OMNIBUS CODES

Policy Number: 2017T0535QQ

Effective Date: July 1, 2017

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. 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 Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical 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 Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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.

COVERAGE SUMMARY

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

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<tr>
<th>Code</th>
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<th>Conclusion</th>
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<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>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>0085T</td>
<td>Breath test for heart transplant rejection</td>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>Code</td>
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<td>Conclusion</td>
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</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>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>0207T</td>
<td>Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral</td>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>0269T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)</td>
<td>Refer to Coverage Rationale and Clinical Evidence</td>
</tr>
<tr>
<td>0270T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)</td>
<td>Refer to Coverage Rationale and Clinical Evidence</td>
</tr>
<tr>
<td>0271T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)</td>
<td>Refer to Coverage Rationale and Clinical Evidence</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>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>0293T</td>
<td>Insertion of left atrial hemodynamic monitor; complete system, includes implanted communication module and pressure sensor lead in left atrium including transseptal access, radiological supervision and interpretation, and associated injection procedures, when performed</td>
<td>Unproven</td>
</tr>
<tr>
<td>Code</td>
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<tr>
<td>0294T</td>
<td>Pressure sensor lead at time of insertion of pacing cardioverter-defibrillator pulse generator including radiological supervision and interpretation and associated injection procedures, when performed (List separately in addition to code for primary procedure)</td>
<td>Unproven</td>
</tr>
<tr>
<td>0330T</td>
<td>Tear film imaging, unilateral or bilateral, with interpretation and report</td>
<td>Unproven</td>
</tr>
<tr>
<td>0335T</td>
<td>Extra-osseous subtalar joint implant for talotarsal stabilization</td>
<td>Unproven</td>
</tr>
<tr>
<td>0340T</td>
<td>Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance</td>
<td>Unproven</td>
</tr>
<tr>
<td>0341T</td>
<td>Quantitative pupillometry with interpretation and report, unilateral or bilateral</td>
<td>Unproven</td>
</tr>
<tr>
<td>0346T</td>
<td>Ultrasound, elastography (List separately in addition to code for primary procedure)</td>
<td>Unproven</td>
</tr>
<tr>
<td>0347T</td>
<td>Placement of interstitial device(s) in bone for radiostereometric analysis (RSA)</td>
<td>Unproven</td>
</tr>
<tr>
<td>0348T</td>
<td>Radiologic examination, radiostereometric analysis (RSA); spine (includes cervical, thoracic and lumbosacral, when performed)</td>
<td>Unproven</td>
</tr>
<tr>
<td>0349T</td>
<td>Radiologic examination, radiostereometric analysis (RSA); upper extremity(ies) (includes shoulder, elbow, and wrist, when performed)</td>
<td>Unproven</td>
</tr>
<tr>
<td>0350T</td>
<td>Radiologic examination, radiostereometric analysis (RSA); lower extremity(ies) (includes hip, proximal femur, knee, and ankle, when performed)</td>
<td>Unproven</td>
</tr>
<tr>
<td>0355T</td>
<td>Gastrointestinal tract imaging, intraluminal (e.g., capsule endoscopy), colon, with interpretation and report</td>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>0358T</td>
<td>Bioelectrical impedance analysis whole body composition assessment, with interpretation and report</td>
<td>Unproven</td>
</tr>
<tr>
<td>0377T</td>
<td>Anoscopy with directed submucosal injection of bulking agent for fecal incontinence</td>
<td>Unproven</td>
</tr>
<tr>
<td>0387T</td>
<td>Transcatheter insertion or replacement of permanent leadless pacemaker, ventricular</td>
<td>Unproven</td>
</tr>
<tr>
<td>0388T</td>
<td>Transcatheter removal of permanent leadless pacemaker, ventricular</td>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>0394T</td>
<td>High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed</td>
<td>Unproven</td>
</tr>
<tr>
<td>0395T</td>
<td>High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed</td>
<td>Proven for breast cancer</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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</td>
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<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>
<td>Unproven</td>
</tr>
<tr>
<td>0402T</td>
<td>Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed)</td>
<td>Unproven</td>
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<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>
<td>Unproven</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>
<td>Unproven</td>
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<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>
<td>Unproven</td>
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<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>
<td>Unproven</td>
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<tr>
<td>0412T</td>
<td>Removal of permanent cardiac contractility modulation system; pulse generator only</td>
<td>Unproven</td>
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<tr>
<td>0413T</td>
<td>Removal of permanent cardiac contractility modulation system; transvenous electrode (atrial or ventricular)</td>
<td>Unproven</td>
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<tr>
<td>0414T</td>
<td>Removal and replacement of permanent cardiac contractility modulation system pulse generator only</td>
<td>Unproven</td>
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<tr>
<td>0415T</td>
<td>Repositioning of previously implanted cardiac contractility modulation transvenous electrode, (atrial or ventricular lead)</td>
<td>Unproven</td>
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<tr>
<td>0416T</td>
<td>Relocation of skin pocket for implanted cardiac contractility modulation pulse generator</td>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>0421T</td>
<td>Transurethral waterjet ablation of prostate, including control of post-operative bleeding, including ultrasound guidance, complete (vasectomy, meatoctomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included when performed)</td>
<td>Unproven</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>
<td>Unproven</td>
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<tr>
<td>0425T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
<td>Unproven</td>
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<tr>
<td>0426T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; stimulation lead only</td>
<td>Unproven</td>
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<tr>
<td>0427T</td>
<td>Insertion or replacement of neurostimulator system for treatment of central sleep apnea; pulse generator only</td>
<td>Unproven</td>
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<tr>
<td>0428T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only</td>
<td>Unproven</td>
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<tr>
<td>0429T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
<td>Unproven</td>
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<tr>
<td>0430T</td>
<td>Removal of neurostimulator system for treatment of central sleep apnea;</td>
<td>Unproven</td>
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<tr>
<td>0431T</td>
<td>Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only</td>
<td>Unproven</td>
</tr>
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<tr>
<td>0432T</td>
<td>Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only</td>
<td>Unproven</td>
</tr>
<tr>
<td>0433T</td>
<td>Repositioning of neurostimulator system for treatment of central sleep apnea; sensing lead only</td>
<td>Unproven</td>
</tr>
<tr>
<td>0434T</td>
<td>Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea</td>
<td>Unproven</td>
</tr>
<tr>
<td>0435T</td>
<td>Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session</td>
<td>Unproven</td>
</tr>
<tr>
<td>0436T</td>
<td>Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study</td>
<td>Unproven</td>
</tr>
<tr>
<td>0438T</td>
<td>Transperineal placement of biodegradable material, peri-prostatic (via needle), single or multiple, includes image guidance</td>
<td>Unproven</td>
</tr>
<tr>
<td>0440T</td>
<td>Ablation, percutaneous, cryoablation, includes imaging guidance; upper extremity distal/peripheral nerve</td>
<td>Unproven</td>
</tr>
<tr>
<td>0441T</td>
<td>Ablation, percutaneous, cryoablation, includes imaging guidance; lower extremity distal/peripheral nerve</td>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>0465T</td>
<td>Suprachoroidal delivery of pharmacologic agent (does not include supply of medication)</td>
<td>Unproven</td>
</tr>
<tr>
<td>0469T</td>
<td>Retinal polarization scan, ocular screening with on-site automated results, bilateral</td>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>0472T</td>
<td>Device evaluation, interrogation, and initial programming of intra-ocular 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>
<td>Unproven</td>
</tr>
<tr>
<td>0473T</td>
<td>Device evaluation and interrogation of intra-ocular 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>
<td>Unproven</td>
</tr>
<tr>
<td>20985</td>
<td>Computer-assisted surgical navigational procedure for musculoskeletal procedures, image-less</td>
<td>Unproven</td>
</tr>
<tr>
<td>22899</td>
<td>Unlisted procedure, spine (cooled radiofrequency ablation)</td>
<td>Unproven</td>
</tr>
<tr>
<td>27299</td>
<td>Unlisted procedure, pelvis or hip joint (cooled radiofrequency ablation)</td>
<td>Unproven</td>
</tr>
<tr>
<td>27599</td>
<td>Unlisted procedure, femur or knee (cooled radiofrequency ablation)</td>
<td>Unproven</td>
</tr>
<tr>
<td>28446</td>
<td>Open osteochondral autograft, talus (includes obtaining graft[s])</td>
<td>Unproven</td>
</tr>
<tr>
<td>29799</td>
<td>Unlisted procedure – Kinesio taping</td>
<td>Unproven</td>
</tr>
<tr>
<td>30999</td>
<td>Unlisted procedure, nose (Rhinophototherapy, intranasal application of ultraviolet and visible light, bilateral)</td>
<td>Unproven</td>
</tr>
<tr>
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<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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</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[s])</td>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>43206</td>
<td>Esophagoscopy, flexible, transoral; with optical endomicroscopy</td>
<td>Unproven</td>
</tr>
<tr>
<td>43252</td>
<td>Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy</td>
<td>Unproven</td>
</tr>
<tr>
<td>48160</td>
<td>Pancreatectomy, total or subtotal, with autologous transplantation of pancreas or pancreatic islet cells</td>
<td>Proven</td>
</tr>
<tr>
<td>48999</td>
<td>Unlisted procedure, pancreas</td>
<td>Proven in certain circumstances</td>
</tr>
<tr>
<td>52441</td>
<td>Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; single implant</td>
<td>Unproven</td>
</tr>
<tr>
<td>52442</td>
<td>Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; each additional permanent adjustable transprostatic implant (List separately in addition to code for primary procedure)</td>
<td>Unproven</td>
</tr>
<tr>
<td>53855</td>
<td>Insertion of a temporary prostatic urethral stent, including urethral measurement</td>
<td>Unproven</td>
</tr>
<tr>
<td>60659</td>
<td>Unlisted laparoscopy procedure, endocrine system</td>
<td>Proven in certain circumstances</td>
</tr>
<tr>
<td>64999</td>
<td>Unlisted procedure, nervous system</td>
<td>Proven in certain circumstances for surgical treatment of a Tarlov cyst; unproven for cooled radiofrequency ablation</td>
</tr>
<tr>
<td>76120</td>
<td>Cineradiography/videoradiography, except where specifically included</td>
<td>Unproven</td>
</tr>
<tr>
<td>76125</td>
<td>Cineradiography/videoradiography to complement routine examination (List separately in addition to code for primary procedure)</td>
<td>Unproven</td>
</tr>
<tr>
<td>76496</td>
<td>Unlisted fluoroscopic procedure (e.g., diagnostic, interventional)</td>
<td>Unproven</td>
</tr>
<tr>
<td>76499</td>
<td>Unlisted diagnostic radiographic procedure</td>
<td>Unproven/Proven</td>
</tr>
<tr>
<td>77424</td>
<td>Intraoperative radiation treatment delivery, x-ray, single treatment session</td>
<td>Proven for breast cancer; unproven for all other indications, including nonmelanoma skin cancer</td>
</tr>
<tr>
<td>77425</td>
<td>Intraoperative radiation treatment delivery, electrons, single treatment session</td>
<td>Proven for breast cancer; unproven for all other indications, including nonmelanoma skin cancer</td>
</tr>
<tr>
<td>77469</td>
<td>Intraoperative radiation treatment management</td>
<td>Proven in certain circumstances</td>
</tr>
<tr>
<td>81538</td>
<td>Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival</td>
<td>Proven in certain circumstances</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td>Conclusion</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure [when used to report VeriStrat]</td>
<td>Proven in certain circumstances</td>
</tr>
<tr>
<td>85547</td>
<td>Mechanical fragility, RBC</td>
<td>Unproven</td>
</tr>
<tr>
<td>86849</td>
<td>Unlisted immunology procedure</td>
<td>Unproven</td>
</tr>
<tr>
<td>88375</td>
<td>Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session</td>
<td>Unproven</td>
</tr>
<tr>
<td>92499</td>
<td>Multifocal electroretinography (mfERG) and Pattern Electroretinography (PERG)</td>
<td>Unproven</td>
</tr>
<tr>
<td>93668</td>
<td>Peripheral arterial disease (PAD) rehabilitation, per session</td>
<td>Unproven</td>
</tr>
<tr>
<td>93702</td>
<td>Bioimpedance spectroscopy (BIS), extracellular fluid analysis for lymphedema assessment(s)</td>
<td>Unproven</td>
</tr>
<tr>
<td>93799</td>
<td>Unlisted cardiovascular service or procedure</td>
<td>Unproven</td>
</tr>
<tr>
<td>94011</td>
<td>Measurement of spirometric forced expiratory flows in an infant or child through 2 years of age</td>
<td>Unproven</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>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>94799</td>
<td>Unlisted pulmonary service or procedure</td>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>97139</td>
<td>Unlisted therapeutic procedure (specify) [when used to report Kinesio Taping]</td>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>99174</td>
<td>Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with remote analysis and report</td>
<td>Proven in certain circumstances</td>
</tr>
<tr>
<td>99177</td>
<td>Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with on-site analysis</td>
<td>Proven in certain circumstances</td>
</tr>
<tr>
<td>E1399</td>
<td>Durable medical equipment, miscellaneous [when used to report robotic lower body exoskeleton device]</td>
<td>Unproven</td>
</tr>
<tr>
<td>G0341</td>
<td>Percutaneous islet cell transplant, includes portal vein catheterization and infusion</td>
<td>Unproven</td>
</tr>
<tr>
<td>G0342</td>
<td>Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion</td>
<td>Unproven</td>
</tr>
<tr>
<td>G0343</td>
<td>Laparotomy for islet cell transplant, includes portal vein catheterization and infusion</td>
<td>Unproven</td>
</tr>
<tr>
<td>L2999</td>
<td>Lower extremity orthoses, not otherwise specified [when used to report robotic lower body exoskeleton device]</td>
<td>Unproven</td>
</tr>
<tr>
<td>L3999</td>
<td>Upper limb orthotic, not otherwise specified [when used to report MyoPro™]</td>
<td>Unproven</td>
</tr>
<tr>
<td>L5781</td>
<td>Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system</td>
<td>Unproven</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>
<td>Unproven</td>
</tr>
<tr>
<td>L8605</td>
<td>Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, anal canal</td>
<td>Unproven</td>
</tr>
<tr>
<td>L8607</td>
<td>Injectable bulking agent for vocal cord medialization, 0.1 ml, includes shipping and necessary supplies</td>
<td>Proven in certain circumstances</td>
</tr>
<tr>
<td>P2031</td>
<td>Hair analysis (excluding arsenic)</td>
<td>Unproven</td>
</tr>
<tr>
<td>P2033</td>
<td>Thymol turbidity, blood</td>
<td>Unproven</td>
</tr>
<tr>
<td>P2038</td>
<td>Blood Mucoprotein</td>
<td>Unproven</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td>Conclusion</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
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<tr>
<td>Q2026</td>
<td>Injection Radiesse 0.1ML</td>
<td>Proven in certain circumstances</td>
</tr>
<tr>
<td>Q2028</td>
<td>Injection, Sculptra, 0.5 mg</td>
<td></td>
</tr>
<tr>
<td>Q4115</td>
<td>AlloSkin, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4123</td>
<td>AlloSkin RT, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4131</td>
<td>Epifix or Epicord, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4132</td>
<td>Grafix Core, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4133</td>
<td>Grafix Prime, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4134</td>
<td>HMMatrix, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4135</td>
<td>Mediskin, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4136</td>
<td>Ez-derm, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4137</td>
<td>AmnioExcel or BioDExCel, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4138</td>
<td>BioDFence DryFlex, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4139</td>
<td>AmnioMatrix or BioDMatrix, injectable, 1 cc</td>
<td>Unproven</td>
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<tr>
<td>Q4140</td>
<td>BioDFence, per sq cm</td>
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</tr>
<tr>
<td>Q4141</td>
<td>AlloSkin AC, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4142</td>
<td>Xcm biologic tissue matrix, per square centimeter</td>
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<tr>
<td>Q4143</td>
<td>Repriza, per square centimeter</td>
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</tr>
<tr>
<td>Q4145</td>
<td>EpiFix, injectable, 1 mg</td>
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</tr>
<tr>
<td>Q4146</td>
<td>Tensix, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4147</td>
<td>Architect, Architect PX, or Architect FX, extracellular matrix, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4148</td>
<td>Neox 1k, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4149</td>
<td>Excellagen, 0.1 cc</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4150</td>
<td>AlloWrap DS or dry, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4151</td>
<td>AmnioBand or Guardian, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4152</td>
<td>DermaPure, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4153</td>
<td>Dermavest and Plurivest, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4154</td>
<td>Biovance, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4155</td>
<td>Neox Flo or Clarix Flo 1 mg</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4156</td>
<td>Neox 100, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4157</td>
<td>Revitalon, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4158</td>
<td>Marigen, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4159</td>
<td>Affinity, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4160</td>
<td>Nushield, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4161</td>
<td>Bio-connekt wound matrix, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4162</td>
<td>Amniopro flow, bioskin flow, biorenew flow, woundex flow, amniogen-a,</td>
<td>Unproven</td>
</tr>
<tr>
<td></td>
<td>amniogen-c, 0.5 cc</td>
<td></td>
</tr>
<tr>
<td>Q4163</td>
<td>Amniopro, bioskin, biorenew, woundex, amniogen-45, amniogen-200, per</td>
<td>Unproven</td>
</tr>
<tr>
<td></td>
<td>square centimeter</td>
<td></td>
</tr>
<tr>
<td>Q4164</td>
<td>Helicoll, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4165</td>
<td>Keramatrix, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4166</td>
<td>Cyal, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4167</td>
<td>Truskin, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4168</td>
<td>Amnioband, 1 mg</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4169</td>
<td>Artacent wound, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4170</td>
<td>Cygnus, per square centimeter</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4171</td>
<td>Interfyl, 1 mg</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4172</td>
<td>PuraPly or PuraPly AM, per sq cm</td>
<td>Unproven</td>
</tr>
<tr>
<td>Q4173</td>
<td>Palingen or palingen xplus, per square centimeter</td>
<td>Unproven</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.

