demonstrated definitely and will require additional studies with a focus on durability of outcomes and improvements in quality of life. (Bendermacher et al., 2006)

There is insufficient evidence in the medical literature demonstrating superior outcomes of such supervised exercise programs over exercise without supervision.

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>93702</td>
<td>Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)</td>
</tr>
</tbody>
</table>

The use of bioimpedance spectroscopy is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
A Hayes report on bioelectrical impedance (bioimpedance) analysis (BIA) for assessment of lymphedema states that there is insufficient evidence to draw definitive conclusions regarding the diagnostic value of BIA in assessing lymphedema (2016).

Bundred et al. (2015) conducted a comparative study of bioimpedance with perometry for early detection and intervention of lymphedema after axillary node clearance. The primary outcome measure was the incidence of lymphedema at 2 and 5 years following node clearance. Study results indicate that arm volume measurements remain the gold standard and it is not clear if bioimpedance is clinically effective and useful to detect lymphedema.
Erdogan et al. (2015) conducted a small study of 37 patients with breast cancer who underwent bioimpedance spectroscopy to assess lymphedema. During a one-year follow-up period where investigators used bioimpedance measures, a statically significant relationship was apparent between the incidence of lymphedema and disease characteristics, including the total number of lymph nodes and the region of radiotherapy. Study authors concluded that preliminary results indicate that bioimpedance may be a reasonable method regular monitoring to detect lymphedema.

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

In a position statement on the diagnosis and management of lymphedema, the National Lymphedema Network (NLN) reports that bioimpedance spectroscopy (BIS) has been shown to provide reliable data in the diagnosis of breast cancer-related lymphedema and that it can detect early changes associated with lymphedema. The organization further states that BIS may show promise for detecting smaller areas of localized lymphedema, but this application has not been subjected to adequate study to recommend it. BIS is not as accurate in advanced, fibrotic edema. As in measures of volume, BIS cannot differentiate lymphedema from other types of edema and does not determine when temporary post-operative arm edema becomes chronic lymphedema. (NLN, 2011)

NCCN guidelines on breast cancer do not address BIS in the diagnosis of breast cancer-related lymphedema. (NCCN, 2017)

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>93799</td>
<td>Unlisted cardiovascular service or procedure (when used to report inert gas rebreathing)</td>
</tr>
<tr>
<td>94799</td>
<td>Unlisted pulmonary service or procedure (when used to report inert gas rebreathing)</td>
</tr>
</tbody>
</table>

The use of inert gas re-breathing for measuring cardiac output is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy in published peer-reviewed clinical literature.

Clinical Evidence
Inert gas rebreathing is a noninvasive pulmonary gas exchange method for determining cardiac output. Tests measure the relative levels of two inert gases - one blood soluble and one insoluble component - over a few respirations (about 5 breaths or 15 seconds). The method relies on the principle that the rate of disappearance of the blood soluble gas from the alveolar space is proportional to the flow of blood perfusing the ventilated parts of the lungs. This is equal to cardiac output in the absence of a significant intrapulmonary shunt. The test can be used in patients at rest or during exercise (Innovision website).

Hassan et al. (2017) conducted a study to validate cardiac output measurement using inert gas rebreathing (IGR) against other methods of cardiac output quantification in a cohort of 97 patients with heart failure and reduced ejection fraction. Cardiac output was measured using 4 methods (IGR, cardiac magnetic resonance imaging, cardiac catheterization and echocardiography) and indexed to body surface area (cardiac index). All studies were performed within 48 hours. Median cardiac index measured by IGR was 1.75, by cardiac magnetic resonance imaging was 1.82, by cardiac catheterization was 1.65 and by echo was 1.7 L/min/m2. The authors concluded that IGR is a simple, accurate and reproducible noninvasive method for quantification of cardiac output in patients with advanced heart failure; however, the prognostic value of this measurement needs to be studied prospectively.
When assessing the accuracy and precision of a new technique for cardiac output measurement, the commonly quoted criterion for acceptability of agreement with a reference standard is that the percentage error (95% limits of agreement/mean cardiac output) should be 30% or less. Peyton and Chong (2010) reviewed published data on four different minimally invasive methods adapted for use during surgery and critical care: pulse contour techniques, esophageal Doppler, partial carbon dioxide rebreathing and transthoracic biopedance. The authors assessed the bias, precision and percentage error in agreement with thermodilution. For each method a meta-analysis was done using studies in which the first measurement point for each patient could be identified. Forty-seven studies were included. None of the four methods achieved agreement with bolus thermodilution which meets the expected 30% limits.

Preliminary results suggest that cardiac output (CO) measurements using inert gas rebreathing (IGR) might be an eligible method to tailor atrioventricular (AV) and ventriculo-ventricular (VV) programming of cardiac resynchronization therapy (CRT) devices. Reinsch et al. (2010) evaluated whether an optimization of CRT can be obtained by noninvasive CO measurements and whether acute hemodynamic improvements obtained by this approach relate into increase in cardiac exercise capacity. In 24 patients on CRT, iterative VV- and AV-delay optimization was done using the IGR method. This blinded, randomized, crossover study compared the responses to optimization during two periods: a 4-week optimized and a 4-week standard programming. Exercise capacity after optimization was assessed after each period by NYHA classification, a 6-minute walking test and quality of life (QoL) questionnaire. The NYHA class decreased by 17.8%, the mean distance walked in 6 minutes was 9.3% greater after optimization and the QoL improved by 14.5%. The portion of responders to CRT increased from 66.5% to 87.5%. The authors concluded that CRT optimization by iterative CO measurements leads to an increase in CO and an improvement of exercise capacity. These results suggest that this method might become an additive tool to adjust CRT programming. However, additional studies are warranted to better define the role of this technology in the clinical management of cardiac disease.

In a prospective, observational study (n=42), Kotake et al. (2009) investigated the accuracy of a noninvasive cardiac output (NICO) monitor equipped with newer software. Cardiac output was continuously monitored using both the NICO monitor and continuous cardiac output (CCO) measured by a pulmonary artery catheter. A NICO monitor equipped with ver. 4.2 software was used for the first 21 patients while a NICO monitor equipped with ver. 5.0 software was used for the rest of the patients. Cardiac output measured by bolus thermodilution (BCO) at 30 min intervals was used as a reference. The bias +/- precision of the NICO monitor was 0.18 +/- 0.88 l/min with ver. 4.2 software (n = 182) and 0.18 +/- 0.83 l/min with 5.0 software (n = 194). The accuracy of the NICO monitor is comparable to CCO, whose bias +/- precision against BCO is 0.19 +/- 0.81 l/min (n = 376). At the same level of CO(2) production and minute ventilation, PaCO(2) was lower in the patients monitored by NICO with ver. 5.0 software than patients with ver. 4.2 software. This study demonstrated the improved performance of the NICO monitor with updated software. The performance of the NICO monitor with ver. 4.2 or later software is similar to CCO. However, the cardiac output measurement did not fulfill the criteria of interchangeability to the cardiac output measurement by bolus thermodilution.

Inert gas rebreathing using low-concentration soluble and insoluble inert gases can derive cardiac output (CO) by the Fick principle. In a case series, Lang et al. (2007) assessed the practicality of the Innovor rebreathing system in measuring CO and peak oxygen consumption (VO2) during exercise in patients with heart failure (HF). Ninety-two consecutive exercise tests were prospectively performed in 88 patients with HF using the Innovor system. Eighty-six percent of the tests had successful measurement of metabolic and cardiac output data. Mean CO at rest was 3.5 +/- 1.1 L/min and increased to 7.2 +/- 2.7 L/min. Mean peak VO2 was 12.6 +/- 4.7 ml/kg/min. A significant linear correlation was observed between peak VO2 and peak CO (r = 0.64, p <0.0001). The authors concluded that the widespread clinical application of this technique in the evaluation of patients with HF remains to be determined by a large study with longer follow-up of clinical events to fully determine its prognostic value.

The American College of Cardiology and American Heart Association joint guidelines on the management of heart failure state that noninvasive cardiac output monitoring has not yet been validated for the diagnostic evaluation of patients with heart failure. (Yancy et al., 2013)

Reference(s)

Innovision website.
http://www.innovision.dk/Products/Innovor/Hemodynamic_Measurements_%E2%88%92_Inert_Gas_Rebreathing_Method.aspx


Spirometry and other pulmonary function tests are unproven and not medically necessary in children under the age of three due to insufficient evidence of safety and/or efficacy in published peer-reviewed clinical literature. Children in this age group are unable to perform the complex steps involved in these tests which require patient understanding and cooperation.

Clinical Evidence

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

The ATS, in a 2013 clinical guideline on the classification, evaluation, and management of childhood interstitial lung disease in infancy, suggests infant PFT be utilized to better characterize physiologic alterations (weak recommendation). However, no controlled clinical trials were identified on this topic and therefore, observational evidence and clinical experience informed judgments were made regarding PFT. Strong recommendations for initial diagnostic testing include echocardiography and thin-section CT using the lowest radiation dose that provides adequate diagnostic information. (Kurland et al., 2013)

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

In a separate guideline, the ATS states that children aged 2 to 6 represent one of the major challenges in lung function assessment. These children are generally too old to sedate, as is done with infants, and measurement of lung function under anesthesia is neither ethically acceptable nor physiologically relevant to clinical management. Children in this age group are not able to perform many of the physiological maneuvers required for the pulmonary function tests used in older children and adults. They have a short attention span and are easily distracted. (Beydon et al., 2007)

The 2015 Global Initiative for Asthma (GINA) guidelines specific to children 5 years and younger state that making a diagnosis of asthma in children 5 years and younger may be difficult because episodic respiratory symptoms such as wheezing and cough are also common in children who do not have asthma, particularly in those younger than 3 years. Due to the inability of most children 5 years and younger to perform reproducible expiratory maneuvers, lung function testing, bronchial provocation testing, and other physiological tests do not have a major role in the diagnosis of asthma at this age. The diagnosis of asthma in early childhood has to be based largely on clinical judgment and an assessment of symptoms and physical findings.

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


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96902</td>
<td>Microscopic examination of hairs plucked or clipped by the examiner (excluding hair collected by the patient) to determine telogen and anagen counts, or structural hair shaft abnormality</td>
</tr>
</tbody>
</table>

Microscopic analysis of hair is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
Trichograms are the microscopic examination of hair and identifies hair growth rate and anagen (hair growth) and/ or telogen (hair resting phase) ratio. Alopecia is the most common indication for completing this test.

Microscopic analysis of hair for hair loss issues is not supported by the clinical evidence. The utility of hair analysis is limited by the inability to discern endogenous and exogenous References. Interpretation is unreliable and there are no referenced norms to support the establishment that hair can be a consistent biological marker or that completion of such tests will change medical management (Chiang, 2001; Hryhorczuk and Eng, 2001).

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>97139</td>
<td>Unlisted therapeutic procedure (specify) [when used to report Kinesio Taping]</td>
</tr>
</tbody>
</table>

The use of Kinesio taping is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

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

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

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

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

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

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

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

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

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

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

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

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

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

No professional society guidelines addressing this technology were identified.
Once that after ReWalk training, some rs with UnitedHealthcare Oxford Clinical Policy Omnibus Codes confident in the st patients and only 8 learned to ascend and descend stairs with assistance; therefore, the authors were somewhat less assistance in that setting. Regarding ability on stairs, however, only 2 ReWalk studies assessed this task in 17 rehabilitation setting, and that a few of those who learned to walk also learned to ascend and descend stai patients with SCI who were unable to walk can walk unassisted for a short distance at a slow rate of speed in a rehabilitation centers. The authors of this review concluded with low confide These studies include outcomes data on only 129 patients with SCI who underwent exoskeleton training in to 10 short

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 clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

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 quality of life. 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.

ECRI (2016) conducted an evidence review of medical literature to evaluate powered wearable exoskeletons in the rehabilitation and community settings. Evidence for powered wearable exoskeleton use by patients with SCI is limited to 10 short-term noncomparative studies: 7 assess the ReWalk, 1 assesses the Ekso GT, and 2 assess the Indego. These studies include outcomes data on only 129 patients with SCI who underwent exoskeleton training in rehabilitation centers. The authors of this review concluded with low confidence that after ReWalk training, some patients with SCI who were unable to walk can walk unassisted for a short distance at a slow rate of speed in a rehabilitation setting, and that a few of those who learned to walk also learned to ascend and descend stairs with assistance in that setting. Regarding ability on stairs, however, only 2 ReWalk studies assessed this task in 17 patients and only 8 learned to ascend and descend stairs with assistance; therefore, the authors were somewhat less confident in the strength of evidence for this conclusion than in the conclusion on walking ability.
The authors of the ECRI (2016) review also concluded with low confidence that with minimal assistance some patients with SCI who were unable to walk or had difficulty walking can walk for a short distance at a slow rate of speed and walk on outdoor surfaces, ramps, and grass wearing an Indego exoskeleton in a rehabilitation setting. In the larger of the 2 Indego studies (n = 40), most patients (38/40; 95%) were able to complete a single-session walk of 600 meters. The authors rated the strength of evidence as low (rather than very low) for walking performance and advanced walking skills based on the fact that no other variables would affect the ability to perform these tasks in patients with paraplegia. The authors commented that no studies assessed short- or long-term safety and efficacy of these devices in the home/community setting; therefore, determining the optimal training required for personal use and whether using this technology in the home/community setting offers a benefit in terms of independence and quality of life compared with other assistive devices used to enable standing or mobility is not possible at this time.

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.

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.

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>99174</td>
<td>Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with remote analysis and report</td>
</tr>
<tr>
<td>99177</td>
<td>Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with on-site analysis</td>
</tr>
</tbody>
</table>

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

- As a mass screening instrument for children 1 - 3 years of age (ends on 4th birthday).
• Children 4 years of age and older who are developmentally delayed and are unable or unwilling to cooperate with routine visual acuity screening. Click here for a list of Allowable Diagnoses.

**Instrument-based ocular screening using photoscreening is unproven and not medically necessary for all other patient populations including children younger than 1 year of age.**

More age-appropriate screening methods are available for these populations.

**Clinical Evidence**

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

The U.S. Preventive Services Task Force (USPSTF, 2016) recommends vision screening for all children at least once between the ages of 3 and 5 years, to detect the presence of amblyopia or its risk factors. The USPSTF concluded 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, and stated that various screening tests that are feasible in primary care are used to identify visual impairment among children. These tests include visual acuity tests, stereoacuity tests, the cover-uncover test, and the Hirschberg light reflex test (for ocular alignment/strabismus), as well as the use of photoscreeners (instruments that detect amblyogenic risk factors and refractive errors).

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

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

**Professional Societies**

National Center for Children’s Vision and Health (NCCVH) Vision Screening for Children 36 to <72 Months: Recommended Practices (2015) have provided the following recommendations:

- All children aged 36 months to younger than 72 months should be screened annually (best practice) or at least once (acceptable minimum standard) during the interval between their third and sixth birthdays. Exceptions to this include children with the following: readily observable ocular abnormalities, neurodevelopmental disorders, systemic conditions that have associated ocular abnormalities, first-degree relatives with strabismus or amblyopia, a history of prematurity (<32 completed weeks), and parents who believe their child has a vision problem. These children should be referred directly to an ophthalmologist or optometrist for a comprehensive eye examination. Children who have received an eye examination from an eye care professional within the prior 12 months do not need to be screened. A vision screening program based on best practice standards should be the goal.

- Children who are unable or refuse to complete testing are considered untestable. These children are more likely to have vision problems than testable children, and thus should be rescreened either the same day or soon afterward, but in no case later than 6 months. Children with cognitive, physical, or behavioral issues likely to preclude rescreening and those unable to be rescreened in a timely manner because of administrative or other issues should be referred directly for a comprehensive eye examination.

- Currently, there are two best practice vision screening methods for children aged 36 to younger than 72 months: (1) monocular vision acuity testing and (2) instrument-based testing using autorefraction.
  - For visual acuity testing, appropriately scaled (logMAR) single crowded HOTV letters or LEA Symbols surrounded by crowding bars at a 5-ft (1.5-m) test distance with the child matching or reading the optotypes aloud should be used. A passing score is the correct identification of three of three or three of four optotypes with each eye at the 20/50 level for children aged 36 through 47 months and at the 20/40 level for children aged 48 to younger than 72 months. Acceptable practices are to use the HOTV or LEA Symbols calibrated for a 10-ft (3-m) test distance or to use a single line of these optotypes surrounded by a rectangular crowding bar on all four sides. Other optotypes like Allen pictures and the Tumbling E should not be used.
The body of published evidence on Relizorb is very small, and studies reviewed medical literature.

The American Academy of Ophthalmology (AAO) Preferred Practice Patterns for Pediatric Eye Evaluations (2012) state that after 6 months of age, an assessment of binocular alignment should be performed because children should have aligned eyes at age 4 to 6 months. Instrument-based screening with photoscreening or autorefraction devices can be valuable in detecting amblyopia risk factors in this age group because the tests are rapid and noninvasive and minimal cooperation is required on the part of the child. The authors of the report state that instrument-based vision-screening techniques, such as photoscreening and autorefraction, are useful alternatives to visual acuity screening using eye charts for very young and developmentally delayed children and compare well with standard vision-testing techniques and cycloplegic refraction. They are not superior to quantitative visual acuity testing for children who are able to perform those tests. Most instrument-based vision-screening methods detect the presence of risk factors for amblyopia, including strabismus, high or asymmetric refractive errors, media opacities (e.g., cataract), retinal abnormalities (e.g., retinoblastoma), and ptosis.

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

**Reference(s)**


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B4104</td>
<td>Additive for enteral formula (e.g., fiber)</td>
</tr>
<tr>
<td>B9998</td>
<td>NOC for enteral supplies</td>
</tr>
</tbody>
</table>

**Digestive enzyme cartridges (e.g., Relizorb™) for use with enteral tube feeding are unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

**Clinical Evidence**

Synonyms: enteral feeding in-line cartridge (EFIC), immobilized lipase

The body of published evidence on Relizorb is very small, and studies using human subjects are lacking.
On November 20, 2015, Alcresta Therapeutics received de novo approval from the FDA to market Relizorb. (DEN150001) The device is indicated for use in adults to hydrolyze fats and is for use with enteral feeding only.

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

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

Two clinical trials evaluating Relizorb have been completed; however, no results have been published at this time. Clinicaltrials.gov #NCT02750501 and NCT02598128.

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3999</td>
<td>Upper limb orthotic, not otherwise specified (when used to report MyoPro™)</td>
</tr>
</tbody>
</table>

The use of the upper limb orthotic known as the MyoPro™ is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
There is very limited information related to the use and ability of the device known as the Myopro.

According to the manufactures website, the MyoPro™ myoelectric limb orthosis is a powered brace that can reinitiate movement of a partially paralyzed arm to enhance function and quality of life. It is designed for individuals with stroke, MS, ALS; brain & spinal cord injury and other neuromuscular disorders. The procedure code within the Healthcare Common Procedure Coding System (HCPCS) to accurately describe the MyoPro Orthosis is code L3999. A recent coding clarification advisory article issued on 5/8/2012 was published by the Medicare Pricing, Data Analysis, and Coding (PDAC) contractor Noridian Health Care Solutions: “The distinction in coding relates to the indicated use of the joint and the beneficiary's medical condition(s). The Concentric adjustable torsion-style joints used solely to provide an assistive function for joint motion must be coded L2999 or L3999.” See the following website for more information: http://www.myopro.com/. (Accessed May 26, 2017)

An April 2017 ECRIs Health Technology Assessment concluded that MyoPro alone improved activities of daily living as much as supervised therapy alone in the short term for some stroke patients. Adding MyoPro to supervised therapy provided little to no additional benefit. These conclusions are based on limited evidence from 4 very small published studies and 1 conference abstract reporting on 91 stroke patients. Additional controlled studies are needed to confirm these results, provide longer-term results, and to study different patient populations; however, no such trials are ongoing.
Willigenburg and colleagues (2017) examined the efficacy of an 8-week regimen combining repetitive task-specific practice (RTP) with a myoelectric brace (RTP+Myomo) on paretic upper extremity (UE; use in valued activities, perceived recovery, and reaching kinematics) in 12 patients. Seven were administered RTP+Myomo therapy, and 5 were administered RTP only. Both groups participated in individualized, 45-min therapy sessions occurring 3 days/week over an 8-week period. The arm, hand ability, activities of daily living, and perceptions of recovery subscales of the Stroke Impact Scale (SIS), as well as UE reaching kinematics, assessed before and after the intervention. The RTP+Myomo group showed greater improvements on all SIS subscales. Patients in the RTP-only group showed a greater increase in hand velocity in the reach up task, but no changes were observed in the range of shoulder flexion or elbow extension during reaching. None of the changes in kinematic outcome measures significantly correlated with any of the changes in SIS subscales. The authors concluded that RTP integrating myoelectric bracing may be more beneficial than RTP only in improving self-reported function and perceptions of overall recovery. The authors observed no changes in the range of elbow extension, and no relationship between self-reported improvements and changes in reaching kinematics. This study is limited by small sample size and short follow-up period.

A randomized controlled pilot trial was conducted by Page et al. (2013) to compare the efficacy of a repetitive task-specific practice in a person with chronic, moderate upper extremity impairment. A total of 16 people were utilized (7 males; mean age 57.0 ± 11.02 years; mean time post stroke 75.0 ± 87.63 months; 5 left-sided strokes) all exhibiting chronic, stable, moderate upper extremity impairment. Each person was given a repetitive task-specific practice in which they participated in valued, functional tasks using their paretic upper extremities. Both groups were supervised by a therapist and were administered therapies targeting their paretic upper extremities that were 30 minutes in duration, occurring 3 days/week for eight weeks. One group participated in repetitive task-specific practice entirely while wearing the portable robotic, while the other performed the same activity regimen manually. Upon completion of the study itself each group showed the same Fugl-Meyer score increases of ≈2.1 points; the group using robotics exhibited larger score changes on all but one of the Canadian Occupational Performance Measure and Stroke Impact Scale subscales, including a 12.5-point increase on the Stroke Impact Scale recovery subscale. It was noted that the finding suggest that therapist supervised task specific practice with an integrated robotic device could be as efficacious as manual practice in some subjects with moderate upper extremity impairment. Additional studies are needed as there is still insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

No professional society guidelines addressing this technology were identified.

The U.S. Food and Drug Administration (FDA) cleared the Myomo e100 for marketing through the 510(k) process in April 2007 (K062631). 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

No separate FDA clearance for the MyoPro Motion-G was identified.

**Reference(s)**


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L5781</td>
<td>Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system</td>
</tr>
<tr>
<td>L5782</td>
<td>Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system, heavy duty</td>
</tr>
</tbody>
</table>

The use of vacuum pumps for residual limb volume management and moisture evacuation systems among amputees is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

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

The current evidence base is insufficient to definitively establish the safety and efficacy of vacuum pump residual limb volume management and moisture evaluation systems, used with lower limb prostheses, in amputees. The few available comparative studies did not assess patient-relevant health outcomes, such as functional capabilities and quality of life (QOL), following use of these systems.

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

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

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

Trabeallesi et al. (2012) conducted a randomized controlled study to evaluate the effects of a vacuum-assisted socket system (VASS) in a sample of trans-tibial amputees with wounds or ulcers on the stump. Prosthesis use was the primary outcome measure. Secondary outcome measures were mobility with the prosthesis, pain associated with its use, and wound or ulcer healing. The study also included a control group of patients who were trained to use a standard suction socket system prosthesis after ulcer and wound healing. At 12 weeks following rehabilitation, all VASS users were able to walk independently with their prosthesis (median Locomotor Capability Index (LCI) value = 42); whereas only 5 control patients were able to walk independently. At the 2-month follow-up, the participants used their VASS prostheses for 62 hours a week, which was significantly longer than the control group using the standard prosthesis for 5 hours per week (P=0.003). However, after 6 months of follow-up, any significant differences observed between the VASS and control groups were no longer apparent. In addition, pain and wound healing did not significantly differ between the two groups. The authors concluded that these findings showed that the VASS prosthesis allowed early fitting with prompt ambulation recovery without inhibiting wound healing or increasing pain.

A clinical trial (NCT01559909) to assess if the socket height alters the motion of the leg and changes the way one walks when using VAS compared to conventional socket suspension technology has been completed, but results have not been published. For more information, please go to www.clinicaltrials.gov.

No professional society guidelines addressing this technology were identified.

Reference(s)


The use of an injectable bulking agent such as Solesta® is unproven and not medically necessary for treating fecal incontinence due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

**Clinical Evidence**

Solesta Injectable Gel (Salix Pharmaceuticals, Inc.) is a sterile gel that is injected into the anal canal to treat the symptoms of fecal incontinence (FI). It is composed of naturally-made materials, dextranomer and sodium hyaluronate. Solesta is classified by the U.S. Food and Drug Administration (FDA) as a medical device (injectable bulking agent for gastrourology use) and not a drug. Solesta Injectable Gel (Salix Pharmaceuticals Inc.) received FDA premarket approval (PMA) on May 27, 2011 (P100014; product code LNM). See the following website for more information: [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm). (Accessed April 6, 2017)

The overall quality of the evidence is low given the paucity of controlled studies and small study sizes, which are further compromised by the numbers of dropouts. In most studies, surgeons were not blinded and/ the assessment of outcomes lacked blinding. Given the large placebo effect observed in studies of treatments for FI, larger, independent, randomized, sham-controlled studies are needed to further evaluate the efficacy, durability, and safety of this treatment. Future studies should compare non-animal stabilized hyaluronic acid/dextranomer (NASHA Dx) with standard therapies such as sacral nerve stimulation and other minimally invasive alternatives. Although NASHA Dx may be a viable alternative for patients with intractable FI who do not respond to conservative measures, and who refuse surgery or are not appropriate surgical candidates, there is also a need to better define the patient selection criteria by examining variables that predict which patients will derive the most clinical benefit from this therapy. (Hayes, Inc., October 2014. Updated October 2016.)

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

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

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

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

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

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

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

Alavi et al. (2015) completed a literature review of the etiology, diagnosis, and treatment of fecal incontinence. They identified that newer office-based procedures, such as the Solesta injection, are showing promising results in properly selected patients, and that Solesta is found to be effective with patients experiencing improvement in their fecal incontinence symptoms at up to 24 months. Common side effects noted in their review include pyrexia and proctalgia that resolved within 1 month of therapy.

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

Reference(s)

Three-dimensional (3-D) printed cranial implants (e.g., OssDsign® Cranial Patient-Specific Implant, OsteoFab™ Patient Specific Cranial Device) are unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
On February 18, 2013, Oxford Performance Materials (OPM) received FDA 510(k) clearance for the OsteoFab™ Patient Specific Cranial Device (OPSCD). OsteoFab is OPM's brand for Additively Manufactured (also called 3D Printing) medical and implant parts produced from PEKK polymer. See the following for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf12/k121818.pdf. (Accessed June 2, 2017)

On January 19, 2017, the Food and Drug Administration (FDA) granted OssDsigan AB (Uppsala, Sweden) 510(k) marketing clearance for its three-dimensional (3-D) printed OssDsigan® 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 OssDsigan Cranial PSI is made from a calcium phosphate–based ceramic material, reinforced by a titanium skeleton. The implant's interconnecting tile design purportedly allows fluid movement through the device. See the following for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf16/k161090.pdf. (Accessed June 2, 2017)

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

Choi and Kim (2015) conducted a systematic review of the literature to investigate the current status of 3D printing technology and its clinical application. Thirty-five articles were selected for review. In addition, the benefits and possibilities of the clinical application of 3D printing in craniofacial surgery were reviewed, based on personal experiences with more than 500 craniofacial cases conducted using 3D printing tactile prototype models. According to the authors, 3D printing technology is innovative since there is insufficient scientific data to support the use of this application.