U.S. Food and Drug Administration (FDA): The FDA regulates computer-assisted navigation systems as Class II devices.

**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

Yaffee 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 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.

Hayes (2006) conducted a search of 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.

The largest study, 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.

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. 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.

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.

**Reference(s)**


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0085T</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: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H030004. (Accessed May 18, 2016)

No professional society guidelines addressing this technology were identified.

Reference(s)


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<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 intra-ocular 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 intra-ocular 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 postimplant clinical follow-up, device fitting, and visual rehabilitation. Eligibility determination requires that patients with no residual light perception undergo testing for evidence of intact inner-layer retinal function. The procedure description indicates that patients with phakic eyes have their natural lens removed during the implant procedure. The device is intended for use in one eye—the worse-seeing eye. The HDE approval required the company to conduct 2 post-approval studies, including an extended (10-year) follow-up of patients receiving the implant and a 5-year, prospective, multicenter study of the visual function, device
In a systematic review, Chuang et al. (2014) compared selected retinal implant models by examining publications describing five representative retinal prostheses: Argus II, Boston Retinal Implant Project, Epi-Ret 3, Intelligent Medical Implants (IMI) and Alpha-IMS (Retina Implant AG). Publications were analyzed using three criteria for interim success: clinical availability, vision restoration potential and long-term biocompatibility. Clinical availability: Argus II is the only device with FDA approval. Argus II and Alpha-IMS have both received the European CE Marking. All others are in clinical trials, except the Boston Retinal Implant, which is in animal studies. Vision restoration: resolution theoretically correlates with electrode number. Among devices with external cameras, the Boston Retinal Implant leads with 100 electrodes, followed by Argus II with 60 electrodes and visual acuity of 20/1262. Instead of an external camera, Alpha-IMS uses a photodiode system dependent on natural eye movements and can deliver visual acuity up to 20/546. Long-term compatibility: IMI offers iterative learning; Epi-Ret 3 is a fully intraocular device; Alpha-IMS uses intraocular photosensitive elements. The authors concluded that based on the review of these three criteria, Alpha-IMS is the most likely to achieve long-term success decades later, beyond current clinical availability.

In a multicenter, single-arm, prospective clinical trial, Ho et al. (2015) evaluated the safety, reliability, and benefit of the Argus II Retinal Prosthesis System in restoring some visual function to subjects completely blind from retinitis pigmentosa (RP). The authors reported clinical trial results at 1 and 3 years after implantation in 30 subjects. Subjects served as their own controls, that is, implanted eye versus fellow eye, and system on versus system off (native residual vision). The Argus II System was implanted on and in a single eye (typically the worse-seeing eye) of blind subjects. Subjects wore glasses mounted with a small camera and a video processor that converted images into stimulation patterns sent to the electrode array on the retina. The primary outcome measures were safety (the number, seriousness, and relatedness of adverse events) and visual function, as measured by 3 computer-based, objective tests. A total of 29 of 30 subjects had functioning Argus II Systems implants 3 years after implantation. Eleven subjects experienced a total of 23 serious device- or surgery-related adverse events. All were treated with standard ophthalmic care. As a group, subjects performed significantly better with the system on than off on all visual function tests and functional vision assessments. The authors concluded that the 3-year results of the Argus II trial support the long-term safety profile and benefit of the Argus II System for patients blind from RP. According to the investigators, in this small study of 30 subjects, it is difficult to complete a robust statistical analysis of the safety results because of limited power.

In a single-center, prospective, internally-controlled case series, Luo et al. (2014) evaluated the use of the Argus® II retinal prosthesis system by blind subjects to achieve object localization and prehension in 3-dimensional space. The study included 5 blind Retinitis Pigmentosa (RP) subjects who received the Argus® II implant. The subjects were instructed to visually locate, reach and grasp (i.e., prehension) a small white cuboid object placed at random locations on a black worktop. A flashing LED beacon was attached to the reaching index finger (as a finger marker) to assess the effect of enhanced finger visualization on performance. Tasks were performed with the prosthesis switched "on" or "off" and with the finger marker switched "on" or "off." Forty-eight trials were performed per subject. Trajectory of each subject's hand movement during the task was recorded by a 3D motion-capture unit and analyzed using a MATLAB script. With prosthesis off, none of the subjects were able to visually locate the target object and no initiation of prehension was attempted. With prosthesis on, prehension was initiated on 82.5% (range 59-100%) of the trials with 89.0% (range 66.7-100%) achieving successful prehension. The authors concluded that Argus® II subjects were able to achieve object localization and prehension better with their prosthesis switched on than off. These findings require confirmation in a larger study.

As part of a phase 1/2 feasibility study, Dorn et al. (2013) investigated the ability of blind patients implanted with the Argus II retinal prosthesis system to detect the direction of a moving object. Twenty-eight blind patients (bare light perception or worse in both eyes) with retinitis pigmentosa were included in the study. Patients were tested with the system on, system off, and with the system on but the spatial information scrambled. Fifteen patients experienced a significant improvement in their ability to detect the direction of motion with the system turned on, 2 subjects did worse, and 11 subjects remained the same. Of the 15 better-performing subjects, 11 were available for follow-up testing, and 10 of them had significantly better performance with normal rather than with scrambled spatial information. The authors concluded that this study demonstrates that blind subjects implanted with the Argus II retinal prosthesis were able to perform a motion detection task they could not do with their native vision, confirming that electrical stimulation of the retina provides spatial information from synchronized activation of multiple electrodes. While the results of this study are promising, more research is needed regarding adverse events and improvement of visual functions with this device.

da Cruz et al. (2013) conducted a prospective, internally controlled, multicenter trial of the Argus II system that included 28 subjects with light perception vision who received a retinal implant. Patients completed a force choice letter identification tests and an open-choice word identification test. Letters (L, T, E, J, F, H, I, U) were correctly identified 72.3 ±24.6% of the time with the system on and 17.7 ±(12.9)% of the time with the system off. Letters (K,

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R, G, X, B, Y, S, P) were correctly identified 51.7 ± 28.9% of the time with the system on and 15.3 (7.4)% of the time with the system off. Letters (A, Z, Q, V, N, W, O, C, D, M) were correctly identified 55 ±27.4% and 11.8 ±10.7% of the time with the system on and off, respectively. Average implant duration was 19.9 months. The authors concluded that multiple blind subjects fitted with the Argus II system consistently identified letters and words using the device, indicating reproducible spatial resolution. According to the authors, this, in combination with stable, long-term function, represents significant progress in the evolution of artificial sight. The authors stated that it is not immediately clear how the performance of the controlled tasks identified in this study will translate directly into useful function in daily life, and this is being studied further.

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 May 18, 2016)

Reference(s)

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<th>Code</th>
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<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>
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</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, 2004) and Kadeda (2004).

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 American College of Chest Physicians (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)**


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<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).

The goals of a histopathological validation study performed by Kang et al. (2015) were to determine the accuracy of the grayscale intravascular ultrasound (IVUS) and/or near-infrared spectroscopy (NIRS) detection of a histological
fibroatheroma (FA) and to determine the benefit of the use of combined NIRs and grayscale IVUS. Human coronary specimens were obtained over a 2-year period from 62 autopsied patients. IVUS-attenuated plaque and NIRS were compared with histopathology in 1,943 sections of 103 coronary arteries. Twenty sections showed intimal thickening, 5 sections were found with smooth muscle cell-rich plaque, 2 with bland fibrous plaque, 16 with fibrocalcific plaque, 16 with pathologic intimal thickening, 16 with early FAs, 9 with calcified early FAs, 7 with late FAs, 9 with calcified late FAs, and 3 with thin-cap FAs. Both IVUS attenuation and NIRS showed a high specificity of 96% and 94%, respectively, for predicting a histological FA. Conversely, superficial IVUS had a poor sensitivity of 36% that was explained by greater calcification, smaller plaque burden, and more focal and less advanced FA. When sections showed both IVUS attenuation and NIRS, the positive predictive value improved compared with IVUS attenuation or NIRS alone. The authors concluded that the findings demonstrate the complementary use of both sound (IVUS) and light (NIRS) to characterize plaques. Because this autopsy-based study evaluated hearts from 2 research tissue procurers, the results cannot be extended to the general population. The histological preparation requires dehydration of the tissue specimen before the tissue is embedded which dissolves lipid, leaving an empty vacuole as presumptive evidence of previous lipid accumulation. The impact of the present findings on clinical outcomes needs to be studied.

Curtis and colleagues (2015) conducted a pragmatic randomized controlled trial (RCT) to examine if the use of ultrasound or near-infrared vascular imaging to guide catheterization would be more effective than the standard approach in achieving successful catheter placement on the first attempt. Four hundred and eighteen children in a pediatric emergency department who required peripheral intravenous catheterization were randomly assigned to undergo the procedure with the standard approach, or with the help of either ultrasound or near-infrared vascular imaging. The rate of successful first attempts did not differ significantly between either of the 2 intervention groups and the standard approach group. Among children 3 years and younger, the difference in success rates relative to standard care was also not significant for ultrasound imaging, but it was significantly worse for near-infrared imaging. Among children older than 3 years, the differences in success rates relative to standard care were smaller but not significant. The authors concluded that neither technology improved first-attempt success rates of peripheral intravenous catheterization in children. These findings do not support investment in these technologies for routine peripheral intravenous catheterization in children.

Waxman et al. (2009) reported on a diagnostic, nonrandomized, open label, uncontrolled trial designed to determine whether catheter-based near-infrared spectroscopy (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 LCP with this novel system yet does not establish the utility of testing.

No professional society guidelines addressing this technology were identified.

Reference(s)

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<th>Code</th>
<th>Description</th>
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<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>
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</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).

Electrocardiogram (ECG) signal analysis technologies are enhanced versions of the standard resting or exercise ECG that utilizes 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).