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

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

Gillardino et al. (2015) performed a review of all autologous and custom computer-generated implants (CCGI) cranioplasties performed at their institution over 7 years. All implants were preoperatively designed using either Synthes Pro-Plan three-dimensional CT-based planning software alone (for cranioplasties of cranial defects) or in combination with direct modeling on three-dimensional cranial molds of the patient's bony defect (for cases requiring additional bony contouring/volume augmentation). Total average cost did not differ statistically between the autologous group (n = 15; $25,797.43) and the CCGI cohort (n = 12; $28,560.58). Operative time, need for ICU admission, and number of complications were all statistically significantly less in the CCGI group. The length of hospital stay and number of cases needing transfusion were fewer in the CCGI group but did not reach statistical significance. The authors concluded that CCGI cranioplasty technique was associated with a statistically significant decrease in operative time and need for ICU admission when compared with those patients who underwent autologous bone cranioplasty. According to the authors, the study has limitations that force cautious interpretation of the results. A major limitation is that the results represent a preliminary study, based on an analysis of a small study population.

Reference(s)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2031</td>
<td>Hair analysis (excluding arsenic)</td>
</tr>
</tbody>
</table>

Hair analysis is unproven and not medically necessary for evaluating any disorder or condition due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

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

Wolowiec et al. (2013) conducted a systematic review on the relation between the mineral composition of hair or 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.

According to Quackwatch, hair analysis is not useful for assessing the body’s nutritional status or serving as a basis for dietary or supplement recommendations. Nor should these tests be routinely used to screen people for heavy metal toxicity.

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.

**Professional Societies**

Several society guidelines discuss hair analysis for allergies, but none recommend its use [National Institute of Allergy and Infectious Diseases 2010, American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI) 2014; American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology 2008].

**The American Academy of Neurology and Child Neurology Society**

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)

**The American Society of Addiction Medicine (ASAM)**

In 2013, 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 hair samples do not allow for the determination of when drugs were taken and recent exposures cannot be detected. The ASAM notes that one distinct disadvantage to hair testing is that some drug classes (e.g., benzodiazepines) are poorly detected in hair. (ASAM, 2013)

**Reference(s)**


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2033</td>
<td>Thymol turbidity, blood</td>
</tr>
</tbody>
</table>

**Testing for Thymol turbidity is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**
**Clinical Evidence**
This test is considered obsolete by CMS and other lab references.

**Reference(s)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2038</td>
<td>Mucoprotein, blood (seromucoid) (medical necessity procedure)</td>
</tr>
</tbody>
</table>

Testing for blood mucoprotein is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

**Clinical Evidence**
This test is considered obsolete by CMS and other lab references.

**Reference(s)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L8607</td>
<td>Injectable bulking agent for vocal cord medialization, 0.1 ml, includes shipping and necessary supplies</td>
</tr>
<tr>
<td>Q2026</td>
<td>Injection, Radiesse, 0.1ML</td>
</tr>
<tr>
<td>Q2028</td>
<td>Injection, Sculptra, 0.5 mg</td>
</tr>
</tbody>
</table>

**Radiesse is proven and medically necessary and reconstructive for the following:**
- Facial defects due to facial lipidatrophy in persons with human immunodeficiency virus (HIV)

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

**Sculptra is proven and medically necessary and reconstructive for treating facial defects due to facial lipidatrophy in persons with human immunodeficiency virus (HIV).**

Other uses of these devices may be cosmetic.

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

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

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

The Radiesse Laryngeal Implant (BioForm Medical Inc.) received FDA 510(k) clearance (K070090) as substantially equivalent to legally marketed predicate devices on March 1, 2007, for vocal fold medialization and treatment of vocal fold insufficiency that can be improved by injection of a soft-tissue bulking agent. The Radiesse Laryngeal Implant is intended to augment the size of the displaced or deformed vocal fold so that it may meet the opposing vocal fold at the midline for improved phonation.
On December 22, 2006, the FDA approved Radiesse, an injectable (under the skin) implant to restore or correct signs of facial lipoatrophy, or fat loss, in people with human immunodeficiency virus (HIV). For additional information, refer to the following website: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?id=k070090. (Accessed April 21, 2017)

The expanded indication for the improvement in the appearance in the back of the hand due to volume loss in adults over the age of 21, was approved by the FDA on June 4, 2015 for the Radiesse Injectable Implant. For additional information, refer to the following website: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm451776.htm. (Accessed April 21, 2017)

On August 3, 2004, the FDA approved Sculptra, an injectable filler to correct facial fat loss in people with human immunodeficiency virus (HIV) (FDA, 2004). Sculptra is an injectable form of poly-L-lactic acid, a biodegradable, biocompatible synthetic polymer from the alpha-hydroxy-acid family.

In a multicenter prospective study, Rosen et al. (2007) evaluated the effectiveness of CaHA injection for patients with glottal incompetence. Voice-related outcome measures were collected for pre-injection and at one, three and six months. Sixty-eight patients were available for evaluation. Fifty percent of the injection procedures were done in the office setting. Fifty-seven percent were diagnosed with unilateral paralysis and 42% with glottal incompetence with mobile vocal folds. Patient satisfaction at six months post-procedure showed 56% had significantly improved voice, and 38% reported moderately improved voice. Information regarding the value and results of CaHA vocal fold augmentation beyond six months are presently not available but will be forthcoming with the 12- and 24-month reports from this prospective, open-label clinical trial.

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

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

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

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

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


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4100</td>
<td>Skin substitute, not otherwise specified (when used to report Amniofix, CorMatrix, or Conexa)</td>
</tr>
<tr>
<td>Q4115</td>
<td>AlloSkin, per sq cm</td>
</tr>
<tr>
<td>Q4123</td>
<td>AlloSkin RT, per sq cm</td>
</tr>
<tr>
<td>Q4131</td>
<td>Epifix or Epicord, per sq cm</td>
</tr>
<tr>
<td>Q4132</td>
<td>Grafix Core and GrafixPL Core, per sq cm</td>
</tr>
<tr>
<td>Q4133</td>
<td>Grafix Prime and GrafixPL Prime, per sq cm</td>
</tr>
<tr>
<td>Q4134</td>
<td>HMatrix, per sq cm</td>
</tr>
<tr>
<td>Q4135</td>
<td>Mediskin, per square centimeter</td>
</tr>
<tr>
<td>Q4136</td>
<td>Ez-derm, per square centimeter</td>
</tr>
<tr>
<td>Q4137</td>
<td>AmnioExcel or BioDEXcel, per sq cm</td>
</tr>
<tr>
<td>Q4138</td>
<td>BioDFence DryFlex, per sq cm</td>
</tr>
<tr>
<td>Q4139</td>
<td>AmnioMatrix or BioDMatrix, injectable, 1 cc</td>
</tr>
<tr>
<td>Q4140</td>
<td>BioDFence, per sq cm</td>
</tr>
<tr>
<td>Q4141</td>
<td>AlloSkin AC, per sq cm</td>
</tr>
<tr>
<td>Q4142</td>
<td>Xcm biologic tissue matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4143</td>
<td>Repriza, per square centimeter</td>
</tr>
<tr>
<td>Q4145</td>
<td>EpiFix, injectable, 1 mg</td>
</tr>
<tr>
<td>Q4146</td>
<td>Tensix, per square centimeter</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td>Q4147</td>
<td>Architect, Architect PX, or Architect FX, extracellular matrix, per sq cm</td>
</tr>
<tr>
<td>Q4148</td>
<td>Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per sq cm</td>
</tr>
<tr>
<td>Q4149</td>
<td>Excellagen, 0.1 cc</td>
</tr>
<tr>
<td>Q4150</td>
<td>AlloWrap DS or dry, per sq cm</td>
</tr>
<tr>
<td>Q4151</td>
<td>AmnioBand or Guardian, per sq cm</td>
</tr>
<tr>
<td>Q4152</td>
<td>DermaPure, per sq cm</td>
</tr>
<tr>
<td>Q4153</td>
<td>Dermavest and Plurivest, per sq cm</td>
</tr>
<tr>
<td>Q4154</td>
<td>Biovance, per square centimeter</td>
</tr>
<tr>
<td>Q4155</td>
<td>Neox Flo or Clarix Flo 1 mg</td>
</tr>
<tr>
<td>Q4156</td>
<td>Neox 100 or Clarix 100, per sq cm</td>
</tr>
<tr>
<td>Q4157</td>
<td>Revitalon, per square centimeter</td>
</tr>
<tr>
<td>Q4158</td>
<td>Kerecis Omega3, per sq cm</td>
</tr>
<tr>
<td>Q4159</td>
<td>Affinity, per square centimeter</td>
</tr>
<tr>
<td>Q4160</td>
<td>Nushield, per sq cm</td>
</tr>
<tr>
<td>Q4161</td>
<td>Bio-connekt wound matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4162</td>
<td>WoundEx Flow, BioSkin Flow, 0.5 cc</td>
</tr>
<tr>
<td>Q4163</td>
<td>WoundEx, BioSkin, per sq cm</td>
</tr>
<tr>
<td>Q4164</td>
<td>Helicoll, per square centimeter</td>
</tr>
<tr>
<td>Q4165</td>
<td>Keramatrix, per square centimeter</td>
</tr>
<tr>
<td>Q4166</td>
<td>Cytal, per square centimeter</td>
</tr>
<tr>
<td>Q4167</td>
<td>Truskin, per square centimeter</td>
</tr>
<tr>
<td>Q4168</td>
<td>Amnioband, 1 mg</td>
</tr>
<tr>
<td>Q4169</td>
<td>Artacent wound, per square centimeter</td>
</tr>
<tr>
<td>Q4170</td>
<td>Cygnus, per square centimeter</td>
</tr>
<tr>
<td>Q4171</td>
<td>Interfyl, 1 mg</td>
</tr>
<tr>
<td>Q4172</td>
<td>PuraPly or PuraPly AM, per sq cm</td>
</tr>
<tr>
<td>Q4173</td>
<td>Palingen or palingen xplus, per square centimeter</td>
</tr>
<tr>
<td>Q4174</td>
<td>Palingen or promatrix, 0.36 mg per 0.25 cc</td>
</tr>
<tr>
<td>Q4175</td>
<td>Miroderm, per square centimeter</td>
</tr>
<tr>
<td>Q4176</td>
<td>Neopatch, per square centimeter</td>
</tr>
<tr>
<td>Q4177</td>
<td>Floweramnioflo, 0.1 cc</td>
</tr>
<tr>
<td>Q4178</td>
<td>Floweramniopatch, per square centimeter</td>
</tr>
<tr>
<td>Q4179</td>
<td>Flowerderm, per square centimeter</td>
</tr>
<tr>
<td>Q4180</td>
<td>Revita, per square centimeter</td>
</tr>
<tr>
<td>Q4181</td>
<td>Amnio wound, per square centimeter</td>
</tr>
<tr>
<td>Q4182</td>
<td>Transcyte, per square centimeter</td>
</tr>
</tbody>
</table>

**TransCyte is proven and medically necessary for treating surgically excised full-thickness thermal burn wounds* and deep partial-thickness thermal burn wounds** in persons who require such a covering before autograft placement.

**TransCyte is unproven and not medically necessary for all other indications due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

*A full-thickness burn (third degree burn) is a burn with destruction of all layers of the skin. These burns involve all of the epidermal and dermal layers, with varying amounts of the sub-cutaneous layer involvement (Committee on Trauma American College of Surgeons, 1999).

**A partial-thickness burn (second degree burn) involves the epidermis and only part of the dermis. Deep partial thickness burns involve the epidermis and most parts of the dermis, leaving few intact skin appendages and nerve endings (Committee on Trauma American College of Surgeons, 1999).
The following are unproven and not medically necessary for any indication due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature:

- Affinity
- Alloskin®
- Allowrap®
- Amnio Wound™
- Amnioband
- Amnioexcel™ or Biodexcel™
- AmnioFix®
- AmnioGen-A™, AmnioGen-C™, AmnioGen-45™, or AmnioGen-200™
- Amniomatrix™ or Biodmatrix™
- Architect Extracellular Matrix®
- Artacent®
- Bio-ConneKt®
- Biodfence™ or Biodfence Dryflex™
- BioSkin™
- BioSkin™ Flow
- Biovance®
- Clarix®
- Clarix® Flo
- Conexa™ Reconstructive Matrix
- CorMatrix®
- Cygnus™
- Cytal™
- Dermapure™
- Dermavest® or Plurivest
- Epicord™
- Epifix®
- Excellagen®
- Ez-derm®
- Floweramnioflo™ or FlowerFlo™
- Floweramniopatch™ or FlowerPatch™
- FlowerDerm™
- Grafix®
- GrafixPL®
- Guardian
- Helicoll™
- Hmatrix®
- Interfyl™
- Keramatrix®
- Kerecis™ or Marigen™
- Mediskin™
- Miroderm™
- NeoPatch™
- Neox®
- Neox Flo®
- Nushield®
- PalinGen® Amniotic Tissue Allograft and PalinGen® Flow products
- ProMatrX™
- PuraPly™ or PuraPly™ Antimicrobial
- Repriza®
- Revita™
- Revitalon®
- Tensix®
- TruSkin™
- WoundEx™
- WoundEx™ Flow
- Xcm Biologic Tissue Matrix®

**Clinical Evidence**

**Affinity**

Affinity is a fluid membrane allograft that is intended for clinical use in wound repair and healing.
There are few published studies addressing the use of Affinity for wound treatment. Therefore, it is not possible to conclude whether Affinity has a beneficial effect on health outcomes.

**AlloSkin**

AlloSkin (AllosSource) is a meshed human allograft skin for acute and chronic wound therapy. It is comprised of cadaveric epidermis and dermis.

There are few published studies addressing the use of Alloskin for wound treatment. Therefore, it is not possible to conclude whether Alloskin has a beneficial effect on health outcomes.

Moravvej et al. (2016) evaluated allogeneic fibroblasts on meshed split thickness skin grafts (STSGs) in 14 patients. After debridement and wound excision, meshed STSG was used to cover the entire wound. Alloskin (allogibroblasts cultured on a combination of silicone and glycosaminoglycan) was applied on one side and petroleum jelly-impregnated gauze (Iran Polymer and Petrochemical Institute) was applied on the other. The healing time, scar formation, and pigmentation score were assessed for the patients. Alloskin demonstrated good properties compared to petroleum jelly-impregnated gauze. The average healing time and hypertrophic scar formation were significantly different between the two groups. In addition, the skin pigmentation score in the alloskin group was closer to normal. The authors concluded that alloskin grafting, including fibroblasts on meshed STSG, may be a useful method to reduce healing time and scar size and may require less autologous STSG in extensive burns where a high percentage of skin is burned and there is a lack of available donor sites. Larger prospective, controlled clinical studies are needed to compare the effectiveness of human skin allograft to standard care.

**Allowrap**

Allowrap (Allosource) is a human amniotic membrane designed to provide a biologic barrier following surgical repair.

There are few published studies addressing the use of Allowrap for wound treatment. Therefore, it is not possible to conclude whether Allowrap has a beneficial effect on health outcomes.

**Amnio Wound**

Amnio Wound (Alpha Tissue, LLC) is a lyophilized human amniotic membrane allograft comprised of an epithelial layer and two fibrous connective tissue layers specifically processed to be used for the repair and replacement of lost or damaged dermal tissue.

There are few published studies addressing the use of Amnio Wound for wound treatment. Therefore, it is not possible to conclude whether Amnio Wound has a beneficial effect on health outcomes.

**Amnioband and Guardian**

Amnioband and Guardian (Musculoskeletal Transplant Foundation) are human tissue allografts made of donated placental membrane. Although marketed under two different brand names, the products are identical.

There are few published studies addressing the use of Amnioband or Guardian for wound treatment. Therefore, it is not possible to conclude whether Amnioband or Guardian have a beneficial effect on health outcomes.

DiDomenico et al. (2016) compared aseptically processed dehydrated human amnion and chorion allograft (dHACA) versus standard of care (SOC) in facilitating wound closure in nonhealing diabetic foot ulcerations (DFUs). Patients with DFUs treated with SOC (off-loading, appropriate debridement, and moist wound care) after a 2-week screening period were randomized to either SOC or wound-size-specific dHACA (AmnioBand, Musculoskeletal Transplant Foundation) applied weekly for up to 12 weeks plus SOC. Primary endpoint was the percentage of wounds healed at 6 weeks between groups. At 6 weeks, 70% (14/20) of the dHACA-treated DFUs healed compared with 15% (3/20) treated with SOC alone. At 12 weeks, 85% (17/20) of the DFUs in the dHACA group healed compared with 25% (5/20) in the SOC group, with a corresponding mean time to heal of 36 and 70 days, respectively. At 12 weeks, the mean number of grafts used per healed wound for the dHACA group was 3.8. The mean wastage at 12 weeks was 40%. One adverse event and 1 serious adverse event occurred in the dHACA group; neither was graft related. Three adverse events and 1 serious adverse event occurred in the SOC group. The authors concluded that aseptically processed dHACA heals diabetic foot wounds significantly faster than SOC at 6 and 12 weeks with minimal graft wastage. The authors indicated that the limitations of this trial include the lack of blinding (patient and investigator) and lack of a soft-tissue matrix comparator. Future studies may consider comparing different amniotic tissue forms and allowing wounds of greater severity or depth.
Amnioexcel or Biodexcel

AmnioExCel (also marketed under trade name BioDExCel(Derma Sciences, Inc.) is a dehydrated human amnion-derived tissue allograft with intact extracellular matrix that is intended to advance soft tissue repair, replacement and reconstruction.

There are few published studies addressing the use of Amnioexcel or Biodexcel for wound treatment. Therefore, it is not possible to conclude whether Amnioexcel or Biodexcel has a beneficial effect on health outcomes.

Snyder et al. (2016) conducted a study to evaluate dehydrated amniotic membrane allograft (DAMA) (AMNIOEXCEL) plus standard of care (SOC) compared to SOC alone for the closure of chronic diabetic foot ulcers (DFUs). This prospective, open-label, randomized, parallel group trial was implemented at 8 clinical sites in the United States. Eligibility criteria included adults with type 1 or type 2 diabetes mellitus who have 1 or more ulcers with a Wagner classification of grade 1 or superficial 2 measuring between 1 cm2 and 25 cm2 in area, presenting for more than 1 month with no signs of infection/osteomyelitis; ABI > 0.7; HbA1c Less than 12%; and serum creatinine less than 3.0 mg/dL. Eligible subjects were randomized (1:1) to receive either SOC alone (n = 14) or DAMA+SOC (n = 15) until wound closure or 6 weeks, whichever occurred first. The endpoint was the proportion of subjects with complete wound closure (defined as complete reepithelialization without drainage or need for dressings. Thirty-five percent of subjects in the DAMA+SOC cohort achieved complete wound closure at or before week 6, compared with 0% of the SOC alone cohort. There was a more robust response noted in the per protocol population, with 45.5% of subjects in the DAMA+SOC cohort achieving complete wound closure, while 0% of SOC-alone subjects achieved complete closure. No treatment-related adverse events were reported. According to the authors, the results of this study suggest that DAMA is safe and effective in the management of DFUs, but additional research is needed.

AmnioFix

AmnioFix (MiMedx Group, Inc.) is a composite amniotic tissue membrane minimally manipulated to protect the collagen matrix and its natural properties. It is available in sheet/membrane, particulate, and wrap configurations for use in surgical (e.g., spinal fusion and discectomy), soft tissue, tendon, and nerve applications. Other AmnioFix products include AmnioFix Injectable that is intended for treatment of tendon and soft tissue injuries.

In a systematic review and network meta-analysis, Tsikopoulos et al. (2016) compared the efficacy of different injection therapies for plantar fasciopathy (historically known as 'plantar fascitis'). Randomized trials comparing various injection therapies in adults with plantar fasciopathy were included. The primary outcome was pain relief. Secondary outcomes included functional disability, composite and health-related outcomes. All outcomes were assessed (1) in the short term (up to 2 months), (2) the intermediate term (2–6 months) and (3) the medium term (more than 6 months to 2 years). Quality assessment was performed using the Cochrane risk of bias tool. Twenty-two trials comprising 1216 patients were included in the review. Dehydrated amniotic membrane injections were significantly superior to corticosteroids in the short term in achieving the primary and composite outcomes. The authors concluded that although the dehydrated amniotic membrane provided significant clinical relief at 0–2 months, there were no data about this treatment at 2 months and beyond.

Zelen et al. (2013a) reported the results of a randomized clinical trial examining the efficacy of micronized dehydrated human amniotic/chorionic membrane (mDHACM) injection as a treatment for chronic refractory plantar fasciitis. Forty-five patients were randomized to receive injection of 2 cc 0.5% Marcaine plain, then either 1.25 cc saline (controls), 0.5 cc mDHACM, or 1.25 cc mDHACM. Follow-up visits occurred over 8 weeks to measure function, pain, and functional health and well-being. Significant improvement in plantar fasciitis symptoms was observed in patients receiving 0.5 cc or 1.25 cc mDHACM versus controls within 1 week of treatment and throughout the study period. The authors concluded that in patients with refractory plantar fasciitis, mDHACM is a viable treatment option. According to the authors, larger studies are needed to confirm these findings.

Patel et al. (2015) conducted an observational study with retrospective data collection and propensity-matched analysis of patients undergoing placement of dehydrated human amnion/chorion membrane (dHACM) around the neurovascular bundle (NVB) during nerve-sparing (NS) robot-assisted laparoscopic prostatectomy (RARP). AmnioFix was placed over each neurovascular bundles (NVBs) as a nerve wrap in 58 patients. A similar group of 58 patients was computer-matched with the AmnioFix group. dHACM use did not increase operative time, blood loss, or oncologic outcomes. Minimum 8-week follow-up was conducted for all patients in both groups, with an average follow-up of 4 months. Continence at 8 weeks returned in 81.0% of dHACM patients and 74.1% of control patients (not significant). The mean time to continence was significantly shorter in dHACM patients (1.21 months) than in control patients (1.83 months). Potency at 8 weeks returned in 65.5% of dHACM patients and 51.7% of control patients. The mean time to potency was significantly shorter in dHACM patients (1.34 months) than in control patients (3.39 months). According to the authors, dHACM accelerated the return of continence and potency in patients following NS RARP, with no adverse effects. The authors indicated this study has several limitations; it is an observational study with retrospective data collection and is subject to patient recall bias. An adequately powered, prospective randomized trial and cost-
benefit analysis of dHACM around the prostatic NVB needs to be conducted to further understand the treatment effect of this new approach.

**AmnioGen-A, AmnioGen-C, AmnioGen-45, AmnioGen-200**

AmnioGen A Injectable Liquid Amniotic Tissue Allograft is an ambient temperature, flowable tissue allograft intended to be used as a physical wound covering, a foundation for regeneration, to modulate correct tissue reconstruction, and to regulate inflammation and pain. It is processed from human amniotic and placental tissues.

AmnioGen C Injectable Liquid Amniotic Tissue Allograft is a cryopreserved, flowable tissue allograft intended to be used as a physical wound covering, a foundation for regeneration, to modulate correct tissue reconstruction, and to regulate inflammation and pain. It is derived from human amniotic tissue.

AmnioGen 45 Amniotic Membrane Allograft is a dehydrated biologic allograft used as a physical wound covering, a foundation for regeneration, modulate correct tissue reconstruction, and to regulate inflammation and pain. It is derived from human amniotic tissue.

AmnioGen 200 Amniotic Membrane Allograft is a thicker dehydrated allograft used as a physical wound covering, a foundation for regeneration, modulate correct tissue reconstruction, and to regulate inflammation and pain. It is derived from human amniotic tissue.

There are few published studies addressing the use of AmnioGen A, AmnioGen C, AmnioGen 45 or AmnioGen 200 for wound treatment. Therefore, it is not possible to conclude whether AmnioGen A, AmnioGen C, AmnioGen 45 or AmnioGen 200 have a beneficial effect on health outcomes.

**Amniomatrix or Biodmatrix**

AmnioMatrix (also marketed under the trade name BioDMatrix) is a viable human placental allograft composed of morselized amniotic membrane and amniotic fluid components recovered from the same human donor. AmnioMatrix may be mixed with normal saline for application to surgical sites and open, complex or chronic wounds or mixed with the recipient’s blood to fill soft tissue defects.

There are few published studies addressing the use of Amniomatrix or Biodmatrix for wound treatment. Therefore, it is not possible to conclude whether Amniomatrix or Biodmatrix has a beneficial effect on health outcomes.

**Architect Extracellular Matrix**

The Harbor MedTech BriDGE Extracellular Collagen Matrix Wound Dressing is a sterile, extracellular collagen matrix (ECM) that is intended to treat partial or full thickness skin wounds.

There are few published studies addressing the use of extracellular matrix for wound treatment. Therefore, it is not possible to conclude whether extracellular matrix has a beneficial effect on health outcomes.

**Artacent**

Artacent (Tides Medical) is a dual-layer human amniotic membrane graft used for acute and chronic wound applications. It is derived from the submucosa of donated human placenta and it consists of collagen layers, including basement membrane and stromal matrix.

There are few published studies addressing the use of Artacent for wound treatment. Therefore, it is not possible to conclude whether Artacent has a beneficial effect on health outcomes.

**Bio-ConneKt**

The bio-ConneKt Wound Matrix is a wound dressing used for moderately to heavily exuding wounds and ulcers. It is made of reconstituted collagen derived from equine tendon.

There are few published studies addressing the use of bio-ConneKt for wound treatment. Therefore, it is not possible to conclude whether bio-ConneKt has a beneficial effect on health outcomes.

**Biodfence or Biodfence Dryflex**

BioDfence and BioDfence DryFlex are human placental-derived amniotic tissue based allografts composed of an epithelial layer and a stromal layer specifically processed for the repair and replacement of lost or damaged dermal tissue or the prohibition of adhesion formation.

There are few published studies addressing the use of BioDfence or BioDfence DryFlex for wound treatment. Therefore, it is not possible to conclude whether BioDfence or BioDfence DryFlex has a beneficial effect on health outcomes.
BioSkin
BioSkin (Human Regenerative Technologies LLC) is a biological tissue graft.

There are few published studies addressing the use of BioSkin for wound treatment. Therefore, it is not possible to conclude whether BioSkin has a beneficial effect on health outcomes.

BioSkin Flow
There are few published studies addressing the use of BioSkin Flow for wound treatment. Therefore, it is not possible to conclude whether BioSkinFlow has a beneficial effect on health outcomes.

Biovance
Biovance is a dehydrated amniotic membrane allograft intended for the treatment of acute and chronic wounds including burns, diabetic ulcer, pressure ulcers and surgical wounds.

There are few published studies addressing the use of Biovance for wound treatment. Therefore, it is not possible to conclude whether Biovance has a beneficial effect on health outcomes.

Clarix
Clarix (Amniox Medical, Inc.) is comprised of cryopreserved human amniotic membrane. It is intended for wound healing and surgical coverings.

There are few published studies addressing the use of Clarix for wound treatment. Therefore, it is not possible to conclude whether Clarix has a beneficial effect on health outcomes.

Clarix Flo
Clarix Flo (Amniox Medical, Inc.) is a biological particulate amniotic membrane and umbilical cord product derived from human placental tissue. It is intended to facilitate replacement or supplement damaged or inadequate integumental tissue.

There are few published studies addressing the use of Clarix Flo for wound treatment. Therefore, it is not possible to conclude whether Clarix Flo has a beneficial effect on health outcomes.

Conexa Reconstructive Matrix
Conexa Reconstructive Matrix (Tornier, Inc.) is a porcine dermis tissue substitute that is intended for the reinforcement of soft tissue repaired by sutures or suture anchors during tendon repair surgery and reinforcement for rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Other indications include the repair of body wall defects which require the use of reinforcing or bridging material to obtain the desired surgical outcome.

There are few published studies addressing the use of Conexa. Therefore, it is not possible to conclude whether Conexa has a beneficial effect on health outcomes.