Multifunction cardiogram (MCG) evaluation in diagnosis of functional coronary ischemia study (MED-FIT) was designed as a single-center, prospective study enrolling 100 stable patients with suspected coronary artery disease scheduled for coronary angiography. The primary and secondary analyses evaluated the diagnostic performance of the MCG severity score to detect functional myocardial ischemia and angiographically significant coronary stenosis by quantitative coronary angiography. Kawaiji et al. (2015) performed a current analysis set consisting of 91 patients in whom MCG data with good quality was obtained. The prevalence of positive functional myocardial ischemia and angiographically significant stenosis in the current study was 42.7% and 41.8%, respectively. Area under the receiver operating characteristics curve (AUC) of the MCG severity score was low as was the sensitivity and specificity of the MCG severity score (32%/67% and 37%/72%). The authors concluded that 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 new computerized, multiphase, resting electrocardiogram analysis device (MultiFunction-CardioGram(sm) or MCG a.k.a. 3DMP) for the detection of relevant coronary stenosis. A total of 1076 patients were included in the analysis. The authors concluded that the new computerized, multiphase, resting ECG analysis device (MultiFunction-CardioGram(sm)) has been shown in this meta-analysis to safely and accurately identify 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)


Premier Heart website.

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.

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<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>0207T</td>
<td>Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral</td>
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</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. (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 (29.0±4.6) to 1 month (14.7±4.3) but returned to BL levels at 3 years (22.5±5.4). The SPEED scores decreased from BL (13.4±1.0) to 1 month (6.5±1.3), and this improvement persisted at 3 years (9.5±1.6). The investigators concluded that thermal pulsation may be a uniquely efficacious treatment option for DED secondary to MGD in that a single 12-min procedure is associated with significant improvement in MGS and SPEED scores for up to 3 years. The limitations in this study include a lack of control and small sample size.

In a prospective, randomized, crossover, observer-masked clinical trial, Finis et al. (2014) compared the effectiveness of a single LipiFlow treatment with combined lid warming and massage in patients with meibomian gland dysfunction (MGD). Study participants were randomized to receive either a single 12-min LipiFlow Thermal Pulsation (LTP) system treatment or to perform combined twice-daily lid warming and massage for 3 months. All subjects were examined before, and 1 and 3 months after initiation of treatments. A total of 31 subjects completed the 3-month follow-up. At 1 and 3 months, patients in the LipiFlow treatment group had a significant reduction in Ocular Surface Disease Index (OSDI) scores compared with those in the lid-margin hygiene group. Both treatments produced a significant improvement in expressible meibomian glands compared to the baseline parameters, but no significant difference was noted between the two groups. The other investigated objective parameters did not show a significant difference. The authors concluded that a single LipiFlow treatment is as least as effective as a 3-month, twice-daily lid margin hygiene regimen for MGD. According to the authors, a limitation of the present study was that it was observer-masked only.
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.


Reference(s)


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<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>
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<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>
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<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>
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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 cell 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 remodeling of collateral vessels to reduce the symptoms of peripheral vascular disease and prevent amputation. For autologous cell transplantation in humans, bone marrow and peripheral blood are rich sources of stem and progenitor cells. Bone marrow is currently the most frequent source of cells used for clinical repair trials, because it is easy to obtain and no complex purification steps are required. Another advantage is that it contains a variety of stem and progenitor cells. At present angiogenic gene and stem cell therapy are still being investigated, and it is too early to give firm recommendations (Tendera et al., 2011).

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

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

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

**Reference(s)**


<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<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>
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<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>0269T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)</td>
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<td>0270T</td>
<td>Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)</td>
</tr>
<tr>
<td>0271T</td>
<td>Revision or removal 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>
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<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>
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**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.**

The Barostim neo™ legacy™ hypertension therapy device is approved by the U.S. Food and Drug Administration (FDA) as a Humanitarian Use Device (HUD). The device is indicated for use in patients with resistant hypertension who have had bilateral implantation of the Rhoes® Carotid Sinus Leads (models 1010R, 1010L, 1014L and 1014R) which have been discontinued and are obsolete and were determined responders in the Rhoes® pivotal clinical study. Additional information available at: [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H130007](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H130007). (Accessed May 24, 2016)
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**

Baroreflex activation therapy (BAT), or baroreflex stimulation, uses a pacemaker-like implantable pulse generator to deliver electrical signals to baroreceptors in the carotid arteries through electrodes placed in the carotid sinus. The baroreflex system is a network of natural blood pressure sensors (baroreceptors) located throughout the arteries and veins that help regulate blood pressure. When pressure in the carotid arteries rises, carotid artery baroreceptors (located in the carotid sinus) are stimulated and transfer the pressure information to the brain through the carotid sinus nerve. The brain then signals other parts of the body to lower systemic blood pressure by dilating blood vessels, reducing heart rate and increasing fluid excretion through the kidneys. In chronic hypertension, the carotid baroreflex signal is often insufficient; therefore, investigators are evaluating carotid sinus baroreceptors as a potential nonpharmacotherapy for treatment-resistant hypertension. The available data are few and from several small clinical trials and reported results vary in the amount of blood pressure reduction achieved, but BAT reportedly achieved modest reductions in mean blood pressure. Very few data are available regarding the technology’s ability to reduce patients’ use of antihypertensive drugs. The few available data indicate it did not eliminate the need for medication; but reduced the amount needed by some patients. More substantive and longer term data from trials demonstrating benefits that outweigh potential harms are needed (ECRI, 2013; updated 2015).

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 nighttime 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 chronic 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.

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; NCT01720160).

Gronda et al. (2014) assessed the effects of BAT in clinical heart failure (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.

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.

Georgakopoulos et al. (2011) review the evidence suggesting that BAT may be a promising therapy for heart failure with preserved ejection fraction (HFpEF) and introduces the HOPE4HF trial (ClinicalTrials.gov NCT00957073), a randomized outcomes trial designed to evaluate the clinical safety and efficacy of BAT in the HFpEF population.

Scheffers et al. (2010) assessed the safety and efficacy of a novel implantable device therapy in resistant hypertension patients. The Rheos system (CVRx, Inc.) activates the carotid baroreflex. Forty-five patients with systolic blood pressure ≥160 mm Hg or diastolic ≥90 mm Hg despite at least 3 antihypertensive drugs were enrolled in a prospective, nonrandomized feasibility study to assess whether Rheos therapy could safely lower blood pressure. Subjects were followed up for as long as 2 years. After 3 months of device therapy, mean blood pressure was reduced by 21/12 mm Hg. This result was sustained in 17 subjects who completed 2 years of follow-up, with a mean reduction of 33/22 mm Hg. The device exhibited a favorable safety profile. This novel approach holds promise for patients with resistant hypertension and is currently under evaluation in a prospective, placebo-controlled clinical trial.

Heusser et al. (2010) studied the effects of electric field stimulation of carotid baroreceptors on blood pressure. Seven men and five women (ages 43 to 69 years) with treatment-resistant arterial hypertension received an implantable bilateral electric baroreflex stimulator at the level of the carotid sinus (Rheos). Intra-arterial blood pressure was 193+/-9/94+/-5 mm Hg on medications. Acute electric baroreflex stimulation decreased systolic blood pressure by 32+/-10 mm Hg (range: +7 to -108 mm Hg; P=0.01). The authors concluded that electric field stimulation of carotid sinus baroreflex afferents acutely decreased arterial blood pressure in hypertensive patients, without negative effects on physiological baroreflex regulation.

The Food and Drug Administration-monitored phase II Rheos Feasibility Trial was performed to assess the response of patients with multidrug-resistant hypertension to electrical stimulation of the carotid sinus baroreflex system. The system consists of an implantable pulse generator with bilateral perivascular carotid sinus leads. Implantation is performed bilaterally. Ten patients with resistant hypertension (taking a median of six antihypertensive medications) underwent implantation. Results showed a significant acute decrease in blood pressure without significant side effects (Illig, et al. 2006).

**Reference(s)**

Abraham WT, Zile MR, Weaver FA, et al. Baroreflex Activation Therapy for the Treatment of Heart Failure with a Reduced Ejection Fraction. JACC Heart Fail. 2015 Apr 28. pii: S2213-1779(15)00125-0. [Epub ahead of print]


Clinical Evidence

The phase III Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy (LAPTOP-HF) trial is underway. The purpose of this clinical study is to evaluate the safety and clinical effectiveness of the use of a physician-directed, patient self-management system, guided by left atrial pressure measurements, for use in patients with heart failure. The system allows patients to adjust heart failure (HF) medications daily based on a physician-directed prescription plan and current HF status, similar to the manner in which diabetes patients manage their insulin therapy. The goal of the LAPTOP-HF study is to demonstrate reductions in episodes of worsening HF and hospitalizations in patients who are managed with the left atrial pressure (LAP) management system (treatment group) versus those who receive only the current standard of care (control group).

Ritzema et al. (2010) conducted the HOMEOSTASIS® trial, a feasibility study to evaluate the clinical results of a permanently implanted left atrial pressure (LAP) sensor linked to a physician directed patient self-management treatment paradigm. This small observational study assessed early safety and clinical outcomes with the goal of generating hypotheses for subsequent randomized trials.

Heart Failure Society of America guidelines (Lindenfeld et al., 2010) state that the routine use of invasive hemodynamic monitoring in patients with acute decompensated heart failure (ADHF) is not recommended. (Strength of Evidence = A; based on randomized, controlled trial(s))

Invasive hemodynamic monitoring should be considered in a patient:
- Who is refractory to initial therapy,
- Whose volume status and cardiac filling pressures are unclear,
- Who has clinically significant hypotension (typically SBP !80 mm Hg) or worsening renal function during therapy, or
- Who is being considered for cardiac transplant and needs assessment of degree and reversibility of pulmonary hypertension, or
- In whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered. (Strength of Evidence = C; based on expert opinion)

Clinical trials are ongoing.

Reference(s)


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.

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 punctual 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 punctual 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.

Szczena et al. (2011) measured tear film surface quality in 34 patients with healthy or dry eyes using three noninvasive techniques of tear film quality assessment and evaluated the ability of these noninvasive techniques to predict dry eye. Three noninvasive techniques were applied for measurement of tear film surface quality: dynamic-area high-speed videokeratoscopy (HSV), wavefront sensing (DWS), and lateral shearing interferometry (LSI). To investigate the capability of each method to discriminate dry eye subjects from normal subjects, the receiver operating curve (ROC) was calculated and then the area under the curve (AUC) was extracted. The best result was obtained for the LSI technique, which was followed by HSV. The best result for DWS was an AUC of 0.64 obtained for changes in vertical coma in suppressed blinking conditions (SBC), whereas for natural blinking conditions (NBC), the results were poorer. The authors concluded that noninvasive techniques of tear film surface assessment can be used for predicting dry eye. In this study, LSI showed the best detection performance, closely followed by the dynamic-area HSV. The DWS technique was less powerful, particularly in NBC. The study did not confirm the utility of such findings in improving care and outcome of patients.


Reference(s)
**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 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 subtalar arthroereisis (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 (FF) 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. The safety profile of the procedure appears to be favorable, with pain and sinus tarsi tenderness being the most frequent complications. These symptoms usually improve after removal of the implant. Based on the current published evidence, the following Hayes Ratings are assigned: C – For SA for the treatment of FF deformity, associated with pain or impairment of function and not responsive to conservative treatment, in children. This Rating is based on the results from six studies of poor quality consistently suggesting that SA improves pain, functionality, and radiographic findings associated with FF, and on the favorable safety profile of the procedure. D2 – For SA for the treatment of FF deformity, associated with pain or impairment of function and not responsive to conservative treatment, in adults. This Rating is based on the lack of sufficient evidence to evaluate the procedure for this population (Hayes, 2012; updated 2015).

A recent controlled study compared subtalar arthroereisis 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).

There is currently no published evidence from randomized controlled trials on subtalar arthroereisis. 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.

The evidence in the published medical literature on subtalar arthroereisis is inadequate to permit scientific conclusions. The main limitation is the lack of controlled studies comparing use of the implants with other surgical procedures, alone or in combination. Another limitation of the published data is the lack of long-term outcomes.

**Professional Societies**

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

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

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)

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<td>0340T</td>
<td>Ablation, pulmonary tumor(s), including pleura or chest wall when involved by tumor extension, percutaneous, cryoablation, unilateral, includes imaging guidance</td>
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Percutaneous cryoablation of pulmonary tumors, including the pleura or chest wall when involved by tumor extension, is unproven 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.

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, 3 years are 96%, 88%, 88% at 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.

Colak et al. (2014) evaluated CT-guided cryoablation to treat lung tumors that were adjacent to critical organ or other structures (n=8; 11 malignant tumors). After 24 hours, imaging showed that no patients had any residual tumors. A total of 5 tumors recurred, 3 of which were re-ablated. There were several complications reported. Pneumothorax developed following six procedures (60%). All patients developed pleural effusions. Transient hemoptysis occurred after six procedures (60%).

Moore et al. (2015) conducted a retrospective analysis to evaluate long-term survival in patients with early stage non-small cell lung cancer (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).

Niu et al. (2013) investigated the therapeutic effect of cryoablation treatment and palliative treatment in patients with stage IV lung cancer (n=54). Thirty-one patients received cryoablation treatment (including intra- and extrapulmonary tumors), and 23 patients had palliative treatment (no cryoablaction). Both the safety of the procedure and overall survival (OS) for stage IV lung cancer were assessed during a 6.5year follow-up period. The OS of patients in both groups and the effects of treatment timing and frequency were compared. The OS in the cryoablation group was significantly longer than in the palliative group (median OS: 14months vs. 7months, P=0.0009). The OS of those who received delayed cryoablation treatment was longer than that observed for those who received timely treatment (median OS: 18.5months vs. 10months, P=0.0485), but this was not observed in those who received palliative treatment (median OS: 7months vs. 7.5months, P=0.9814). Multiple treatments played an important role in improving the OS of patients who received cryoablation treatment (median OS: 18months vs. 14months, P=0.0376).

There was a significant difference between cryoablation and palliative treatment, in terms of OS. In addition, multiple cryoablation treatments may have an advantage over single treatments.

In a prospective, before-and-after study, Zhang et al. (2012) evaluated the feasibility of computed tomography (CT)-guided cryoablation for patients with peripheral Non-Small Cell Lung Cancer (NSCLC) (n=43). CT was used to monitor the extent of cryoablation during the procedures. Results up to 24 months following the procedure were assessed using enhanced CT scans and/or PET-CT scans. The average tumor CT values were 32±10 HU and -21±8 HU before and after cryoablation, respectively. At 24 months, there were 36 cases of complete response (83.7%), 7 cases of partial response (16.3%), and no cases of stable disease or progressive disease. Three patients died due to multiple metastases.