CorMatrix
CorMatrix porcine SIS-ECM (CorMatrix Cardiovascular, Inc.) is a non-cross-linked extracellular matrix made from porcine small intestinal submucosa (SIS), which supposedly contains structural proteins (such as collagens) and adhesion molecules to promote tissue ingrowth and regeneration. CorMatrix is also available in envelope form (CorMatrix Kangaroo®) to hold and restrict migration of implantable electronic devices and impede infection. CorMatrix has been used in a wide variety of cardiac applications including congenital cardiac and vascular surgery, pericardial reconstruction, valve reconstruction, and acquired vascular defects at different sites.

The published studies addressing the use of CorMatrix do not confirm that CorMatrix promotes growth of native tissue in the adult or pediatric population. Therefore, it is not possible to conclude whether CorMatrix has a beneficial effect on health outcomes.

Mosala Nezhad et al. (2016) attempted to systematically review the preclinical and clinical literature on the use of CorMatrix in cardiovascular surgery. The authors found that the published clinical and preclinical studies lacked systematic reporting of functional and pathological findings in sufficient numbers of subjects. The authors identified only one level II study and only four studies that could reasonably be classified as level III studies, the remainder representing level IV studies that were case reports or small case series. The majority of published studies only reported immediate or very early postoperative findings although a handful of case reports examined outcomes past a year or more. According to the authors, there are emerging reports to suggest that, contrary to expectations, an undesirable inflammatory response may occur in CorMatrix® implants in humans and longer-term outcomes at particular sites, such as the heart valves, may be suboptimal. According to the authors, large-scale clinical studies are needed driven by robust protocols that aim to quantify the pathological process of tissue repair.
Kelley et al. (2017) reported on the treatment of Carpentier type IIIa and type IIIb mitral regurgitation (MR) with a large patch anterior mitral valve leaflet augmentation technique using CorMatrix extracellular matrix (ECM). A single-site chart review was conducted on patients who underwent anterior leaflet augmentation performed with the Da Vinci surgical robot or through a median sternotomy. Only patients who had anterior leaflet augmentation with porcine intestine ECM or autologous pericardium were included. Follow-up echocardiography was performed on all patients. Histologic specimens were available on ECM patches from a subset of patients who required reoperation. At total of 44 patients (mean age, 62.6 ± 12.2 years) underwent anterior leaflet augmentation with either porcine intestinal ECM or autologous pericardium. Eight (32%) of the patients with ECM had recurrence of severe mitral regurgitation (MR) on echocardiography at an average time of 201 ± 98 days. Seven (28%) patients required reoperation because of failure of the ECM patch including perforation (4%), excessive patch dilation (20%), and suture line dehiscence (4%). In contrast, none of the patients with pericardial augmentation developed severe MR or required operation. The authors concluded that for type III MR, a large anterior leaflet patch technique with porcine ECM was associated with a 32% recurrence rate of severe MR related directly to patch failure. According to the authors, further research and development should be performed on the use of ECM materials with a goal to decrease the failure rate experienced in this study.

Rosario-Quinones et al. (2015) reviewed a series of congenital cardiac patients who had a reoperation after the implantation of CorMatrix patches. Of 25 patients who had received CorMatrix patches during cardiac operations, 6 patients had undergone reoperations. All patients had hemodynamically significant lesions at the site of the CorMatrix implantation. Explanted specimens were associated with an intense inflammatory reaction consisting of numerous eosinophils, histiocytes, and plasma cells, with accompanying granulation tissue and fibrosis. The authors concluded that reaction to implanted CorMatrix patches may cause hemodynamic dysfunction and produce an intense, predominantly eosinophilic inflammatory response with developing fibrosis. The authors indicated that although this study is limited to a small sample of congenital cardiac patients, precautions should be taken in its use in pediatric cardiac patients, and long-term follow-up is warranted.

Padalino et al. (2015) conducted a multicentric study to outline surgical indications and evaluate mid-term outcomes of porcine extracellular matrix (ECM) in surgery for congenital heart disease (CHD). The use of ECM was categorized into four major groups: A, valve repair; B, septal reconstruction; C, arterial plasty; D, other use. Primary endpoints of analysis were reintervention (either surgical or interventional) when related to ECM, and functional ECM failure. Secondary endpoints were evidence of calcification and of persistent inflammation at follow-up. One hundred and three patients (M/F = 61/42, median age 19.7 months, 1 day-62 years) underwent surgical repair for CHD. Among ECM use categories, 38 patients were in Group A, 16 in Group B, 71 in Group C and 7 in Group D. There were neither complications nor deaths related to ECM. At a median follow-up of 23.3 months, 19 patients underwent reoperation (ECM-related in 6); 11 patients underwent interventional cardiology procedures (ECM-related in 8). Re-interventions were significantly more frequent on the aortic valve and pulmonary arteries. In addition, interventional procedures on pulmonary arteries were significantly more frequent in infants <12 months. The authors concluded that surgical use of ECM in CHD repair is characterized by a suboptimal functional late performance on reconstruction of valve leaflet or pulmonary artery wall. According to the authors, longer follow-up and larger clinical experience may support these preliminary results on mid-term outcomes, so as to assess the optimal indication for an ECM graft.

Cygnus
Cygnus (Vivex Biomedical, Inc.) is a dried human amnion membrane allograft composed of a single layer of epithelial cells, a basement membrane, and an avascular connective tissue matrix. It is intended to treat acute wounds, chronic wounds, and burns.

There are few published studies addressing the use of Cygnus for wound treatment. Therefore, it is not possible to conclude whether Cygnus has a beneficial effect on health outcomes.

Cytal
Cytal (ACell, Inc.) is composed of a porcine-derived extracellular matrix, also known as urinary bladder matrix. Cytal is intended for the management of wounds and second-degree burns and injuries.

There are few published studies addressing the use of Cytal for wound treatment. Therefore, it is not possible to conclude whether Cytal has a beneficial effect on health outcomes.

Dermapure
Dermapure is a decellularized human dermis product.

There are few published studies addressing the use of Dermapure for wound treatment. Therefore, it is not possible to conclude whether Dermapure has a beneficial effect on health outcomes.
**Dermavest and Plurivest**

Dermavest and Plurivest are human placental connective tissue matrixes intended to replace or supplement damaged or inadequate integumental tissue and re-stabilize a debrided wound.

There are few published studies addressing the use of Dermavest or Plurivest for wound treatment. Therefore, it is not possible to conclude whether Dermavest or Plurivest has a beneficial effect on health outcomes.

**Epicord**

EpiCord (MiMedx Group, Inc.) is a minimally manipulated, dehydrated, non-viable cellular umbilical cord allograft. Epicord is intended to be used in the treatment and management of chronic and acute wounds and burns.

There are few published studies addressing the use of Epicord for wound treatment. Therefore, it is not possible to conclude whether Epicord has a beneficial effect on health outcomes.

**EpiFix**

EpiFix is a dehydrated amniotic membrane extracellular collagen allograft comprised of an epithelial layer and two fibrous connective tissue layers.

Zelen et al. (2015) conducted a prospective, randomized, controlled, parallel group, multi-center clinical trial at three sites to compare the healing effectiveness of treatment of chronic lower extremity diabetic ulcers with either weekly applications of Apligraf (Organogenesis, Inc.), EpiFix (MiMedx Group, Inc.), or standard wound care with collagen-alginate dressing. The primary study outcome was the percent change in complete wound healing after 4 and 6 weeks of treatment. Secondary outcomes included percent change in wound area per week, velocity of wound closure and a calculation of the amount and cost of Apligraf or EpiFix used. A total of 65 subjects entered the 2-week run-in period and 60 were randomized (20 per group). The proportion of patients in the EpiFix group achieving complete wound closure within 4 and 6 weeks was 85% and 95%, significantly higher than for patients receiving Apligraf (35% and 45%), or standard care (30% and 35%). After 1 week, wounds treated with EpiFix had reduced in area by 83-5% compared with 53-1% for wounds treated with Apligraf. Median time to healing was significantly faster with EpiFix (13 days) compared to Apligraf (49 days) or standard care (49 days). The mean number of grafts used and the graft cost per patient were lower in the EpiFix group compared to the Apligraf group. According to the authors, the results of this study demonstrate the clinical and resource utilization superiority of EpiFix compared to Apligraf or standard of care, for the treatment of diabetic ulcers of the lower extremities. The authors indicated patients were followed for only 1 week after healing, and they were allowed to withdraw from the study after 6 weeks if their wound had not reduced in size by at least 50%. Therefore, the authors were unable to compare the rates of healing at 12 weeks, or the rates of wound recidivism in this study. In addition, this study includes a variety of lower extremity diabetic ulcers, both plantar and dorsal. The sample size was not sufficient to stratify by location, nor was it possible to perform any meaningful sub-group analysis to determine factors influencing outcomes or speed of healing. This study was funded by the manufacturer, MiMedx Group, Inc, which has the potential for financial affiliations with MiMedx.

Zelen et al. (2016) continued the above study (Zelen et al. 2015) in order to achieve at least 100 patients and to assess rates and time to closure. With the larger cohort, clinical outcomes were compared at 12 weeks in 100 patients with chronic lower extremity diabetic ulcers treated with weekly applications of Apligraf (n = 33), EpiFix (n = 32) or SWC (n = 35) with collagen-alginate dressing as controls. A Cox regression was performed to analyze the time to heal within 12 weeks, adjusting for all significant covariates. A Kaplan-Meier analysis was conducted to compare time-to-heal within 12 weeks for the three treatment groups. Clinical characteristics were well matched across study groups. The proportion of wounds achieving complete closure within the 12-week study period were 73% (24/33), 97% (31/32), and 51% (18/35) for Apligraf, EpiFix and SWC, respectively. Subjects treated with EpiFix had a very significant higher probability of their wounds healing compared to SWC alone. No difference in probability of healing was observed for the Apligraf and SWC groups. Patients treated with Apligraf were less likely to heal than those treated with EpiFix. Increased wound size and presence of hypertension were significant factors that influenced healing. Mean time-to-heal within 12 weeks was 47-9 days with Apligraf, 23-6 days with EpiFix group and 57-4 days with the SWC alone group. Median number of grafts used per healed wound were six (range 1-13) and 2-5 (range 1-12) for the Apligraf and EpiFix groups, respectively. The investigators concluded that these results provide further evidence of the clinical and resource utilization superiority of EpiFix compared to Apligraf for the treatment of lower extremity diabetic wounds. The authors indicated that the following limitation for this study: patients were followed for only 1 week after complete healing, and wound recidivism was not recorded. According to the authors, additional studies will evaluate the recurrence rate over time. This study did not report a funding source.

In a Cochrane database systematic review, Santema et al. (2016) evaluated the benefits and harms of skin grafting and tissue replacement for treating foot ulcers in people with diabetes. The review included seventeen randomized clinical trials (RCTs) studies with a total of 1655 participants. Risk of bias was variable among studies. Blinding of participants, personnel and outcome assessment was not possible in most trials because of obvious differences.
between the treatments. The lack of a blinded outcome assessor may have caused detection bias when ulcer healing was assessed. However, possible detection bias is hard to prevent due to the nature of the skin replacement products that were assessed, and the fact that they are easily recognizable. Strikingly, nearly all studies (15/17) reported industry involvement; at least one of the authors was connected to a commercial organization or the study was funded by a commercial organization. In addition, the funnel plot for assessing risk of bias appeared to be asymmetrical; suggesting that small studies with ‘negative’ results are less likely to be published. Thirteen of the studies included in this review compared a skin graft or tissue replacement with standard care. Four studies compared two grafts or tissue replacements with each other. When the results were pooled for the individual studies, the skin grafts and tissue replacement products that were used in the trials increased the healing rate of foot ulcers in patients with diabetes compared to standard care (risk ratio (RR) 1.55, 95% confidence interval (CI) 1.30 to 1.85, low quality of evidence). However, the strength of effect was variable depending on the specific product that was used (e.g., EpiFix® RR 11.08, 95% CI 1.69 to 72.82 and OrCel® RR 1.75, 95% CI 0.61 to 5.05). Based on the four included studies that directly compared two products, no specific type of skin graft or tissue replacement showed a superior effect on ulcer healing over another type of skin graft or tissue replacement. Sixteen of the included studies reported on adverse events in various ways. No study reported a statistically significant difference in the occurrence of adverse events between the intervention and the control group. Only two of the included studies reported on total incidence of lower limb amputations. The authors found fewer amputations in the experimental group compared with the standard care group when we pooled the results of these two studies, although the absolute risk reduction for amputation was small (RR 0.43, 95% CI 0.23 to 0.81; risk difference (RD) -0.06, 95% CI -0.10 to -0.01, very low quality of evidence). The authors concluded that based on the studies included in this review, the overall therapeutic effect of skin grafts and tissue replacements used in conjunction with standard care shows an increase in the healing rate of foot ulcers and slightly fewer amputations in people with diabetes compared with standard care alone. However, the data available was insufficient to draw conclusions on the effectiveness of different types of skin grafts or tissue replacement therapies. In addition, evidence of long term effectiveness is lacking and cost-effectiveness is uncertain.

Serena et al. (2014) conducted a multicenter, randomized, controlled study to evaluate the safety and efficacy of one or two applications of dehydrated human amnion/chorion membrane allograft and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers (VLU). Patient inclusion criteria included presence of a VLU extending through the full thickness of the skin but not down to muscle, tendon, or bone, VLU present for at least 1 month, and VLU has been treated with compression therapy for at least 14 days. The primary study outcome was the proportion of patients achieving 40% wound closure at 4 weeks. Of the 84 participants enrolled, 53 were randomized to receive allograft and 31 were randomized to the control group of multilayer compression therapy alone. At 4 weeks, 62% in the allograft group and 32% in the control group showed a greater than 40% wound closure, thus showing a significant difference between the allograft-treated groups and the multilayer compression therapy alone group at the 4-week surrogate endpoint. After 4 weeks, wounds treated with allograft had reduced in size a mean of 48.1% compared with 19.0% for controls. The authors concluded that venous leg ulcers treated with allograft had a significant improvement in healing at 4 weeks compared with multilayer compression therapy alone. According to the authors, lack of long-term follow-up data did not allow for the validation of duration of healed wounds.