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 were91%, 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 identified 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 82%, 97% and 91% of treated lesions at 1-, 3- and 6-months CT follow-up scan, respectively (p<.000). Comparing the tumor longest diameter between the baseline and at 6 month CT images, technical success was revealed in 92% cases (p<.000).

Bang et al. (2012) assessed the feasibility, complications, local tumor recurrences, overall survival (OS) for multisite cryoablation (MCA) of oligometastatic non-small-cell lung cancer (NSCLC). A total of 49 CT- and/or ultrasound-guided (US) percutaneous cryoablation procedures were performed on 60 tumors in 31 patients with oligometastatic NSCLC. Average patient age was 65 years. Tumor location was grouped according to common metastatic sites. Median OS was determined by Kaplan-Meier method. A mean of 1.6 procedures per patient were performed, with a median
clinical follow-up of 11 months. Major complication and local recurrence rates were 8% (4/49) and 8% (5/60), respectively. Median OS was 1.33 years, with an estimated 1-year survival rate of approximately 53%.

Reference(s)

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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>0341T</td>
<td>Quantitative pupillometry with interpretation and report, unilateral or bilateral</td>
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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
Several small clinical trials have been recently identified in the peer-reviewed 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 tests 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)

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<tr>
<td>0346T</td>
<td>Ultrasound, elastography (List separately in addition to code for primary procedure)</td>
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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.

Omnibus Codes

UnitedHealthcare Commercial Medical Policy

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Effective 07/01/2017

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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)**


J. Ophir, S. Alam, B. Garra, F. Kallel, E. Konofagou, T. Krouskop, and T. Varghese,


Trombetti J. Sonoelastography and musculoskeletal imaging.

<table>
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<tr>
<th>Code</th>
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<tr>
<td>0347T</td>
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<td>Radiologic examination, radiostereometric analysis (RSA); lower extremity(ies), (includes hip, proximal femur, knee, and ankle, when performed)</td>
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The use of radiostereometric analysis in bone is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

**Clinical Evidence**
Radiostereometric analysis (RSA) is an imaging procedure intended to detect changes in implant position after orthopedic surgery. The process involves the insertion of spherical tantalum markers into the bone during surgery and then using a pair of x-rays of the surgical site with a RSA calibration cage to take simultaneous images from two different directions.

RSA has recently been investigated as a tool to measure lateral calcaneal lengthening osteotomies (Martinkevich, 2015) and assessment of spinal fusion (Humadi, 2013). However, both studies were limited in scope. The Martinkevich study was performed on 6 cadaver feet and the Humadi study was performed on 9 animals (sheep).

Pijls et al (2012a) conducted a randomized controlled trial to investigate the long-term migration HA-coated, uncoated, and cemented tibial components in total knee amputation (TKA) as measured by RSA. Their rationale for this study was that, in contrast to early migration, the long-term migration of hydroxyapatite- (HA-) coated tibial components in TKA has been inadequately reported. In this study 68 knees were randomized to HA-coated, uncoated, and cemented components and all knees were prospectively followed for 11-16 years or until death or revision. 742 RSA analyses were used to evaluate migration at yearly intervals utilizing clinical and radiographic evaluations designed according to the Knee Society system and analyzed via a generalized linear mixed model to account for the repeated measures design. Results of this study showed that the mean migration at 10 years was 1.66 mm for HA, 2.25 mm for uncoated and 0.79 mm for the cemented group. The reduction of migration by HA compared to uncoated components was greatest for subsidence and external rotation. It was noted that 3 tibial components were revised for aseptic loosening (2 uncoated and 1 cemented), 3 for septic loosening (2 uncoated and 1 cemented), and 1 for instability (HA-coated). Also of interest is that 2 of these cases were revised for secondary loosening after a period of stability, including 1 case of osteolysis and 1 case with late onset of infection. There were no statistically significant differences between the fixation groups regarding clinical or radiographic scores. The authors concluded that HA reduces migration of uncremented tibial components with this beneficial effect lasting more than 10 years. The authors further noted that longitudinal follow-up of TKA with RSA allows early detection of secondary loosening.
Pijls et al (2012b) performed 2 parallel systematic reviews and meta-analyses to determine the association between early migration of acetabular cups and late aseptic revision. The two reviews covered early migration data from RSA studies and revision rates for aseptic loosening from long-term survival studies respectively. Following an elaborate literature search, 26 studies involving 700 cups were included in the RSA review and 49 studies involving 38,013 cups were included in the survival review. Results of the study showed that for every mm increase in 2-year proximal migration, there was a 10% increase in revision rate, which remained after correction for age, sex, diagnosis, hospital type, continent, and study quality. The authors found a clinically relevant association between early migration of acetabular cups and late revision due to loosening and concluded that the proposed migration thresholds can be implemented in a phased evidence-based introduction, given that they allow early detection of high-risk cups while exposing a small number of patients.

Bottner et al. (2005) conducted an analysis at Hospital for Special Surgery to evaluate the migration and wear of orthopaedic implants using radiostereometric analysis. The authors concluded after their analysis that RSA may have benefit of noting migration of implants before clinical failure is evident. More long-term randomized controlled studies are needed in the future.

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

FDA cleared Model-based RSA software for marketing under the 510(k) process in March 2014.

The evidence in the published medical literature for radiostereometric analysis in bone is inadequate to permit scientific conclusions The ability of RSA and associated interstitial markers to improve clinical health outcomes has not been established The main limitation is the lack of controlled studies, small sample size as well as the lack of long-term outcomes. Further study to improve RSA standardization and large randomized clinical trials are needed to establish the clinical utility of this technology.

Reference(s)
Bostrom M, Su E, Wright, T. Hospital for Special Surgery. Radiosteometric analysis at HSS. January 2012

<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>0355T</td>
<td>Gastrointestinal tract imaging, intraluminal (e.g., capsule endoscopy), colon, with interpretation and report</td>
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Pillcam Colon 2 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 Colon 2 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 Colon 2 on January 29, 2014. The device was approved for use under the de novo classification utilized for devices with low to moderate risk. Pillcam Colon 2 was approved for use only in patient who have had an incomplete optical colonoscopy with adequate preparation, and a complete evaluation of the colon was not technically possible. On January 14, 2016, the FDA approved an expanded
indicating 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 or www.accessdata.fda.gov/cdrh_docs/pdf15/k153466.pdf. (Accessed May 18, 2016)

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

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

In a five-center feasibility study, Eliakim et al. (2009) prospectively compared the second-generation capsule endoscopy (PillCam Colon 2) 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.

Health Quality Ontario (2015) performed a literature search for studies on Pillcam Colon 2 (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 Colon 2 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.

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 (≥6 mm size, or ≥3 polyps irrespective of size) was 58% substantially improving to 86% with the second generation CCE (CCE-2) devices (Eliakim 2009; Spada 2011).

The United States Preventive Services Task Force (USPSTF) 2016 final recommendation statement on colorectal cancer screening (an update to the 2008 USPSTF recommendation) does not include a statement related to the use of the Pillcam Colon 2 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)
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.

In a multicenter randomized double-masked clinical trial, Walters et al. (2015) evaluated the safety and efficacy of dexamethasone as a sustained-release drug depot when placed in the canaliculus for the treatment of ocular inflammation and pain in cataract surgery patients. Patients were randomized (1:1) to receive either the sustained-release dexamethasone or a placebo vehicle punctum plug inserted into the inferior distal canaliculus of the operated eye intraoperatively during cataract surgery. The primary endpoints were the proportions of patients with absence of cells or pain in the anterior chamber at 8 days. Secondary endpoints included cells, flare, pain, and the presence of the device at various timepoints through 30 days. Approximately one fifth (20.7%) of patients in the sustained-release dexamethasone group had an absence of anterior chamber cells at 8 days compared with 10.0% in the placebo group. A higher proportion of patients in the sustained-release dexamethasone group (79.3%) than in the placebo group (30.0%) had an absence of ocular pain at 8 days and at all other timepoints. There were significantly higher proportions of patients in the sustained-release dexamethasone group than in the placebo group with an absence of anterior chamber cells, anterior chamber flare, and pain at several timepoints through 30 days. The investigators concluded that sustained-release dexamethasone provided elution of drug for up to 1 month after cataract surgery, providing clinically significant reductions in inflammation and pain. According to the investigators, the results in this study warrant further examination of the safety and efficacy of the device in a controlled phase III trial.

Chee (2012) assessed the safety and feasibility of a moxifloxacain-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 moxifloxacain 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 moxifloxacain concentrations in the tear film ranged from 155 to

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<td>0356T</td>
<td>Insertion of drug-eluting implant (including punctal dilation and implant removal when performed) into lacrimal canaliculus, each</td>
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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 its 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.

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 change, Bland-Altman plots indicated no proportional bias. However, 95 % limits of agreement were wide (TBW 15-22 L, %fat 19-20 %). According to the authors, BIA may be appropriate for evaluating group level response among severely obese adults. The authors state that clinically meaningful differences in the accuracy of BIA between individuals exist.

Reference(s)


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 bradyarrhythmia. 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 Pacemaker Study
The Micra Transcatheter Pacemaker 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. 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.

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**Omnibus Codes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>0388T</td>
<td>Transcatheter removal of permanent leadless pacemaker, ventricular</td>
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<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>
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<tr>
<td>0390T</td>
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</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>
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</table>
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.

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, nonrandomized, 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 endpoint 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.

No professional society guidelines addressing this technology were identified.

Reference(s)


High dose rate electronic brachytherapy is proven and medically necessary for treating breast cancer.

High dose rate electronic brachytherapy is unproven and not medically necessary for treating nonmelanoma (i.e., basal cell or squamous cell carcinomas) skin cancer.

Additional studies with larger numbers of patients and longer follow-up are needed to confirm preliminary results. High dose rate electronic brachytherapy may be covered for treating certain facial nonmelanoma skin cancers when location can impact treatment outcomes. Requests for these exceptions will be evaluated on a case-by-case basis.

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

Clinical Evidence

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 (ASTRO, 2012).

In a practice guideline on high dose rate brachytherapy, the American College of Radiology (ACR) and the American Brachytherapy Society (ABS) support the use of brachytherapy and do not differentiate between the use of radionuclides or electronic x-ray sources (ACR/ABS, 2015).

Breast Cancer

Strnad et al. (2016) reported 5-year follow-up results from a randomized, phase 3, multicenter, non-inferiority trial, in which accelerated partial breast irradiation (APBI) for patients with stage 0, I, and IIA breast cancer who underwent breast-conserving treatment was compared with whole-breast irradiation. Between April 20, 2004, and July 30, 2009, 1184 patients with low-risk invasive and ductal carcinoma in situ treated with breast-conserving surgery were centrally randomized to either whole-breast irradiation or APBI using multicatheter brachytherapy. 551 patients had whole-breast irradiation with tumour-bed boost and 633 patients received APBI using interstitial multicatheter brachytherapy. The primary endpoint was local recurrence. Analysis was done according to treatment received. At 5-year follow-up, nine patients treated with APBI and five patients receiving whole-breast irradiation had a local recurrence; the cumulative incidence of local recurrence was 1.44% with APBI and 0.92% with whole-breast irradiation. No grade 4 late side-effects were reported. The 5-year risk of grade 2-3 late side-effects to the skin was 3.2% with APBI versus 5.7% with whole-breast irradiation and 5-year risk of grade 2-3 subcutaneous tissue late side-effects was 7.6% versus 6.3%. The risk of severe (grade 3) fibrosis at 5 years was 0.2% with whole-breast irradiation and 0% with APBI. The authors concluded that as the difference between treatments was below the relevance margin of 3 percentage points, adjuvant APBI using multicatheter brachytherapy after breast-conserving surgery in patients with early breast cancer is not inferior to adjuvant whole-breast irradiation with respect to 5-year local control, disease-free survival, and overall survival.

Vaidya et al. (2010) completed a multi-centered, non-blinded, randomized control trial that included 2,232 patients ages 45 and older, with early invasive ductal breast carcinoma suitable for excision who were undergoing breast conserving surgery. Specific population characteristics include median age of 63 years, tumor sizes of <1 cm in 36%, 1-2cm. in 50% and 14% were >than 2 cm. Most tumors were grade 1 (34%) or grade 2 (50%) with 15% being grade 3. Nodes were not involved in 83% of the sample. Nearly half of the patients (1113) were randomly allocated to targeted intraoperative radiotherapy using the Intrabeam system and the other group (1119 patients) was randomly allocated to external beam radiotherapy. A total of 996 patients completed the intraoperative radiotherapy portion of the trial with 854 (86%) receiving targeted therapy alone and 142 (14%) had targeted radiotherapy plus external beam radiotherapy. No significant differences in adverse events, complications or local recurrence were noted between the two groups. Four year follow up noted that for 739 patients at risk, there was no local recurrence in either group. The authors concluded that the targeted intraoperative radiotherapy approach was non-inferior in terms of efficacy of control and “might be adequate for selected patients”.

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<th>Code</th>
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<tbody>
<tr>
<td>0394T</td>
<td>High dose rate electronic brachytherapy, skin surface application, per fraction, includes basic dosimetry, when performed</td>
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<tr>
<td>0395T</td>
<td>High dose rate electronic brachytherapy, interstitial or intracavitary treatment, per fraction, includes basic dosimetry, when performed</td>
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<td>77424</td>
<td>Intraoperative radiation treatment delivery, x-ray, single treatment session</td>
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<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>
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</tbody>
</table>
Accelerated partial breast irradiation (APBI) may be used to deliver radiation to the tumor bed post-lumpectomy in eligible patients with breast cancer. Dooley et al. (2011) describe a lumpectomy procedure and examine patient, tumor and surgical characteristics from a prospective, multicenter study of electronic brachytherapy. 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.

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 11%. Cosmetic evaluation was rated as good or excellent (minimal or no identifiable effects of radiation). The authors concluded that 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. The evidence demonstrates benefits of the therapy given the lack of need for external beam radiation and lack of need for special loading precautions or procedures. Additional patient benefits include decreased toxicity to surrounding tissue.

The National Comprehensive Cancer Network (NCCN) indicates that preliminary studies of accelerated partial breast irradiation (APBI) 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 does not differentiate between intraoperative or cavitary electronic brachytherapy (NCCN, 2016).

Patient selection criteria based on a low risk of recurrence consider age, tumor size, histology, hormone receptor status, surgical margins and nodal status (American Society of Breast Surgeons, 2011; Smith et al., 2009; Shah et al., 2013). Shah et al. (2016) add lymphovascular space invasion (LVSI) to this patient selection criteria.

**Skin Cancer**

Bhatnagar (2013) reported clinical outcomes at 1 year or more after high-dose-rate (HDR) electronic brachytherapy (EBT) using surface applicators for nonmelanoma skin cancer (NMSC). A total of 122 patients with 171 NMSC lesions were treated with EBT to a dose of 40 Gy 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 do not address electronic brachytherapy (NCCN, 2016).

Several clinical trials are ongoing.
**Other Indications**

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

**Reference(s)**


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<th>Code</th>
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<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>
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</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.

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
Three clinical trials of the Verasense in TKA were found on the ClinicalTrials.gov database. Two are randomized and blinded (NCT02290119, NCT02286739) and 1 is an observational study (NCT01469299). These 3 trials will enroll more than 1000 patients undergoing TKA. Results are not presently available from any of these studies.

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)**


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<tbody>
<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>
</tbody>
</table>

**Magnetic resonance image guided high intensity focused ultrasound (MRgFUS) intracranial stereotactic ablation is unproven and not medically necessary for treating movement disorders due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

**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.

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 a case series, Gallay et al. (2016) described the first results of the magnetic resonance (MR)-guided focused ultrasound (MRgFUS) cerebellothalamic tractotomy (CTT). Twenty-one consecutive patients suffering from chronic (mean disease duration 29.9 years), therapy-resistant ET were treated with MRgFUS CTT. Three patients received bilateral treatment with a 1-year interval. Primary relief assessment indicators were the Essential Tremor Rating Scale (ETRS) taken at follow-up (3 months to 2 years) with accent on the hand function subscores (HF16 for treated hand and HF32 for both hands) and handwriting. The evolution of seven patients with HF32 above 28 points over 32 (group 1) differentiated itself from the others' (group 2) and was analyzed separately. Global tremor relief estimations were provided by the patients. Lesion reconstruction and measurement of targeting accuracy were done on 2-day post-
Omnibus Codes

improve biopsy sensitivity with modest effect on biopsy specificity. The author noted that the MelaFind information, when incorporated into the final biopsy MelaFind to 22 of 101 with MelaFind (p = 0.00006) while specificity remained relatively equivalent (23 % vs. 21 %, p < 0.00001). The number of dermatologists detecting over 90 % of specificity (9.2 % vs. 55.9 %, one

Hauschild et al. (2014) performed a randomized two-armed online reader study to determine the biopsy sensitivity to melanoma of dermatologists in Germany and the impact of MelaFind® on their decisions to biopsy melanomas. The study presented case information, clinical/dermatoscopic images of pigmented skin lesions and MelaFind results (Arm 2). Each participant was asked to review 130 pigmented skin lesions. Biopsy decisions of dermatologists without MelaFind versus MelaFind and dermatologists without MelaFind versus dermatologists with MelaFind were compared. Dermatologists without MelaFind had average sensitivity to melanoma of 69.5 % and average specificity of 55.9 %. MelaFind had greater sensitivity than dermatologists alone (96.9 % vs. 69.5 %, one-sided p < 0.00001) and lower specificity (9.2 % vs. 55.9 %, one-sided p < 0.00001). Dermatologists with MelaFind had higher sensitivity than those without MelaFind (78 % vs. 69.5 %, one-sided p < 0.00001) and a lower specificity (45.8 % vs. 55.9 %, one-sided p < 0.00001). The number of dermatologists detecting over 90 % of melanomas increased from 3 of 101 without MelaFind to 22 of 101 with MelaFind (p = 0.00006) while specificity remained relatively equivalent (23 % vs. 21 %, p = 0.99). The author noted that the MelaFind information, when incorporated into the final biopsy decision, can improve biopsy sensitivity with modest effect on biopsy specificity.

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.

Reference(s)


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<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>
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<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>
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</table>

Clinical Evidence

Hauschild et al. (2014) performed a randomized two-armed online reader study to determine the biopsy sensitivity to melanoma of dermatologists in Germany and the impact of MelaFind® on their decisions to biopsy melanomas. The study presented case information, clinical/dermatoscopic images of pigmented skin lesions and MelaFind results (Arm 2). Each participant was asked to review 130 pigmented skin lesions. Biopsy decisions of dermatologists without MelaFind versus MelaFind and dermatologists without MelaFind versus dermatologists with MelaFind were compared. Dermatologists without MelaFind had average sensitivity to melanoma of 69.5 % and average specificity of 55.9 %. MelaFind had greater sensitivity than dermatologists alone (96.9 % vs. 69.5 %, one-sided p < 0.00001) and lower specificity (9.2 % vs. 55.9 %, one-sided p < 0.00001). Dermatologists with MelaFind had higher sensitivity than those without MelaFind (78 % vs. 69.5 %, one-sided p < 0.00001) and a lower specificity (45.8 % vs. 55.9 %, one-sided p < 0.00001). The number of dermatologists detecting over 90 % of melanomas increased from 3 of 101 without MelaFind to 22 of 101 with MelaFind (p = 0.00006) while specificity remained relatively equivalent (23 % vs. 21 %, p = 0.99). The author noted that the MelaFind information, when incorporated into the final biopsy decision, can improve biopsy sensitivity with modest effect on biopsy specificity.
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."

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 of 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 of 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%) (P=.02). The author concluded that MelaFind is a safe and effective tool to assist in the evaluation of pigmented skin lesions.

**Reference(s)**


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<tr>
<td>0402T</td>
<td>Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed)</td>
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</tbody>
</table>

**Collagen cross-linking of cornea analysis is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.**

**Clinical Evidence**

Collagen cross-linking is a technique designed to increase the biomechanical rigidity of the cornea by increasing the biochemical bonds between collagen fibers. This is achieved by local photo-polymerization using ultraviolet-A (UV-A) light and topical riboflavin as a photosensitizing agent. Collagen cross-linking has the potential to reduce the risk of progressive ectasia (particularly in its early stages) and stabilize the corneal contour (American Academy of Ophthalmology (AAO) 2013 Cornea/External Disease Preferred Practice Pattern (PPP) Panel, 2013).

The primary aim of corneal crosslinking is to stop the progression of keratoconus or secondary corneal ectasia, which is a progressive corneal thinning associated with alterations of stromal collagen matrix resulting in irregular protrusion of the cornea. This procedure aims to decrease progressive visual loss due to the evolution of the pathology and delay or avoid invasive surgical procedures such as corneal transplantation (Mastropasqua, 2015).

Bikbova and Bikbov (2016) conducted a randomized controlled trial of 149 eyes of 119 patients with keratoconus I-II of Amsler classification. Patients were divided into two groups: (1) 73 eyes with standard crosslinking (CXL) and (2) 76 eyes with transepithelial iophtithesis-assisted CXL. Depending on the group, epithelium removal or administration of riboflavin solution by iophtithesing for 10 min was performed, after which standard surface UVA irradiation (370 nm, 3 mW/cm²) was performed at a 5-cm distance for 30 min. The authors concluded that transepithelial iophtithesing-assisted collagen crosslinking showed to be less effective than standard CXL after 24 months of follow-up, possibly due to a more superficial formation of corneal collagen crosslinks; however the stopping of disease progression was achieved 24 months after procedure.

Raiskup et al. (2015) conducted a retrospective interventional case series to analyze the 10-year results of corneal collagen crosslinking (CXL) for keratoconus. The study included eyes treated for progressive keratoconus from 2000 to 2004. Corneal collagen crosslinking was performed by applying riboflavin and ultraviolet-A. The corrected distance visual acuity (CDVA), corneal topography, and endothelial cell count (ECC) were recorded preoperatively and 10 years postoperatively. The study enrolled 24 patients (34 eyes). The mean age of the 18 men and 6 women was 28.4 years ± 7.3 (SD) and the mean follow-up, 131.9 ± 20.1 months. The mean apical keratometry (K) value was 61.5 diopters (D) preoperatively and 55.3 D 10 years postoperatively; the decrease was statistically significant (P<.001). The mean
values for maximum K (53.2 D and 49.56 D, respectively) and minimum K (47.5 D and 45.5 D, respectively) were also significantly lower (P<.001). The preoperative and postoperative CDVA were statistically significantly different (P=.002). The mean CDVA improved by 0.14 logMAR over preoperatively; the change was statistically significant (P=.002). The ECC was unchanged. Corneal CXL was effective in treating progressive keratoconus, achieving long-term stabilization of the condition. It was easy to perform, had a good safety profile, and reduced the need for corneal transplantation.

Ali Fayeza et al. (2015) conducted a prospective trial to compare the safety and efficacy of transepithelial with epithelium-off corneal cross-linking for progressive keratoconus. 70 patients with progressive keratoconus were randomized to undergo corneal cross-linking with intact epithelium (n = 34) or after deepithelialization (n = 36). The main outcome measure was a change in the maximum K reading (Kmax). With 3-year follow-up, Kmax decreased in the epithelium-off group with a mean of 2.4 D and no patient showed evidence of progression. In the transepithelial group, Kmax increased by a mean of 1.1 D, and 20 patients (55%) showed progression of keratoconus. The author concluded that in this study epithelium-off was significantly more effective than transepithelial corneal cross-linking in halting the progression of keratoconus (P < 0.0001).

Graue-Hernandez et al. (2015) conducted a consecutive, nonrandomized, interventional clinical study, comprising patients diagnosed with keratoconus, graded I to II according to Amsler Krumeich classification, who were recruited from a single center. The purpose of the study was to report visual, refractive, and topographic outcomes of sequential, same-day small-incision lenticule extraction and intrastromal corneal collagen crosslinking (CXL) in eyes with mild keratoconus. Fifteen eyes with forme fruste keratoconus and/or irregular corneas, corrected distance visual acuity 20/40 or better, with stable refraction of at least 1 year, age 18 years or older, and residual corneal thickness of greater than 400 μm before performing collagen crosslinking were studied. Patients were treated with small-incision lenticule extraction followed by intrastromal injection of riboflavin inside the pocket. Ultraviolet A light with a wavelength of 370 nm to 3 mW/cm² was applied for 30 minutes. Follow-up was done at 1 day, at 1 week, and at 1, 3, 6, 12, 18, and 24 months. Preoperative uncorrected distance visual acuity improved from 1.6 ± 0.3 LogMAR (Snellen 20/796) to postoperative 0.12 ± 0.20 LogMAR (Snellen 20/26) and was statistically significant (P < .001). Best-corrected distance visual acuity did not change significantly (P = .186), from 0.006 ± 0.02 LogMAR (Snellen 20/20) preoperatively to 0.04 ± 0.05 LogMAR (Snellen 20/21) postoperatively, and spherical equivalent improved from -4.3 ± 1.02 preoperatively to 0.2 ± 0.66 (P < .001). Results suggest that combined small-incision lenticule extraction and intrastromal corneal collagen crosslinking are a promising treatment option for patients for whom conventional laser refractive surgery is contraindicated. The authors noted that further follow-up and larger samples are needed to fully confirm these findings.

Said et al. (2014) conducted a prospective clinical trial of 40 patients to investigate the efficacy and safety of corneal collagen cross-linking (CXL) with photoactivated riboflavin (photoactivated chromophore for infectious keratitis [PACK]-CXL) in the management of infectious keratitis with corneal melting. Twenty-one patients (21 eyes) underwent PACK-CXL treatment in addition to antimicrobial therapy. The control group consisted of 19 patients (19 eyes) who received only antimicrobial therapy. The slit-lamp characteristics of the corneal ulceration, corrected distance visual acuity, duration until healing, and complications were documented in each group. The Mann-Whitney U test was used for statistical analysis. P values less than 0.05 were considered statistically significant. Corneal CXL with photoactivated riboflavin did not shorten the time to corneal healing; however, the complication rate was 21% in the control group, whereas there was no incidence of corneal perforation or recurrence of the infection in the PACK-CXL group. The authors concluded that their results indicate that PACK-CXL may be an effective adjuvant therapy in the management of severe infectious keratitis associated with corneal melting.

Hersh et al. (2011) conducted a prospective randomized controlled clinical trial to evaluate 1-year outcomes of corneal collagen crosslinking (CXL) for treatment of keratoconus and corneal ectasia. Collagen crosslinking was performed in eyes with keratoconus or ectasia. The treatment group received standard CXL and the sham control group received riboflavin alone. Principal outcomes included uncorrected (UDVA) and corrected (CDVA) distance visual acuities, refraction, astigmatism, and topography-derived outcomes of maximum and average keratometry (K) value. The UDVA improved significantly from 0.84 logMAR ± 0.34 (SD) (20/137) to 0.77 ± 0.37 logMAR (20/117) (P = .04) and the CDVA, from 0.35 ± 0.24 logMAR (20/45) to 0.23 ± 0.21 logMAR (20/34) (P<.001). Fifteen patients (21.1%) gained and 1 patient lost (1.4%) 2 or more Snellen lines of CDVA. The maximum K value decreased from baseline by 1.7 ± 3.9 diopters (D) (P<.001), 2.0 ± 4.4 D (P = .002), and 1.0 ± 2.5 D (P = .08) in the entire cohort, keratoconus subgroup, and ectasia subgroup, respectively. The maximum K value decreased by 2.0 D or more in 22 patients (31.0%) and increased by 2.0 D or more in 3 patients (4.2%). Collagen crosslinking was effective in improving UDVA, CDVA, the maximum K value, and the average K value. Keratoconus patients had more improvement in topographic measurements than patients with ectasia. The author concluded that both CDVA and maximum K value worsened between baseline and 1 month, followed by improvement between 1, 3, and 6 months and stabilization thereafter.