Serena et al. (2015) evaluated correct correlation between an intermediate rate of wound reduction (40% wound area reduction after 4-weeks treatment) and complete healing at 24 weeks in patients with a venous leg ulcer (VLU) in a retrospective follow-up of the study by Serena et al. (2014) described above. Outcomes assessed were rates of complete healing within 24 weeks of enrolment and days to healing. Data were divided into two groups based on status at RCT completion (healed at least 40% yes or no). Correct correlation with status at 4 weeks and complete healing within 24 weeks was determined. Clinical characteristics were also compared for patients with and without correct correlation between 4-week and 24-week status. Fifty-five patients at 5 study sites were included. Some 47 without complete healing during the initial study were eligible. As three patients were lost to follow-up, a total of 44 records were evaluated. Of these, 20 (45.4%) had reduced wound size of ≥40% and 24 (55%) had <40% reduction during the initial study. Complete healing occurred in 16/20 (80%) of the ≥40% group at a mean of 46 days and 8/24 (33.3%) of the <40% group at a mean of 103.6 days. Overall, correct correlation of status at 4 weeks and ultimate healing status of VLU occurred in 32/44 patients (73%). The authors indicated that these results confirm that the intermediate outcome used in our initial study is a viable predictor of ultimate VLU healing. According to the authors there are limitations of the present study. During the follow-up period after completion of the initial 4-week RCT, patients received various treatments that may or may not have included initiation of, or additional application of dHACM, or other advanced treatments. Also, in the initial RCT, dHACM was only applied once or twice during the study period, which may not be reflective of how the treatment is used in a real world setting.

In a prospective, randomized, single-center clinical trial, Zelen et al. (2013b) compared healing characteristics of diabetic foot ulcers treated with dehydrated human amniotic membrane allografts (EpiFix®, MiMedx) versus standard of care. The study included patients with a diabetic foot ulcer of at least 4-week duration without infection having adequate arterial perfusion. Patients were randomized to receive standard care alone or standard care with the addition of EpiFix. Wound size reduction and rates of complete healing after 4 and 6 weeks were evaluated. In the
standard care group (n = 12) and the Epifix group (n = 13) wounds reduced in size by a mean of 32.0% ± 47.3% versus 97.1% ± 7.0% after 4 weeks, whereas at 6 weeks wounds were reduced by -1.8% ± 70.3% versus 98.4% ± 5.8%, standard care versus Epifix, respectively. After 4 and 6 weeks of treatment the overall healing rate with application of Epifix was shown to be 77% and 92%, respectively, whereas standard care healed 0% and 8% of the wounds, respectively. The authors concluded that patients treated with Epifix achieved superior healing rates over standard treatment alone and that these results show that using Epifix in addition to standard care is efficacious for wound healing. Limitations of this study include a small sample size. An additional limitation is that the comparative group in the study did not receive other advanced therapies to assess if the Epifix allograft is as good as, or better, than other available advanced wound care products. According to the authors, additional comparative effectiveness studies are required to address this issue. It is also unknown how the Epifix product performs in other patient populations and for other medical or surgical indications since the study was limited to patients with chronic diabetic foot ulcers.

In 2014, Zelen (2014a) published follow-up data from the Zelen et al., 2013 trial described above. Eighteen of 22 eligible patients returned for follow-up examination. At the 9–12 month follow-up visit, 17 of 18 (94.4%) wounds treated with dehydrated human amnion/chorion membrane (dHACM) remained fully healed. According to the authors, the limitations of this study include the retrospective study design and small sample size. The authors stated that larger studies are needed to confirm their findings.

Zelen et al. (2014b) assessed if weekly application of dehydrated human amnion/chorion membrane allograft reduces time to heal more effectively than biweekly application for treatment of diabetic foot ulcers. The study was an institutional review board-approved, registered, prospective, randomized, comparative, non-blinded, single-center clinical trial. Patients with non-infected ulcers of ≥ 4 weeks duration were included and randomized to receive weekly or biweekly application of allograft in addition to a non-adherent, moist dressing with compressive wrapping. The primary study outcome was mean time to healing. Overall, during the 12-week study period, 92-5% (37/40) ulcers completely healed. Mean time to complete healing was 4·1 ± 2·9 versus 2·4 ± 1·8 weeks in the biweekly versus weekly groups, respectively. According to the authors, these results validate previous studies showing that the allograft is an effective treatment for diabetic ulcers and show that wounds treated with weekly application heal more rapidly than with biweekly application. Limitations of this study include a small sample size. The lack of a standard care group not receiving dehydrated human amnion/chorion membrane (dHACM) can be perceived as a study weakness, although according to the authors the intent of the study was solely to examine rates of healing according to frequency of application and not compare with other treatment modalities. The authors state that their findings should be confirmed and expanded with subsequent multicentre clinical trials and long-term follow-up data to validate the durability of healed wounds.

Kirsner et al. (2015) evaluated the comparative effectiveness of a bioengineered living cellular construct (BLCC) (Apligraf) and a dehydrated human amnion/chorion membrane allograft (dHACM) (Epifix) for the treatment of diabetic foot ulcers (DFUs). Using a wound care-specific electronic medical record database, the authors assessed real-world outcomes in 218 patients with 226 DFUs receiving treatment in 2014 at 99 wound care centers. The analysis included DFUs ≥1 and <25 cm² with duration <=1 year and area reduction ≤20% in 14 days prior to treatment (N=163, BLCC; N=63, dHACM). The average baseline areas and durations were 6.0 cm² and 4.4 months for BLCC and 5.2 cm² and 4.6 months for dHACM, respectively. Patients treated with dHACM had more applications compared to those treated with BLCC (median 3.0 vs. 2.0). A Cox model adjusted for key covariates including area and duration found the median time to closure for BLCC was 13.3 weeks compared to 26 weeks for dHACM, and the proportion of wounds healed were significantly higher for BLCC by 12 weeks (48% vs. 28%) and 24 weeks (72% vs. 47%). Treatment with a bioengineered living cellular construct increased the probability of healing by 97% compared with a dehydrated amniotic membrane. This study is limited by its retrospective design and according to the authors, the database used for the study was not designed specifically for research purposes, and as such, there may be missing data or data entry errors.

Miranda et al. (2016) conducted a retrospective analysis of prospectively acquired data for 8 lower extremity free flaps with ulcerations in the context of venous insufficiency and/or lymphedema. The first 4 were flaps that had been treated with conservative wound care to healing. The second group was treated conservatively initially but then converted to treatment with dehydrated human amnion/chorion membrane (Epifix) grafts. The primary endpoint was time to healing. Comparison of Kaplan-Meier survival curves revealed a significant difference between the conservatively and dehydrated human amnion/chorion membrane-treated flap ulcers, favoring graft treatment. In those ulcers that healed, the average time to healing was 87 days for the conservative treatment group and 33 days for the dehydrated human amnion/chorion membrane treatment group (with an average of 1.7 grafts per ulcer). The authors concluded that dehydrated human amnion/chorion membrane may accelerate healing of ulcers on lower extremity free flaps in patient with lymphedema and/or venous disease in the treated leg. The authors stated that the study was limited by a small sample size which limits sweeping conclusions. There is also no true randomized control or comparison group available, so it cannot be firmly concluded that dHACM accelerates healing of ulcers on free flaps with lymphedematous or venous-insufficient limbs.
Several of the studies evaluating EpiFix were sponsored by the manufacturer and had the same primary author. Future studies are needed to determine whether these results could be duplicated at other institutions and with less experienced clinicians. Based on the paucity of studies, the effect of EpiFix on venous leg ulcers cannot be determined. (Hayes, EpiFix for Treatment of Nonhealing Wounds, August 2015, updated June 2016)

**Excellagen**
Excellagen is a pharmaceutically formulated fibrillar Type I bovine collagen gel for wound care management.

There are few published studies addressing the use of Excellagen for wound treatment. Therefore, it is not possible to conclude whether Excellagen has a beneficial effect on health outcomes.

**Ez-Derm**
Ez-Derm is a porcine-derived, biosynthetic xenograft.

Burkey et al. (2016) retrospectively reviewed the medical records of patients with superficial partial-thickness burns treated with Porcine xenograft (PX) (Ex Derm) admitted to a pediatric burn center. A total of 164 patients met the inclusion criteria. Burn total body surface area (TBSA) ranged from 0.5% to 28%. After the placement of PX, significant decreases were seen in the need for narcotic analgesics and burn dressing changes. Only four of 164 patients (2.4%) developed infections, although only one of these infections was at the site of the xenograft. The authors concluded that PX appears to reduce pain and eliminate the need for procedural intravenous sedation in many patients. According to the authors, this can make burn wound care more child-friendly and shorten hospital length of stay. This study is an uncontrolled retrospective review.

In a retrospective review of medical records, Troy et al. (2013) evaluated the use of EZ Derm on partial-thickness burns in 157 patients. The average length of follow-up was 94.2 days. A total of 15.3% of patients (24/157) were lost to follow up. Eighteen complications were reported from 16 patients. Complications were attributed to positioning, infection, incomplete epithelialization at time of separation, need for additional excision and grafting, hypertrophic scarring, and cryptogenic. Clinically significant infections were seen in 22% (4/18) of complications and 3% of patients overall. The authors concluded that EZ Derm has proven to be a robust wound dressing that provides consistent durable wound coverage with minimal complications that resolve without long-term adverse sequelae. This study is limited by the retrospective nature of the data collection.

**Floweramnioflo**
Floweramnioflo, also known as FlowerFlo (Flower Orthopedics Corporation) is a 100% acellular liquid amniotic fluid allograft that is injected on or in the wound site. It is intended for the treatment of non-healing wounds and burn injuries. According to the manufacturer, Floweramnioflo delivers cytokines, proteins and growth factors to help generate soft tissue.

There are few published studies addressing the use of Floweramnioflo for wound treatment. Therefore, it is not possible to conclude whether Floweramnioflo has a beneficial effect on health outcomes.

**Floweramniopatch**
Floweramniopatch, also known as FlowerPatch (Flower Orthopedics Corporation) is a dehydrated (human) amniotic membrane allograft used for the treatment of non-healing wounds and burn injuries. According to the manufacturer, Floweramniopatch delivers cytokines, proteins and growth factors to help generate soft tissue.

There are few published studies addressing the use of Floweramniopatch for wound treatment. Therefore, it is not possible to conclude whether Floweramniopatch has a beneficial effect on health outcomes.

**FlowerDerm**
FlowerDerm (Flower Orthopedics Corporation) hydrated acellular (human) dermal allograft matrix used for the treatment of non-healing wounds and burn injuries. According to the manufacturer, FlowerDerm contains extracellular matrix (ECM) that provides a scaffold for cellular ingrowth vascularization, tissue regeneration and formation of granulation tissue.

There are few published studies addressing the use of FlowerDerm for wound treatment. Therefore, it is not possible to conclude whether FlowerDerm has a beneficial effect on health outcomes.

**Grafix**
Grafix (Osiris Therapeutics, Inc.) is a cryopreserved placental membrane comprised of an extracellular matrix (ECM) containing collagen, growth factors, fibroblasts, mesenchymal stem cells (MSCs), and epithelial cells native to the tissue.
There are few published studies addressing the use of Grafix for wound treatment. Therefore, it is not possible to conclude whether Grafix has a beneficial effect on health outcomes.

In a randomized, controlled study, Lavery et al. (2014) compared the efficacy of Grafix, a human viable wound matrix (hVWM) (N = 50), to standard wound care (n = 47) to heal diabetic foot ulcers (DFUs). The primary endpoint was the proportion of patients with complete wound closure by 12 weeks. Secondary endpoints included the time to wound closure, adverse events and wound closure in the crossover phase. The proportion of patients who achieved complete wound closure was significantly higher in patients who received Grafix (62%) compared with controls (21%). The median time to healing was 42 days in Grafix patients compared with 69.5 days in controls. There were fewer Grafix patients with adverse events (44% versus 66%) and fewer Grafix patients with wound-related infections (18% versus 36%). Among the study subjects that healed, ulcers remained closed in 82% of patients (23 of 28 patients) in the Grafix group versus 70% (7 of 10 patients) in the control group. The authors concluded that treatment with Grafix significantly improved DFU healing compared with standard wound therapy. According to the authors, the results of this well-controlled study showed that Grafix is a safe and more effective therapy for treating DFUs than standard wound therapy. These findings require confirmation in a larger study.

Frykberg et al. (2016) reported the results of a prospective, multicentre, open-label, single-arm clinical trial to establish clinical outcomes when viable cryopreserved human placental membrane (Grafix) is applied weekly to complex diabetic foot ulcers (DFUs) with exposed deep structures. Patients with type 1 or type 2 diabetes and a complex DFU extending through the dermis with evidence of exposed muscle, tendon, fascia, bone and/or joint capsule were eligible for inclusion. Of the 31 patients enrolled, 27 completed the study. The mean wound area was 14.6 cm², and mean duration was 7.5 months. For patients completing the protocol, the primary endpoint, 100% wound granulation by week 16, was met by 96.3% of patients in a mean of 6.8 weeks. Complete wound closure occurred in 59.3% (mean 9.1 weeks). The 4-week percent area reduction was 54.3%. There were no product-related adverse events. Four patients (13%) withdrew, two (6.5%) for non-compliance and two (6.5%) for surgical intervention. This study was limited by a small sample size and lack of a control group.

Johnson et al. (2017) reported on the clinical outcomes in two nonrandomized, however statistically equal and homogenous patient cohorts receiving either a viable intact cryopreserved human placental membrane (vCPM) or a dehydrated human amnion/chorion membrane (dHACM), for the management of wounds at a single center. A total of 79 patients with 101 wounds were analyzed: 40 patients with 46 wounds received vCPM (Grafix) and 39 patients with 55 wounds received dHACM (Epifix). The proportion of wounds achieving complete wound closure was 63.0% (29/46) for vCPM and 18.2% (10/55) for dHACM for all treated wounds combined. According to the authors, the retrospective and nonrandomized nature of this single-center study present significant limitations.

GrafixPL
GrafixPL (Osiris Therapeutics, Inc.) is a cryopreserved placental membrane comprised of an extracellular matrix (ECM) containing collagen, growth factors, fibroblasts, mesenchymal stem cells (MSCs), and epithelial cells native to the tissue. GrafixPL is intended to repair acute and chronic wounds.