Li et al. (2015) conducted a meta-analysis to evaluate the efficacy of corneal collagen cross-linking (CXL) for the treatment of keratoconus. The primary outcome measures included changes of topographic parameters, visual acuity,
and refraction. Efficacy estimates were evaluated by weighted mean difference (WMD) and 95% confidence interval (CI) for absolute changes of the interested outcomes. A total of six randomized controlled trials fulfilling the eligibility criteria were included, with a total of 179 eyes in the CXL group, and 182 eyes included in the control group. Duration of follow-up ranged from three months to 36 months. The authors concluded that their findings indicate that CXL is safe and effective for the treatment of keratoconus, which results in significant reductions in corneal topographic measurements, manifest cylinder error, and improvement in visual outcomes. Further studies with long-term duration and larger sample size will be necessary to conclude in stabilization and absence of iatrogenicity for CXL.

Reference(s)

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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.
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.

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.

Borggreve 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 New York Heart Association (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.

Kloppre 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), New York Heart Association classification (NYHA), 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.
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.

No published studies 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
Transurethral waterjet ablation delivers a high-velocity saline stream under precise electromechanical control and live ultrasound guidance to ablate prostatic glandular tissue without producing heat.

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.

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

Reference(s)


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**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 (CSA) is a respiratory condition in which muscles in the diaphragm that control breathing do not receive proper signals from the brain, causing the patient to periodically stop breathing while asleep. 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).

The International Classification of Sleep Disorders (ICSD) identifies 6 different forms of CSA. However, the underlying pathophysiology of central sleep apnea is due to 1 of 2 mechanisms: hyperventilation or hypoventilation (Aurora, 2012).

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)

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)


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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.”

The SpaceOAR is used to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent to reduce the radiation dose delivered to the anterior rectum. The absorbable spacer maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient’s body over time.

For a complete list of indications and contraindications, refer to the Decision Summary at the following website: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN140030. (Accessed April 1, 2016)

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 20 ng/ml). After insertion of the hydrogel spacer, a subsequent MRI scan was performed to facilitate the radiation planning process by easy visualization of the hydrogel spacer. The authors concluded that the study was able to demonstrate the applicability of dose-escalated IMRT with limited radiation doses to the rectum. The decrease in rectal dose was associated with only mild rectal acute toxicity (no grade 2 or higher) which completely resolved after three months. This may result in a low rate of late toxicity. However, further evaluation is necessary including the definition of patients who might benefit from this approach, as well as a larger patient population.

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

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

**Reference(s)**


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<td>Ablation, percutaneous, cryoablation, includes imaging guidance; nerve plexus or other truncal nerve (e.g., brachial plexus, pudendal nerve)</td>
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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.

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<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>

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.

Reference(s)

Omnibus Codes
UnitedHealthcare Commercial Medical Policy

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Page 52 of 115
Effective 07/01/2017
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.

Currently, there are no U.S. Food and Drug Administration (FDA)-approved sustained-release drug delivery systems for glaucoma. A Phase 2, multicenter, randomized, subject- and examiner-masked, controlled clinical trial designed to evaluate the safety and effectiveness of the Bimatoprost Ocular Insert as compared to topical Timolol Solution (0.5%) in patients with glaucoma or ocular hypertension has been completed. The study was sponsored by ForSight Vision5, Inc. No study results have been published or posted on the ClinicalTrials.gov site. See the following for more information: https://www.clinicaltrials.gov/ct2/show/NCT01915940?term=NCT01915940&rank=1. (Accessed March 18, 2016)

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)

The use of suprachoroidal delivery of pharmacologic agent 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.

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

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<th>Code</th>
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<tbody>
<tr>
<td>0444T</td>
<td>Initial placement of a drug-eluting ocular insert under one or more eyelids,</td>
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<td></td>
<td>including fitting, training, and insertion, unilateral or bilateral</td>
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<tr>
<td>044ST</td>
<td>Subsequent placement of a drug-eluting ocular insert under one or more eyelids,</td>
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<td></td>
<td>including re-training, and removal of existing insert, unilateral or bilateral</td>
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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>046ST</td>
<td>Suprachoroidal delivery of pharmacologic agent (does not include supply of medication)</td>
</tr>
</tbody>
</table>
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 andatraumatically 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 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)**


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<tr>
<td>0469T</td>
<td>Retinal polarization scan, ocular screening with on-site automated results, bilateral</td>
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</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: [https://www.accessdata.fda.gov/cdrh_docs/reviews/den130051.pdf](https://www.accessdata.fda.gov/cdrh_docs/reviews/den130051.pdf). (Accessed April 2017)

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)

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<th>Description</th>
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<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>
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</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).

**References**


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<th>Code</th>
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<tbody>
<tr>
<td>22899</td>
<td>Unlisted procedure, spine</td>
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<td>27299</td>
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<td>27599</td>
<td>Unlisted procedure, femur or knee</td>
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<tr>
<td>64999</td>
<td>Unlisted procedure, nervous system</td>
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</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, and the Coolief Transdiscal Cooled RF Probe in 2007 (Baylis Medical, now Halyard Health).

**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.
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 periarticular injections with steroids or botulinum toxin; and limited for both pulsed radiofrequency and conventional radiofrequency neurotomy. The authors recommend this procedure after appropriate diagnosis confirmed by diagnostic sacroiliac joint injections.

In a systematic review, Hansen et al. (2012) evaluated the accuracy of therapeutic sacroiliac joint interventions. With the primary outcome measure as pain relief (short-term relief = up to 6 months and long-term > 6 months) and secondary outcome measures being improvement in functional status, psychological status, return to work, and reduction in opioid intake, the authors concluded that the evidence was fair in favor of cooled radiofrequency neurotomy and poor for short-term and long-term relief from intraarticular steroid injections, periarticular injections with steroids or botulinum 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 SI joint blocks. The authors observed that the majority of patients with chronic SI joint pain experienced a clinically relevant degree of pain relief and improved function following cooled RF of sacral lateral branches and DR of L5 at 3-4 months follow-up.

The American Society of Anesthesiologists 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. Clinical evidence is limited to case studies and small retrospective review. Further studies with well-designed trials are needed to validate the safety and efficacy of cooled RFA in these patient populations.

Reference(s)


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<tr>
<td>28446</td>
<td>Open osteochondral autograft, talus (includes obtaining graft[s])</td>
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</table>

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

Clinical Evidence

Evidence evaluating the use of autograft for osteochondral defects of the talus is still elusive. The use of osteochondral autograft in ankles is limited to retrospective and prospective case series and few randomized controlled trials, nonrandomized controlled trials involving small patient populations and published reviews. Controlled trials with longer follow-up are needed to demonstrate that use of osteochondral autografts as a primary treatment results in improved clinical outcomes. The evidence base is not as robust when compared to that evaluating the knee, although reported clinical outcomes extend short-to intermediate-term; on average two to eight years post-operatively. In general, the clinical outcomes have been mixed regarding improvement in postoperative pain and function, with some authors reporting high failure rates and the need for further surgery.

In 2004 Kolker et al. reported their concern as to the overall efficacy of the procedure when used in the treatment of full-thickness, advanced, osteochondral defects of the talar dome. Open bone grafting did not predictably improve symptoms and yielded poor results in the patient population studied. The authors have acknowledged further well-designed studies with larger sample size are needed to assess improved long-term outcomes (Balzer and Arnold, 2005; Scranton, et al., 2006 Imhoff et al.,2011, Liu et.al, 2011).

Zengerink M, et. al. (2010), The aim of this study was to summarize all eligible studies to compare the effectiveness of treatment strategies for osteochondral defects (OCD) of the talus. For each treatment strategy, study size weighted success rates were calculated. Fifty-two studies described the results of 65 treatment groups of treatment strategies for OCD of the talus. Nine of the studies were for osteochondral transplantation (OATS). OATS scored success rates of 87%, respectively. However, due to great diversity in the articles and variability in treatment results, no definitive conclusions can be drawn. Further sufficiently powered, randomized clinical trials with uniform methodology and validated outcome measures should be initiated to compare the outcome of surgical strategies for OCD of the talus.

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

Reference(s)


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<th>Code</th>
<th>Description</th>
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<tr>
<td>29799</td>
<td>Unlisted procedure, casting or strapping [when used to report Kinesio Taping]</td>
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See [97139](#) for additional information.

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<tr>
<td>30999</td>
<td>Unlisted procedure, nose (Rhinophototherapy, intranasal application of ultraviolet and visible light, bilateral)</td>
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</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**

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 Rhinocconjunctivitis 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.

Leong (2011) reviewed the use of phototherapy in the treatment of allergic rhinitis with particular emphasis on clinical efficacy, scientific basis and safety. Fourteen full-text articles were included in the review. Most studies demonstrated symptomatic improvement and quality of life scores. No improvement in objective measures of nasal airflow was demonstrated. Beneficial effects of phototherapy on inflammatory markers remain equivocal. Phototherapy treatment results in DNA damage but does not appear to predispose to carcinogenesis. However, long-term prospective studies are required to verify this. According to the authors, the quality of published studies was variable and thus the current strength of recommending intranasal phototherapy is currently weak.

A randomized open study was conducted to compare the efficacy of intranasal phototherapy with that of the new generation antihistamine fexofenadine HCl in seasonal allergic rhinitis (SAR). Thirty-one patients were randomly assigned to receive either intranasal irradiation three times a week for 2 weeks or 180 mg fexofenadine HCl per day for 2 weeks. Each patient kept a diary of symptoms for nasal obstruction, nasal itching, rhinorrhea, sneezing and palate itching. In the rhinophototherapy group the individual scores significantly decreased compared with baseline for all of the parameters. In the fexofenadine HCl group none of the scores improved significantly at the end of the treatment except sneezing. TNS was significantly decreased in the rhinophototherapy group after 2 weeks of treatment. In conclusion, the investigators found that intranasal phototherapy is more efficient than fexofenadine HCl.
in reducing clinical symptoms for SAR (Garaczi et al. 2011). Conclusions from this study are limited because of an extremely small number of study participants. These findings require confirmation in a larger study.

Reference(s)

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<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>
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</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
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.

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.
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. Two endobronchial valves are in development for the treatment of emphysema: the IBV - Endobronchial Valve System (Spiration, Inc.) and the Zephyr Endobronchial Valve System (Pulmonx Corporation).

The IBV device is in clinical trials under investigational device exemption (IDE) status from the U.S. Food and Drug Administration (FDA). In October 2008, the FDA approved a humanitarian device exemption (H060002) of the IBV Valve for use in patients who have undergone lung volume reduction surgery or partial or total removal of a lung lobe and who experience prolonged (longer than seven days) air leaks or significant air leaks that may become prolonged.

In October 2007, the FDA granted an expedited review of the premarket approval (PMA) application for the Zephyr EBV for the treatment of emphysema. However, on December 5, 2008, an FDA panel rejected the application. The advisory panel concluded that the clinical studies presented in support of the PMA did not demonstrate reasonable evidence of clinical effectiveness and that more long-term effectiveness data was necessary (Hayes, 2007; ECRI, 2010).

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

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<table>
<thead>
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<tbody>
<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>
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<tr>
<td>31648</td>
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<tr>
<td>31649</td>
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</table>
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 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), Sciruba 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.

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.
Omnibus Codes

Reference(s)


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<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>
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</table>

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

The Watchman™ LAA closure device (Boston Scientific) received FDA premarket approval (P1300013) on March 13, 2015. Additional information is available at:


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).

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).

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).

A Blue Cross Blue Shield Center for Clinical Excellence (CCE) assessment concluded that percutaneous LAA therapy does not meet CCE criteria. The evidence is insufficient to make conclusions about improvement in net health outcomes compared with established alternatives. Randomized controlled trial data do not provide convincing evidence of a treatment benefit or noninferiority compared with anticoagulation for patients for whom anticoagulation...
is not contraindicated. Case series data are inadequate to support conclusions about efficacy in patients for whom anticoagulation is contraindicated. A preventive treatment should have definitive efficacy evidence, particularly when the treatment, a complicated procedure, has known acute risks and complications (BCBS, 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/bleeding tendencies (93%) was the most common reason for warfarin ineligibility. Serious procedure- or device-related safety events occurred in 13 patients (8.7%). All-cause stroke or systemic embolism occurred in 4 patients (2.3% per year): ischemic stroke in 3 patients (1.7% per year) and hemorrhagic stroke in 1 patient (0.6% per year). The authors concluded that the Watchman device is a reasonable alternative for patients at high risk for stroke but with contraindications to systemic oral anticoagulation. This study is limited by lack of randomization and control.

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 although the concept of LAA closure seems reasonable, the evidence of efficacy and safety is currently insufficient to recommend these approaches for any patients other than those in whom long-term oral anticoagulation (OAC) therapy is contraindicated. However, in the absence of controlled clinical data this recommendation is based on expert consensus only. Additional, adequately powered, randomized studies in patients with high stroke risk and long-term follow-up, comparing interventional/percutaneous/surgical LAA closure with OAC therapy are needed for adequate assessment of such techniques (Camm et al., 2012).
American College of Chest Physicians (ACCP) clinical practice guidelines on antithrombotic therapy for the prevention of stroke in patients with AF make no formal recommendations regarding LAA closure devices and state that more definitive research is needed (You et al., 2012).

**Additional Product Information**
- Amplatzer® Cardiac Plug (St. Jude Medical) – not FDA approved at this time
- Amplatzer™ Amulet™ Left Atrial Appendage Ocluder (St. Jude Medical) - not FDA approved at this time
- PLAAQO – no longer on the market
- Watchman FLX – not FDA approved at this time

**Reference(s)**


Omnibus Codes


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<th>Description</th>
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<tr>
<td>88375</td>
<td>Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session</td>
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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 and for the identification of Helicobacter pylori infection.

In a systematic review and meta-analysis, Su et al. (2013) assessed the effectiveness of confocal laser endomicroscopy (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 colonscopic 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.

Sharma et al. (2011) compared the sensitivity and specificity of probe-based confocal laser endomicroscopy (pCLE) in addition to high-definition white-light endoscopy (HD-WLE) with HD-WLE alone for the detection of high-grade dysplasia (HGD) and early carcinoma (EC) in Barrett’s esophagus (BE). The study was a prospective, multicenter, randomized, controlled trial that included 101 consecutive BE patients presenting for surveillance or endoscopic treatment of HGD/EC. All patients were examined by HD-WLE, narrow-band imaging (NBI), and pCLE, and the findings were recorded before biopsy samples were obtained. The order of HD-WLE and NBI was randomized and performed by 2 independent, blinded endoscopists. The sensitivity and specificity for HD-WLE were 34.2% and 92.7%, respectively, compared with 68.3% and 87.8%, respectively, for HD-WLE or pCLE. The sensitivity and specificity for HD-WLE or NBI were 45.0% and 88.2%, respectively, compared with 75.8% and 84.2%, respectively, for HD-WLE, NBI, or pCLE. The authors concluded that pCLE combined with HD-WLE significantly improved the ability to detect neoplasia in BE patients compared with HD-WLE. Additional large-scale randomized controlled trials comparing confocal laser endomicroscopy with standard endoscopy and biopsy in different patient subpopulations are warranted to confirm the findings in this study.

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 Barrett’s esophagus 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 Barrett’s esophagus or neoplasia can provide improved treatment.
Yeung and Mortensen (2011) conducted a systematic review of the literature reporting on the use of new advances in endoscopic visualization including confocal laser endomicroscopy. The review focused on systematic reviews, national guidelines and randomized controlled trials. The authors concluded that although there is mounting evidence that these new technologies are superior to conventional endoscopy, current guidelines are limited and further large-scale randomized controlled trials comparing these modalities in different patient subpopulations are warranted.

According American Gastroenterological Association (AGA) Technical Review on the Management of Barrett’s Esophagus, clinical trials describe some promising preliminary results for advanced imaging techniques such as confocal laser endomicroscopy in the detection of esophageal metaplasia and dysplasia. To date, however, these advanced techniques have not been shown to provide additional clinical information (beyond that available by high-resolution white light endoscopy) sufficient to warrant their routine application in clinical practice (AGA 2011).

Despite these promising findings, the overall quality of the evidence on pCLE for diagnosis of esophageal neoplasia in patients with Barrett’s Esophagus is low. There is insufficient proof that the results of probe-based confocal laser endomicroscopy (pCLE) can definitively obviate the need for 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 (Hayes, 2015).

**Reference(s)**


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**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 (2015) report of reviewed studies suggest that 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.

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.

Reference(s)


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The UroLift system is unproven and not medically necessary for treating benign prostatic hypertrophy due to insufficient clinical evidence of safety and/or efficacy in the published peer-reviewed medical literature. More studies are needed to determine the safety and efficacy of the treatment.

Clinical Evidence
Benign prostatic hypertrophy (BPH) is a proliferative process of the cells of the prostate that affects up to 30% of men over 50 years of age and nearly 70% of men over 70 years of age, including 8 million men in the United States. BPH causes mild to severe lower urinary tract symptoms (LUTS) such as obstruction, incomplete emptying, intermittent, weak stream, hesitancy, frequency, urgency, and nocturia. BPH may result in decreased quality of life and depression. Men with advanced BPH may develop recurrent urinary tract infections, gross hematuria, bladder calculi, or renal insufficiency. (Hayes, 2015)

On March 9, 2013, the U.S. Food and Drug Administration (FDA) approved the marketing of the UroLift® system (Neotrack Inc.), the first permanent implant indicated for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men age 50 and above. The procedure is typically performed by an urologist in the office or other outpatient setting with the use of local anesthesia and oral sedation. The FDA reviewed the UroLift system through its de novo classification process, a regulatory pathway for some novel low to moderate-risk medical devices that are not substantially equivalent to an already legally marketed device. It is classified as a Class II Implantable Transprostatic Tissue Retractor System (product code PEW).

The FDA has since approved subsequent versions of the Urolift. See the following website for additional details: [http://www.accessdata.fda.gov/cdrh_docs/pdf15/k153584.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf15/k153584.pdf). (Accessed May 3, 2016)

Sønksen et al. (2015) conducted a prospective, randomized, non-blinded control study at 10 European centers involving 80 men with BPH LUTS. The purpose of the BPH6 study was to compare prostatic urethral lift (PUL) versus transurethral resection of the prostate (TURP) with regard to LUTS improvement, recovery, worsening of erectile and ejaculatory function, continence and safety. Non-inferiority was evaluated using a one-sided lower 95% confidence limit for the difference between PUL and TURP performance. The final BPH6 responder endpoint is achieved if a participant meets all six of the criteria: LUTS relief, recovery experience, erectile function, ejaculatory function, continence, and safety. Analysis of BPH6 element endpoints at 12 months post procedure demonstrated that TURP was superior in reducing IPSS (p = 0.05), whereas PUL was superior for quality of recovery (p = 0.008) and preservation of ejaculatory function (p < 0.0001). The authors reported that no significant differences were observed for erectile dysfunction, incontinence, or grade II+ adverse events; this may be a result of insufficient study power for detection of differences in these elements of the BPH6. Both PUL and TURP groups achieved significant symptom relief compared to baseline, with a superior symptom relief rate for TURP. PUL was superior to TURP in terms of quality of recovery and preservation of ejaculatory function. Although designed to detect non-inferiority, the authors concluded that the study demonstrated superiority of PUL over TURP in terms of the BPH6 responder endpoint.

Roehrborn et al. (2015). performed a multicenter, randomized, controlled blinded study in 19 centers over three countries (USA, Canada and Australia) and named it L.I.F.T. - Luminal Improvement Following Prostatic tissue Approximation for the treatment of LUTS secondary to BPH. [4] A total of 206 men were randomized (2:1) and treated with prostatic urethral lift (n = 140) or sham control (n = 66). All subjects had no prior surgical treatment, were at least 50 years old and were required to undergo washouts of 2 weeks for a blocker, 3 months for 5 alfa reductase inhibitor and 3 days for anticoagulants. All patients had AUASI ≥ 13, QMAX ≤ 12 mL/s with a 125 mL voided volume and a 30–80 cc prostate. Patients with median lobe obstruction, retention, PVR > 250 mL, PSA > 10, active infection, cystolithiasis within 3 months and bacterial prostatitis were excluded from the study. At 2 years, 106 men treated
with the Urolift® were evaluable for the per-protocol analysis. In these patients, the AUASI score (−9.2 ± 7.57), QoL (−2.2 ± 1.71), and Qmax (mean 4.2 mL per second) remained improved by 42%, 48%, and 58%, respectively (P<0.0001 for all) (Roehrborn et al., 2014). The reduction in the BPRII score was also sustained compared with baseline (−55.6 ± 3.4) (P<0.0001). The authors conclude that implantation of the Urolift® system for treating the symptoms of benign prostate hyperplasia. The authors included 5 case series and one clinical trial. The patients’ mean age ranged from 65-74.3 years, and the mean prostate volume was 41-55cm3. The mean number of Urolift® implants was 3.7-5.5. The maximum follow-up in months was 24, 12 (3 studies) and one (2 studies). Improvements were found in lower urinary tract symptoms, as measured with the International Prostate Symptom Score, Benign Prostatic Hyperplasia Impact Index (BPRII), maximum urinary flow (Qmax) and postvoid residual (PVR) volume. Improvements were found in sexual dysfunction symptoms, as measured with the Sexual Health Inventory for Men (SHIM) and the Male Sexual Health Questionnaire or Ejaculatory Dysfunction (MHSQ-EJD), and in quality of life (QoL). In the clinical trial, the differences were significant for International Prostate Symptom Score, BPRII, Qmax and QoL (p<.05). The adverse effects were mild. Although the quality of evidence is low, the reviewers concluded that the Urolift® constitutes a good therapeutic alternative for patients with benign prostate hyperplasia. The short to medium-term results show that the technique contributes to improving lower urinary tract symptoms, with no relevant side effects, does not affect sexual function and improves quality of life. The authors stated further research is required, especially on long-term results.

Cantwell et al. (2014) conducted a multicenter prospective crossover study of the ‘prostatic urethral lift’ (PUL) for the treatment of lower urinary tract symptoms secondary to BPH. Men aged ≥ 50 years with an International Prostate Symptom Score of ≥ 13, a maximum urinary flow rate (Qmax) of ≤ 12 mL/s, and a prostate of 30-80 mL were enrolled into a crossover study after completing a prospective, randomized, controlled, ‘blinded’ pivotal study in which they were control subjects receiving a sham procedure. Patients were followed for 1 year after crossover PUL at 19 centers in the USA, Canada and Australia. The sham procedure involved rigid cystoscopy with simulated active treatment sounds. PUL involved placing permanent Urolift® implants into the lateral lobes of the prostate to enlarge the urethral lumen. Urinary symptom relief, health-related quality of life (HRQoL) impact, urinary flow parameters, sexual function, and adverse events were assessed and compared between the sham and PUL using paired statistical analysis. Symptom, flow, HRQoL and sexual function assessments showed response improvements from baseline results, similar to results from other published studies, and most parameters were markedly improved after PUL vs the sham procedure in the same patients. Symptom, flow, and HRQoL improvements were durable over the 12 months of the study. Adverse events associated with the procedure were typically transient and mild to moderate; one patient (2%) required re-intervention with transurethral resection of the prostate in the first year. There were no occurrences of de novo, sustained ejaculatory or erectile dysfunction. The authors concluded that the PUL can be performed under local anaesthesia, causes minimal associated perioperative complications, allows patients to quickly return to normal activity, provides rapid and durable improvement in symptoms, and preserves sexual function. Although 19 centers participated in the study, patient sample size was not provided. In addition, longer term outcome data > 12 months is needed.

Shore (2015) reviewed outcomes of PUL, including clinical studies with an estimate of absolute change and either a 95% confidence interval for the change or a standard deviation. The estimates were combined across studies using the inverse of the variances for individual studies for weighting. Per the Fleiss method, homogeneity was assessed, and where the results were found to be significantly heterogeneous, the combined estimate of change was calculated using the heterogeneity adjustment. Shore reports that multiple studies have demonstrated symptom relief that may initiate within 2 weeks and be potentially sustained through 2 years. LUTS-related quality of life, as measured by the IPSS quality of life question and the BPH Impact Index, also improves after PUL. In addition, randomized and open-label studies have demonstrated that PUL can be delivered using local anesthesia (intraurethral and oral medications) with acceptable patient comfort. Post-operative catheterization, when tested via void trial, has been shown to be 20 to 30% with an average duration of less than 1 day. Durability of the PUL system treatment has been demonstrated to 2 years with a mean IPSS improvement of 47–49% at 1 year and 42–45% at 2 years, indicating a stable response. Re-intervention rates for disease progression occur in approximately 7.5% of patients at 2 years. Shore offers that PUL may appeal to men who are earlier in their BPH disease progression due to the procedure being well tolerated and associated with few risks in comparison to most interventional LUTS alternatives. The ability to beneficially affect a population of younger men who traditionally would have received no therapy or marginally tolerated pharmacological therapy may represent a paradigm shift for interventional BPH therapy with the advent of PUL.
Garrido et al. (2013) issued a report of preliminary results of one of the first series of patients treated with a new simple surgical technique for the treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and to evaluate its safety and feasibility. Surgical treatment of BPH, was performed utilizing the UroLift® System (NeoTract, Inc). It opens the urethra directly by retracting the obstructing prostatic lobes without applying incisions, surgical resection or thermal injury to the prostate. The procedure was carried out in 20 patients with a mean age of 74.3 (43 hyphen; -90) years, with mean prostate volume of 42.6 mL (19 hyphen; 109) using the same operative protocol in all case subjects. Mean operative time was 19.1 min (range: 12-45). International Prostate Symptom Score (IPSS) at 4 weeks reduced from 26.7 to 16.7 and peak urinary flow rate (Qmax) increased from 8.6 mL/s to 13.2 mL/s. No major complications were encountered, neither sexual dysfunction. Mean follow-up: 12.3 (2-22) months. The UroLift® System procedure appears to be safe and efficient at short term. This technique minimizes the bleeding of the urethra and, therefore, makes bladder catheter not always necessary, and can preserve sexual function with low morbidity. According to the authors further studies are warranted to determine long-term outcome.

McNicholas et al. (2013) provided a description of the surgical technique and results of a novel minimally invasive implant procedure known as the UroLift that offers symptom relief and improved voiding flow in an international series of patients. The prostatic urethral lift mechanically opens the prostatic urethra with UroLift implants that are placed transurethrally under cystoscopic visualization, thereby separating the encroaching prostatic lobes. A total of 102 men with symptomatic BPH were consecutively treated at seven centers across five countries. Patients were evaluated up to a median follow-up of 1 yr postprocedure. Average age, prostate size, and International Prostate Symptom Score (IPSS) were 68 yr, 48 cm(3), and 23, respectively. All procedures were completed successfully with a mean of 4.5 implants without serious adverse effects. Patients experienced symptom relief by 2 wk that was sustained to 12 mo. Mean IPSS, QOL, and Qmax improved 36%, 39%, and 38% by 2 wk, and 52%, 53%, and 51% at 12 mo (p<0.001), respectively. Adverse events were mild and transient. There were no reports of loss of antegrade ejaculation. A total of 6.5% of patients progressed to TURP without complication. Study limitations include the retrospective single-arm nature and the modest patient number. The authors concluded prostatic urethral lift has promise for BPH. It is minimally invasive, can be done under local anesthesia, does not appear to cause retrograde ejaculation, and improves symptoms and voiding flow. This study corroborates prior published results. Larger series with randomization, comparator treatments, and longer follow-up are underway. More studies are needed to determine the safety and efficacy of the treatment.

The National Institute for Health and Care Excellence (NICE) (2015) in its medical technology guidance on UroLift for treating lower urinary tract symptoms of BPH, that the UroLift should be considered as an alternative to current surgical procedures for use in an outpatient setting in men with lower urinary tract symptoms of benign prostatic hyperplasia who are aged 50 years and older and who have a prostate of less than 100 ml without an obstructing middle lobe. They observed that the degree of symptom relief outcomes is slightly less than that after transurethral resection of the prostate (TURP) or holmium laser enucleation (HoLEP), but it is sufficient and clinically important. Further, they recognized that the duration of symptom relief after using the UroLift system is uncertain and concluded that further evidence on durability and the need for subsequent procedures would be useful, particularly in relation to symptoms and quality of life, the duration of benefit, and the need for further procedures in the longer term.