There are few published studies addressing the use of GrafixPL for wound treatment. Therefore, it is not possible to conclude whether GrafixPL has a beneficial effect on health outcomes.

Helicoll
Helicoll is a semi occlusive, self-adhering collagen sheet used for wound treatments, second degree burns, and chronic ulcers. This biodegradable skin substitute is made from animal tissues.

There are few published studies addressing the use of Helicoll for wound treatment. Therefore, it is not possible to conclude whether Helicoll has a beneficial effect on health outcomes.

Dhanraj (2015) conducted a prospective randomized controlled study to compare Helicoll, a type I pure collagen dressing, to OpSite dressing and to Scarlet Red dressing in the treatment of standardized split-thickness skin grafts (STSG) donor sites. Thirty patients, over a 3-month period, underwent various reconstructive procedures, necessitating the use of STSGs. Following a simple randomized clinical protocol, the analysis of data included donor site pain, healing time of the donor site, initial absorption of the applied dressing and rate of infection with the three different dressings. Patients in the Helicoll group reported significantly less pain, less infection rate and required no dressing change when compared with the OpSite or the Scarlet Red groups. Healing time of the donor site in the Helicoll group was shorter than that in the Scarlet Red group; however, it was comparable to the OpSite group. The authors concluded that Helicoll, as a donor site dressing, is successful in providing pain-free mobility with a measurable healing rate. Study limitations include a small study population and only one wound type (STSG donor site) was evaluated.

Hmatrix
Hmatrix Acellular Dermis is an allograft derived from donated human skin.
There are few published studies addressing the use of Hmatrix for wound treatment. Therefore, it is not possible to conclude whether Hmatrix has a beneficial effect on health outcomes.

**Interfyl**

Interfyl (Alliqua Biomedical, Inc.) is a decellularized and dehydrated placental disc (chorionic plate) derived extracellular matrix. Interfyl is intended for treating deep dermal wounds, irregularly-shaped and tunneling wounds, augmentation of deficient/inadequate soft tissue, and the repair of small surgical defects.

There are few published studies addressing the use of Interfyl for wound treatment. Therefore, it is not possible to conclude whether Interfyl has a beneficial effect on health outcomes.

**Keramatrix**

Keramatrix is an open-cell wound dressing used for chronic wounds and ulcers. It is comprised of freeze dried acellular, animal-derived keratin protein.

There are few published studies addressing the use of Keramatrix for wound treatment. Therefore, it is not possible to conclude whether Keramatrix has a beneficial effect on health outcomes.

Loan et al. (2016) conducted a controlled study that included 40 patients with superficial or partial thickness burn injuries treated with Keramatrix, compared to 40 historical controls who received standard of care treatment. The results indicated a significantly faster mean healing time in the Keramatrix group than in the control group (8.7 days vs. 14.4 days). This is a small, nonrandomized trial.

Davidson et al. (2013) conducted a randomized controlled trial using a standard care alginate (Algisite) dressing side by side with an experimental dressing (Keramatrix) on 26 patients with partial-thickness donor site wounds. The proximal/distal placement of the control and treatment was randomized. Percentage epithelialization after approximately 7 days was estimated from which time to fully epithelialize can be inferred. Patients were grouped into "young" (<50 y/o) and "old" (>50 y/o). For the "old" patients (n=15), the median epithelialization percentage at 7 days is 5% and was significantly greater for the experimental dressing. For the "young" patients (n=11), the median epithelialization percentage at 7 days was 80% and there is no significant difference between the experimental and Standard Care control dressings. The authors concluded that Keramatrix dressing significantly increases the rate of epithelialization of acute, traumatic partial-thickness wounds in older patients. This study was limited by a small sample size and short follow-up time.

**Kerecis or Marigen**

Kerecis (Kerecis Inc.) formally known as Marigen is an extracellular matrix (ECM) xenograft made from fish (piscine) dermis designed for transplant into damaged tissue such as chronic wounds.

There are few published studies addressing the use of Kerecis or Marigen for wound treatment. Therefore, it is not possible to conclude whether Kerecis or Marigen has a beneficial effect on health outcomes.

Yang et al. (2016) evaluated the use of piscine acellular fish-skin graft product (Kerecis) to treat hard-to-heal ulcers. The primary objective was to assess the percentage of wound closure area from baseline after 5 weekly fish-skin graft applications in 18 patients with at least 1 "hard-to-heal" criteria. Patients underwent application of the fish skin for 5 sequential weeks, followed by 3 weeks of standard care. Wound area, skin assessments, and pain were assessed weekly. A 40% decrease in wound surface area and a 48% decrease in wound depth was seen with 5 weekly applications of the fish-skin graft and secondary dressing. Complete closure was seen in 3 of 18 patients by the end of the study phase. The authors concluded that the fish-skin product appears to provide promise as an effective wound closing adjunctive extracellular matrix (ECM). According to the authors, the limitations of this pilot study include a small sample size and lack of a control arm.

Baldrursson et al. (2015) compared the effect of fish skin acellular dermal matrix (ADM) against porcine small-intestine submucosa extracellular matrix in the healing of 162 full-thickness 4-mm wounds on the forearm of 81 volunteers. The fish skin product was noninferior at the primary end point, healing at 28 days. The wounds treated with fish skin acellular matrix healed significantly faster. These results might give the fish skin ADM an advantage because of its environmental neutrality when compared with livestock-derived products. The study results on these acute full-thickness wounds might apply for diabetic foot ulcers and other chronic full-thickness wounds, and the shorter healing time for the fish skin-treated group could influence treatment decisions. To test the autoimmune reactivity of the fish skin, the participants were tested with the following ELISA (enzyme-linked immunosorbent assay) tests: RF, ANA, ENA, anti-ds-DNA, ANCA, anti-CCP, and anticollagen I and II. These showed no reactivity. The authors concluded that the study results demonstrate the claims of safety and efficacy of fish skin ADM for wound care. Further research with randomized controlled trials is needed to validate these findings.
Mediskin
Mediskin is a porcine-derived decellularized fetal skin product. There are few published studies addressing the use of Mediskin for wound treatment. Therefore, it is not possible to conclude whether Mediskin has a beneficial effect on health outcomes.

In a prospective randomized, 3-arm, clinical study, Karlsson et al. (2014) compared Aquacel, Allevyn, and Mediskin I in the treatment of split-thickness skin graft donor sites in 67 adults. Patients were randomly assigned to treatment with Aquacel, Allevyn, or Mediskin I. The donor site was assessed on postoperative days 3, 14, and 21 for healing, infection, pain, impact on everyday life, ease of use, and cost. The obtained results demonstrate significantly faster re-epithelialization for patients treated with Aquacel or Mediskin I compared with Allevyn. Regarding infections, there were no significant differences between the groups. Patients wearing Aquacel experienced significantly less pain changing the dressing and less impact on everyday life than the patients wearing Allevyn. Aquacel was shown to be significantly easier for the caregiver to use than Allevyn and Mediskin I. The authors stated that their results support the use of Aquacel in the treatment of split-thickness skin graft donor sites.

Miroderm
Miroderm (Miromatrix Medical) is a non-crosslinked acellular wound matrix that is derived from porcine liver and is processed and stored in a phosphate buffered aqueous solution. It is intended for the management of wounds.

There are few published studies addressing the use of Miroderm for wound treatment. Therefore, it is not possible to conclude whether Miroderm has a beneficial effect on health outcomes.

NeoPatch
NeoPatch (CryoLife, Inc.) is a tissue covering derived from sterilized, dehydrated human placental membrane tissue comprised of both amnion and chorion. NeoPatch is intended to be used as a wound covering applied externally to the wound.

There are few published studies addressing the use of NeoPatch for wound treatment. Therefore, it is not possible to conclude whether NeoPatch has a beneficial effect on health outcomes.

Neox
Neox Wound Matrix (Amniox Medical, Inc.) is comprised of cryopreserved human amniotic membrane. It is intended for wound healing and surgical coverings.

There are few published studies addressing the use of Neox for wound treatment. Therefore, it is not possible to conclude whether Neox has a beneficial effect on health outcomes.

Neox Flo
Neox Flo (Amniox Medical, Inc.) is a human amniotic membrane and umbilical cord product in particulate form obtained from donated human placental tissue. It is intended to be used as a wound covering for dermal ulcers and defects such as diabetic ulcers.

There are few published studies addressing the use of Neox Flo for wound treatment. Therefore, it is not possible to conclude whether NeoxFlo has a beneficial effect on health outcomes.

Nushield
Nushield is a protective patch derived from amniotic membrane and is intended for use in spinal surgery and as a protective barrier for tendons and nerves following tendon repair.

There are few published studies addressing the use of Nushield for wound treatment. Therefore, it is not possible to conclude whether Nushield has a beneficial effect on health outcomes.

PalinGen
PalinGen Amniotic Tissue Allografts (Amnio ReGen Solutions LLC) are human allografts comprised of amniotic membrane. They are intended to repair or replace soft tissue defects, soft trauma defects, tendinitis, tendinosis, chronic wound repair and localized inflammation. PalinGen Flow and PalinGen SportFlow (Amnio Technology LLC) are human allografts comprised of amnion and amniotic fluid components, providing a liquid allograft to "aid in the healing" and repair of chronic wounds. These products are marketed for use in the following orthopedic clinical conditions: chronic pain; joint pain; localized inflammation; tendon, fasciae, ligament, and capsule repair; synovial injuries, injured chondral surfaces, chronic tendinopathies, and tendinosis.
There are few published studies addressing the use of PalinGen for treating wounds and other conditions. Therefore, it is not possible to conclude whether PalinGen has a beneficial effect on health outcomes.

Hanselman et al. (2015) compared a novel treatment, cryopreserved human amniotic membrane (c-hAM), to a traditional treatment, corticosteroid. The hypothesis was that c-hAM would be safe and comparable to corticosteroids for plantar fasciitis (PF) in regard to patient outcomes. A randomized, controlled, double-blind, single-center pilot study was conducted. Patients were randomized into one of 2 treatment groups: c-hAM or corticosteroid. Patients received an injection at their initial baseline visit with an option for a second injection at their first 6-week follow-up. Total follow-up was obtained for 12 weeks after the most recent injection. The primary outcome measurement was the Foot Health Status Questionnaire (FHSQ). The secondary outcome measurements were the Visual Analog Scale (VAS) and verbally reported percentage improvement. Data were analyzed between groups for the 2 different cohorts (1 injection versus 2 injections). Twenty-three patients had complete follow-up. Fourteen were randomized to receive corticosteroid and 9 were randomized to receive c-hAM. Three patients in each group received second injections. With the numbers available, the majority of outcome measurements showed no statistical difference between groups. The corticosteroid did, however, have greater FHSQ shoe fit improvement (P = .0244) at 6 weeks, FHSQ general health improvement at 6 weeks, and verbally reported improvement at 12 weeks in the one-injection cohort. Cryopreserved hAM had greater FHSQ foot pain improvement at 18 weeks in the 2-injection cohort. The authors concluded that cryopreserved hAM injection may be safe and comparable to corticosteroid injection for treatment of plantar fasciitis. According to the authors, this is a pilot study and requires further investigation. This study was not sufficiently powered to detect between-group differences; therefore, no definitive conclusions can be made regarding the comparative effectiveness of c-hAM and corticosteroid treatment for patients with chronic PF. Study limitations include small sample size, no comparison of baseline characteristics, limited follow-up, and lack of power analysis.

Zelen et al. (2013) reported the results of a randomized clinical trial examining the efficacy of micronized dehydrated human amniotic/chorionic membrane (mDHACM) injection as a treatment for chronic refractory plantar fasciitis. An institutional review board-approved, prospective, randomized, single-center clinical trial was performed. Forty-five patients were randomized to receive an injection of 2 cc 0.5% Marcaine plain, then either 1.25 cc saline (controls), 0.5 cc mDHACM, or 1.25 cc mDHACM. Follow-up visits occurred over 8 weeks to measure function, pain, and functional health and well-being. Significant improvement in plantar fasciitis symptoms was observed in patients receiving 0.5 cc or 1.25 cc mDHACM versus controls within 1 week of treatment and throughout the study period. At 1 week, American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot scores increased by a mean of 2.2 ± 17.4 points for controls versus 38.7 ± 11.4 points for those receiving 0.5 cc mDHACM and 33.7 ± 14.0 points for those receiving 1.25 cc mDHACM. By week 8 AOFAS Hindfoot scores increased by a mean of 12.9 ± 16.9 points for controls versus 51.6 ± 10.1 and 53.3 ± 9.4 for those receiving 0.5 cc and 1.25 cc mDHACM, respectively. No significant difference in treatment response was observed in patients receiving 0.5 cc versus 1.25 cc mDHACM. The authors concluded that cryopreserved hAM injection may be safe and comparable to corticosteroid injection for treatment of plantar fasciitis. According to the authors, this is a pilot study and requires further investigation. This study was not sufficiently powered to detect between-group differences; therefore, no definitive conclusions can be made regarding the comparative effectiveness of c-hAM and corticosteroid treatment for patients with chronic PF. Study limitations include small sample size, no comparison of baseline characteristics, limited follow-up, and lack of power analysis.

**ProMatrX**

ProMatrX™ (Amnio Technology) is a human allograft comprised of amnion and amniotic fluid that is intended to provide a liquid allograft to aid in the healing and repair of chronic wounds.

There are few published studies addressing the use of ProMatrX for wound treatment. Therefore, it is not possible to conclude whether ProMatrX has a beneficial effect on health outcomes.

**PuraPly or PuraPly Antimicrobial (formerly Called FortaDerm)**

PuraPly (Organogenesis, Inc.) is a dressing made of porcine intestinal collagen matrix that is coated with polyhexamethylene biguanide hydrochloride (PHMB) antimicrobial agent. It is intended for wound care management.

There are few published studies addressing the use of PuraPly or PuraPly Antimicrobial for wound treatment. Therefore, it is not possible to conclude whether PuraPly or PuraPly Antimicrobial has a beneficial effect on health outcomes.

**Repriza**

Repriza is an acellular dermal matrix prepared from human skin allograft. Repriza is intended for implantation for reconstructive surgery wherever an acellular dermal matrix may be used, as for example in breast reconstruction, abdominal wall reconstruction, and augmentation of soft tissue irregularities.

There are few published studies addressing the use of Repriza for wound treatment. Therefore, it is not possible to conclude whether Repriza has a beneficial effect on health outcomes.

**Revita**

Revita (StimLabs, LLC.) is a sterilized, dehydrated human placental allograft. Revita is intended to be used as a wound covering, or barrier membrane, over chronic and acute wounds, including dermal ulcers.
There are few published studies addressing the use of Revita for wound treatment. Therefore, it is not possible to conclude whether Revita has a beneficial effect on health outcomes.

**Revitalon**

Revitalon is comprised of amnion and chorion of placental tissue and is intended to provide wound covering and structural support for native cells.

There are few published studies addressing the use of Revitalon for wound treatment. Therefore, it is not possible to conclude whether Revitalon has a beneficial effect on health outcomes.

**Tensix**

TenSIX Acellular Dermal Matrix (ADM) is an allograft derived from voluntarily donated human tissue.

There are few published studies addressing the use of TenSIX for wound treatment. Therefore, it is not possible to conclude whether TenSIX has a beneficial effect on health outcomes.

**TransCyte**

TransCyte (Organogenesis, Inc.), formally known as Dermagraft TC, is a human fibroblast-derived temporary wound cover consisting of human dermal fibroblasts grown on nylon mesh, combined with a synthetic epidermal layer. As the fibroblasts proliferate within the nylon mesh, they secrete human dermal collagen, matrix proteins and growth factors.


Pham et al. (2007) conducted a systematic review of skin substitutes for the management of burn injuries. A total of 20 randomized controlled trials were included in the review. The evidence suggested that bioengineered skin substitutes, namely TransCyte, Biobrane, Dermagraft, and allogeneic cultured skin, were at least as efficacious as topical agents/wound dressings or allograft. The investigators indicated that there were several methodological limitations across the available studies, which hampered the overall conclusions. According to the investigators, additional well-designed randomized controlled trials with sufficient long-term follow up are necessary to strengthen the overall evidence regarding the efficacy of tissue-engineered skin substitutes.

In a multicenter study, Purdue et al. (1997) compared the use of a biosynthetic human skin substitute [Dermagraft-TC (now known as TransCyte)] with frozen human cadaver allograft for the temporary closure of excised burn wounds. Burn wounds in 66 patients with a mean age of 36 years and a mean burn size of 44% total body surface area (28% total body surface area full-thickness) were surgically excised. Two comparable sites, each approximately 1% total body surface area in size, were randomized to receive either Dermagraft-TC or allograft. Both sites were then treated in the same manner. When clinically indicated (more than 5 days after application) both skin replacements were removed, and the wound beds were evaluated and prepared for grafting. Dermagraft-TC was equivalent or superior to allograft with regard to autograft take at post-autograft day 14. Dermagraft-TC was also easier to remove, had no epidermal slough, and resulted in less bleeding than did allograft while maintaining an adequate wound bed. According to the authors, overall satisfaction was better with Dermagraft-TC. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes of Dermagraft-TC/TransCyte.

In a prospective, randomized, comparison study, Noordenbos et al. (1999) evaluated TransCyte, formerly marketed as Dermagraft-Transitional Covering, for the treatment of partial-thickness burns. A comparison study of silver sulfadiazine and TransCyte was performed with the use of paired wound sites on 14 patients. Wounds treated with TransCyte healed more quickly (mean 11.14 days to 90% epithelialization vs 18.14 days). A non-comparison evaluation was then done for an additional 18 patients, and it confirmed excellent wound healing and an absence of infections. There were no infections in the 32 wound sites treated with TransCyte. In the first study group, late wound evaluations (3, 6, and 12 months postburn) were performed with use of the Vancouver Scar Scale. The results indicated that wound sites treated with TransCyte healed with less hypertrophic scarring than sites treated with silver sulfadiazine. The study limitations included a small sample size, variable length of follow-up, and the study sites covered only limited surface areas.
Kumar et al. (2004) compared the effectiveness of three burns dressings (TransCyte, a bio-engineered skin substitute; Biobrane; and Silvazine cream in treating children with partial-thickness burns. The primary objective was to determine the days until > or =90% re-epithelialization. The secondary objectives were to evaluate the number of wounds requiring autografting and the number of dressing changes/local wound care required. Study wounds were identified on each patient and the patients were randomized to receive TransCyte or Biobrane or Silvazine. Assessment of study wound closure began at 2 days after treatment and continued at least every other day until the wounds re-epithelialized or were autografted. A laser Doppler imaging system was used as an adjunct to assessing the depth of the burn. Thirty-three patients with 58 wound sites were enrolled in the study (TransCyte, n = 20, Biobrane, n = 17; Silvazine, n = 21). Mean time to re-epithelialization was 7.5 days for TransCyte, 9.5 days for Biobrane, and 11.2 days for Silvazine. The number of wounds requiring autografting were 5/21 (24%) for Silvazine, 3/17 (17%) for Biobrane, and 1/20 (5%) for TransCyte. The authors concluded that when used in partial-thickness burns in children, TransCyte promotes fastest re-epithelialization and required less overall dressings then Biobrane or Silvazine. Patients who received Silvazine or Biobrane require more autografting than those treated with TransCyte. The study limitations included a small sample size, lack of blinding methods, and there was no follow-up reported.

In a randomized prospective study, Demling and DeSanti (1999) compared the effect of standard topical antibiotic management versus a biological skin substitute wound closure (TransCyte) for mid-partial thickness burns of the face. Twenty-one adult patients with mid-dermal facial burns produced by flash flames or flame exposure were included in the study. Total daily burn care time, pain (0-10 scale) and healing time were monitored. Immediately after partial thickness debridement, the entire face burn, including ears, was closed with a bioengineered skin substitute coated with fibronectin (TransCyte) (n=10) or treated by the open technique using bacitracin ointment applied 2-3 times daily (n=11). The authors found a significant decrease in wound care time (0.35 +/- 0.1 versus 1.9 +/- 0.5 h), decrease in pain of 2 +/- 1 versus 4 +/- 2 and re-epithelialization time (7 +/- 2 versus 13 +/- 4 days) in the skin substitute group compared to topical antibiotics group. The authors concluded that a bioengineered skin substitute significantly improves the management and healing rate of partial thickness facial burns compared to the standard open topical ointment technique. The limitations of this study include a small sample size and limited follow-up period.

TruSkin
TruSkin (Osiris Therapeutics, Inc) is a split-thickness, cryopreserved human skin allograft that is intended to treat acute and chronic wounds.

There are few published studies addressing the use of TruSkin for wound treatment. Therefore, it is not possible to conclude whether TruSkin has a beneficial effect on health outcomes.

WoundEx
WoundEx (Human Regenerative Technologies, LLC and Skye Biologics) consists of placental connective tissue matrix intended to replace or supplement damaged or inadequate connective tissue. WoundEx membrane allograft consists of dehydrated and decellularized human amniotic membrane. WoundEx membrane is intended to be used as a wound covering in the treatment of chronic and acute wounds.

There are few published studies addressing the use of WoundEx for wound treatment. Therefore, it is not possible to conclude whether WoundEx has a beneficial effect on health outcomes.

In a retrospective cohort study, Lullove (2017) evaluated a dehydrated, human amniotic membrane (WoundEx Membrane, Skye Biologics, Inc.) to treat 20 patients with wounds. The patients underwent a run-in period of 2 weeks, where standard of care was used to clear the wound of bioburden. WoundEx was applied at weeks 1 (2 weeks post-run-in), 3, and 5, if necessary. Wound measurements and photographs were performed weekly. Data were collected through a standard form in each patient’s medical record to improve reliability and reproducibility. Reduction of bias was performed by selecting patients whose wounds already were established and in temporal sequence. In this review of 20 patients treated with WoundEx, the author was able to effectively close all wounds in approximately 9.9 weeks (69.3 days). A linear relationship was discovered between wound size in cm2 and days to closure. Diabetic foot ulcers closed on average in 11.8 weeks (82.6 days) and venous leg ulcers in 9.2 weeks (64.4 days). No adverse events were noted secondary to WoundEx application, which shows this is a safe and effective treatment option. The authors concluded that the use of WoundEx allograft effectively closed diabetic foot ulcerations in 82.6 days and median wound closure in 69.3 days. The lack of a control group limits the validity of the results of this study.

WoundEx Flow
WoundEx Flow (Human Regenerative Technologies, LLC and Skye Biologics) is a wound covering consisting of placental connective tissue matrix intended to replace or supplement damaged or inadequate connective tissue. WoundEx Flow is processed using a proprietary technology that creates an ambient temperature flowable tissue allograft.
There are few published studies addressing the use of WoundEx Flow for wound treatment. Therefore, it is not possible to conclude whether WoundEx Flow has a beneficial effect on health outcomes.

**XCM Biologic**
XCM Biologic is a sterile non-crosslinked 3-D matrix derived from porcine dermis.

Bassetti et al. (2016) conducted a systematic review was to evaluate the efficacy of XCM Biologic Tissue Matrix and other soft-tissue augmentation/correction methods in terms of increasing the peri-implant width of keratinized mucosa (KM) and/or gain of soft tissue volume during second-stage surgery. Overall, eight prospective studies (risk of bias: high) and two case series (risk of bias: high) were included. Depending on the surgical technique and graft material used, the enlargement of keratinized tissue (KT) ranged between -0.20 and 9.35 mm. An apically positioned partial-thickness flap/venteruloplasty (APPTF/VP) in combination with a free gingival graft (FGG) or a xenogeneic graft material (XCM) was most effective. Applying a roll envelope flap (REF) or an APPTF in combination with a subepithelial connective tissue graft (SCTG), mean increases in soft tissue volumes of 2.41 and 3.10 mm, respectively, were achieved. Due to the heterogeneity of studies designs, no meta-analysis could be performed. According to the authors, within the limitations of this review, regarding the enlargement of peri-implant KT, the APPTF in the maxilla and the APPTF/VP in combination with FGG or XCM in the lower and upper jaw seem to provide acceptable outcomes.

Atieh et al. (2016) conducted a systematic review and meta-analysis to evaluate the clinical and patient-centered outcomes of xenogeneic collagen matrix (XCM) compared to other mucogingival procedures. Applying guidelines of the Preferred Reporting Items for Systematic Reviews and Meta analyses statement, randomized controlled trials were searched for in electronic databases and complemented by hand searching. The risk of bias was assessed using the Cochrane Collaboration’s Risk of Bias tool and data were analyzed using statistical software. A total of 645 studies were identified, of which, six trials were included with 487 mucogingival defects in 170 participants. Overall meta-analysis showed that connective tissue graft (CTG) in conjunction with the coronally advanced flap (CAF) had a significantly higher percentage of complete/mean root coverage and mean recession reduction than XCM. Insufficient evidence was found to determine any significant differences in width of keratinized tissue (KT) between XCM and CTG. The XCM had a significantly higher mean root coverage, recession reduction and gain in KT compared to CAF alone. No significant differences in patient’s aesthetic satisfaction were found between XCM and CTG, except for postoperative morbidity in favor of XCM. Operating time was significantly reduced with the use of XCM compared with CTG but not with CAF alone. According to the authors, there is no evidence to demonstrate the effectiveness of XCM in achieving greater root coverage, recession reduction and gain in KT compared to CTG plus CAF. Superior short-term results in treating root coverage compared with CAF alone are possible. There is limited evidence that XCM may improve aesthetic satisfaction, reduce postoperative morbidity and shorten the operating time. The authors stated that further long-term randomized controlled trials are required to endorse the supposed advantages of XCM.

George et al. (2014) reported the first series of using XCM Biologic Tissue Matrix for chest wall reconstruction. It was used either alone or in conjunction with the Synthes titanium system to provide additional support. Since April 2010, 21 (12 females) patients received the device. Average age at operation was 47 ± 17 years. Eleven (52%) patients had the patch inserted alone, while the remaining 10 received it in combination with another implantable medical device. The biological tissue matrix was used to reconstruct chest wall defects in cancer involving chest wall (n = 9), chest wall deformity (n = 6), chest wall hernia (n = 5) and chest wall repair following empyema drainage (n = 1). Complications occurred in 3 patients receiving the combined XCM and Synthes bar mechanisms; infection (n = 2) and bar displacement and infection (n = 1). The authors concluded that the XCM patch can be safely used to provide the strength required for chest wall reconstruction and to replace previously infected reconstructions. This is an uncontrolled study with a small sample size.

**Other Organizations and Technology Assessments**

The National Institute For Health And Care Excellence (NICE) (2015; Updated January 2016) clinical guideline on diabetic foot problems considers dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers only when healing has not progressed and on the advice of the multidisciplinary foot care service. The NICE recommendation does not specify dermal or skin substitutes considered to be effective.

The Agency for Healthcare Research and Quality (AHRQ) Technology Assessment Report on Skin Substitutes for Treating Chronic Wounds states that applicability of the evidence base to address important questions about the effectiveness of skin substitutes in typical populations is limited. The overall applicability of the evidence base is limited to a small number of skin substitute products examining diabetic foot ulcers and venous and/or arterial leg ulcers and to patients in generally good health. According to the authors, the studies that are available are not generalizable to broader patient populations that are not as healthy as the patients in the reviewed studies. According to the AHRQ report, additional studies in this area of wound care would be helpful to provide treatment data for many of the other skin substitute products, to allow better comparisons between wound care products, and to provide better information on wound recurrence when using skin substitute products (AHRQ 2012).
AHRQ (2013) completed a comparative effectiveness review of treatment modalities for chronic venous ulcers. Due to the insufficient evidence, AHRQ was unable to draw conclusions regarding the effectiveness of acellular human skin equivalent dressings vs. compression, or cellular (cryo-preserved human fibroblast-derived dermal substitute) vs. compression.

Reference(s)


The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2018T0535VV]