ClinicalTrials.gov lists ongoing clinical trials that expect to complete by 2017-2018, which may provide longer-term data.

Reference(s)


The insertion of a temporary prostatic urethral stent 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
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:

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 (UVENDA) 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 UVENDA 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.

UnitedHealthcare Commercial Medical Policy

Omnibus Codes

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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.

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 were 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 (AUA, 2010).

Reference(s)


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**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
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.

Reference(s)

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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 the simultaneous visualization of movement of internal body structures, such as the skeleton, intervertebral discs and ligaments, with corresponding external body movement. All of these methods use x-rays to create images either on film, on a video monitor, or on a computer screen. The Spinalyzer is used to visualize and measure the distortion of the spine and skeletal structure.

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

The current literature evaluating the clinical utility of dynamic spinal visualization techniques, including but not limited to digital motion x-ray and cineradiography (videofluoroscopy), for the evaluation and assessment of the spine is limited to a few studies involving very 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.

A 2011 guideline from the American College of Occupational and Environmental Medicine states that for the assessment of acute, subacute, or chronic LBP, videofluoroscopy was “Not Recommended, Insufficient Evidence.”

Reference(s)

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Omnibus Codes
UnitedHealthcare Commercial Medical Policy
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Serum proteomic profiling, using mass spectrometry, is proven and medically necessary for guiding treatment decisions in patients with advanced non-small cell lung cancer (NSCLC) being considered for second-line therapy with an epidermal growth factor receptor (EGFR) inhibitor, such as erlotinib, and whose EGFR mutation status is wild-type (no mutation detected) or unknown.

Clinical Evidence
The VeriStrat® serum-based biomarker test (Biodesix Inc.) is intended to help identify patients with advanced NSCLC who are more likely to benefit from treatment with an EGFR inhibitor. The test stratifies patients into two categories: those with significantly better (Good) and those with significantly worse (Poor) outcomes following treatment with EGFR inhibitor therapy. VeriStrat is not an EGFR mutation test (Biodesix website).

A multicenter, randomized phase III study (PROSE) assessed the predictive power of the VeriStrat test in patients with non-small cell lung cancer treated with second-line erlotinib or chemotherapy. Patients (aged ≥18 years) with histologically or cytologically confirmed, second-line, stage IIIIB or IV non-small-cell lung cancer were included. Patients were stratified according to Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, and center and masked pretreatment serum protein test classification, then randomly assigned in a 1:1 ratio to receive oral erlotinib or intravenous chemotherapy (pemetrexed or docetaxel). The proteomic test classification was masked for patients and investigators who gave treatments, and treatment allocation was masked for investigators who generated the proteomic classification. The primary endpoint was overall survival. One hundred and forty two patients were randomly assigned to chemotherapy and 143 to erlotinib, and 129 (91%) and 134 (94%), respectively, were included in the per-protocol analysis. Eighty eight (68%) patients in the chemotherapy group and 96 (72%) in the erlotinib group had a proteomic test classification of good. Median overall survival was 9.0 months in the chemotherapy group and 7.7 months in the erlotinib group. The authors noted a significant interaction between treatment and proteomic classification. Patients with a proteomic test classification of poor had worse survival on erlotinib than on chemotherapy. There was no significant difference in overall survival between treatments for patients with a proteomic test classification of good. The authors concluded that these findings indicate that serum protein test status is predictive of differential benefit in overall survival for erlotinib versus chemotherapy in the second-line setting. Patients classified as likely to have a poor outcome have better outcomes on chemotherapy than on erlotinib (Gregorc et al., 2014).

A meta-analysis of seven studies (n=706) found that patients with a “Good” status using the VeriStrat test had better clinical outcomes with regard to overall survival and progression-free survival compared to patients with a “Poor” status (Sun et al., 2014).

An ECRI report concluded that evidence from prognostic studies and a meta-analysis suggests that VeriStrat successfully differentiated patients with NSCLC whose disease responded well to erlotinib treatment as measured by improved progression-free survival and/or overall survival. The evidence is relatively consistent in showing statistically significant associations between VeriStrat test results (“Good” versus “Poor”) and one or more outcomes related to disease prognosis (response to erlotinib treatment, progression-free survival and/or overall survival). Patients with a test result categorized as “Good” were more likely to have better treatment response, longer progression-free survival, and longer overall survival than patients with a test result categorized as “Poor” (ECRI, 2015).

Stinchcombe et al. (2013) performed a retrospective analysis of ninety-eight plasma or serum samples collected as part of a randomized phase II trial to investigate the ability of VeriStrat (VS) to predict treatment outcomes. In the original trial, patients were randomized into three treatment groups: gemcitabine (arm A), erlotinib (arm B) and gemcitabine and erlotinib (arm C). The majority of patients had stage IV disease (81%), adenocarcinoma histology (63%) and reported current or previous tobacco use (84%). Similar progression-free survival (PFS) and overall survival (OS) were observed in all arms. In arm A, patients with VS Good (n=20) compared with VS Poor status (n=8) had similar PFS. In arm B, patients with VS Good (n=26) compared with VS Poor (n=12) had a statistically significantly superior PFS. In arm C, patients with VS Good (n=17) compared with Poor (n=15) had a superior PFS and a trend toward superior OS.

In a retrospective analysis, Akerley et al. (2013) assessed the impact of the VeriStrat test on physician treatment recommendations for patients with non-small-cell lung cancer (NSCLC). Pre- and post-test treatment recommendations were collected from ordering physicians on a voluntary basis. Only those tests that had both pre- and post-test treatment information were included in the analysis group. Over the duration of the study, 724 physicians ordered 2854 tests. The analysis group comprised the 226 physicians who provided pre- and post-test treatment information (n=403 tests). Following receipt of the test results, 90.3% of patients who tested as Good received erlotinib recommendations versus 9.6% of patients who tested as Poor. Ninety percent of post-test treatment recommendations positively correlated with test results, with 40% showing a change from pre-test considerations.

Omnibus Codes
UnitedHealthcare Commercial Medical Policy
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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure [when used to report VeriStrat]</td>
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The authors concluded that, among test orderers, serum-based proteomic mass spectrometry testing significantly influenced therapy recommendations in NSCLC. Usage patterns should be monitored as use expands. Lazzari et al. (2012) reported similar results in a separate retrospective study.

Carbone et al. (2012) investigated the predictive and prognostic effects of VeriStrat (VS) on response and survival in a subset of patients enrolled in a phase III trial of erlotinib versus placebo in previously treated advanced non-small-cell lung cancer patients. Pretreatment plasma samples were available for 441 of 731 enrolled patients. VS testing was successful in 436 samples (98.9%), with 61% classified as Good. VS was prognostic for overall survival in both erlotinib-treated patients and those on placebo. For VS Good patients, the median survival was 10.5 months on erlotinib versus 6.6 months for placebo. For VS Poor patients, the median survival was 4 months for patients receiving erlotinib, and 3.1 months for placebo. The authors reported that VS was able to predict response to erlotinib and was a prognostic biomarker in previously treated patients with advanced NSCLC. However, for both overall survival and progression-free survival, VS was not predictive of differential survival benefit versus placebo.

Taguchi et al. (2007) developed and evaluated the proteomic assay that is the basis for the VeriStrat test. Pretreatment serum mass spectrometry analysis of 139 NSCLC patients who were later treated with erlotinib or gefitinib was used to develop an algorithm to predict which patients might benefit from treatment with these agents. A predicted "good" outcome was associated with longer median time to progression and longer overall median survival, when compared with a predicted "poor" outcome.

National Comprehensive Cancer Network (NCCN) guidelines recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. The guidelines state that patients with a “poor” classification should not be offered erlotinib in the second-line setting (NCCN, 2016).

Reference(s)


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<tr>
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<tr>
<td>85547</td>
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The use of red blood cell mechanical fragility testing is unproven and not medically necessary due to insufficient clinical evidence of safety and/or efficacy in published peer-reviewed medical literature.

Clinical Evidence
Mechanical fragility of red blood cells (RBCs) is a critical variable for the hemolysis testing of many important clinical devices, such as pumps, valves, cannulae and gas exchange devices. Unfortunately, no standardized test for RBC mechanical fragility is currently well accepted. Although many test devices have been proposed for the study of mechanical fragility of RBCs, no one has ever shown that their results have any relevance to a blood pump (Gu et al., 2005).

This test is considered obsolete by CMS and other lab references.
Reference(s)

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<thead>
<tr>
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<tr>
<td>86849</td>
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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 fetal loss. Research shows variable sensitivity and a lack of standardization with available tests.

In a practice bulletin, the American College of Obstetricians and Gynecologists (ACOG) makes the following recommendations based on limited or inconsistent scientific evidence:

- Obstetric indications for antiphospholipid antibody testing should be limited to a history of one fetal loss or three or more recurrent embryonic or fetal losses.
- Testing for antiphospholipid antibodies should be performed in women with a prior unexplained venous thromboembolism, a new venous thromboembolism during pregnancy or in those with a history of venous thromboembolism but not tested previously.
- In women with antiphospholipid syndrome (APS) and a history of stillbirth or recurrent fetal loss but no prior thrombotic history, prophylactic doses of heparin and low-dose aspirin during pregnancy and 6 weeks of postpartum should be considered. (ACOG, 2012).

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. 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 1, cardiolipin and for lupus anticoagulant activity. These investigators demonstrated a high degree of concordance between the concentrations of aPS/PT measured with the in-house and commercial assays. Both assays performed comparably relating to the clinical manifestations of APS, such as arterial and venous thromboses and obstetric complications. IgG aPS/PT represented the strongest independent risk factor for the presence of obstetric complications, among all tested aPL. Both IgG and IgM aPS/PT were associated with venous thrombosis, but not with arterial thrombosis. Most importantly, the association between the presence of IgG/IgM aPS/PT and lupus anticoagulant activity was highly significant. The authors concluded that aPS/PT antibodies detected with the in-house or commercial ELISA represent a promising serological marker for APS and its subsets.
Antiprothrombin antibody testing for the diagnosis of APS is a procedure and therefore not subject to FDA regulation. However, any medical devices, drugs, biologics, or tests used as part of this procedure may be subject to FDA regulation.

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

Reference(s)

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<tr>
<td></td>
<td>Multifocal Electoretinography (mfERG) and Pattern Electoretinography (PERG)</td>
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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 provides 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.

Browning et al. (2014) conducted a study to determine the relative sensitivity and specificity of 10-2 visual fields (10-2 VF), multifocal electoretinography (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 electoretinography, which were designed as objective measures of visual function, provide testing free of patient input, but issues prevent their adoption for glaucoma
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 retinotoxicity in patients using these medications. To evaluate the sensitivity and specificity of mfERG when compared with automated visual fields (AVFs), FAF, and OCT. The 2011 AAO recommendations on screening for CQ/HCQ retinopathy recommended a shift toward more objective testing modalities. Multi-focal ERG may be effective in detecting functional change before irreversible structural damage from CQ/HCQ toxicity. These investigators performed a search for records reporting the use of mfERG for screening CQ/HCQ retinopathy in MEDLINE (PubMed and OVID), EMBASE, and Web of Science, and assessed these using the QUADAS-2 risk of bias tool. They conducted an analysis of 23 individual studies and their reported individual patient data (449 eyes of 243 patients) published from January 2000 to December 2014. Multi-focal ERG had the greatest proportion of positive test results, followed by AVF. The pooled sensitivity and specificity of mfERG were 90 % (95 % confidence interval [CI]: 0.62 to 0.98) and 52 % (CI: 0.29 to 0.74), respectively, with AVF as reference standard (13 studies). Sensitivity was high, but specificity was variable when OCT, FAF, and the positivity of 2 of 3 tests was used as the reference standard. When verified against AVF as the reference test, patients with a false-positive mfERG result received higher HCQ cumulative doses (1,068 g) than patients with true-negative (658 g, p < 0.01) and false-negative (482 g, p < 0.01) results. The authors concluded that mfERG was shown to have a high sensitivity but variable specificity when verified against AVF, OCT, FAF, and a combination of tests. The greater average cumulative dose in the false-positive group compared with the true-negative group when mfERG was verified against AVF suggested that mfERG may have the ability to detect cases of toxicity earlier than other modalities. In addition, they state that there is an unclear risk of bias in the available evidence, and future studies should adhere to Standards for Reporting of Diagnostic Accuracy reporting guidelines.

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

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

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

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

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

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

Banitt et al. (2013) conducted a longitudinal cohort study that included 107 adults (201 eyes) at risk of glaucoma and compared pattern electroretinography (PERG) amplitudes and optical coherence tomography (OCT) imaging of retinal nerve fiber layer (RNFL) over a 4-year period in order to determine the time lag between loss of retinal ganglion cells (RGC) function and loss of RNFL thickness. RNFL thickness did not decrease until the PERG amplitude had lost at least 50% of its normal value for age, indicated by post hoc comparisons showing highly significant differences between RNFL thicknesses of eyes in the stratum with the most severely affected PERG amplitude (≤ 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)
Browning DJ, Lee C. Relative sensitivity and specificity of 10-2 visual fields, multifocal electroretinography, and spectral domain optical coherence tomography in detecting hydroxychloroquine and chloroquine retinopathy. Dovexpress. 2014 July 2014:8
Peripheral arterial disease rehabilitation 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.

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 program involving only walking and a combination of exercises, nor between individual and group training.

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)


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

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

Erdogan et al. (2015) conducted a small study of 37 patients with breast cancer who underwent bioimpedance spectroscopy to assess lymphedema. During a one-year follow-up period where investigators used bioimpedance measures, a statistically 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.

A prospective study by Berlit et al. (2012) evaluated resistance (R) and phase angle (Pa) determined by single-frequency whole-body bioelectrical impedance analysis (BIA) as predictors for the early onset of edema of the upper limb in 33 patients undergoing surgical treatment for breast cancer. Whole-body BIA was performed before surgery, as well as at two days, at one and three months after surgery. Four patients developed an edema of the upper limb.
within the first three months after surgery. Both analyzed parameters showed a fairly good performance in terms of sensitivity (R=75%, Pa=75%) and specificity (R=86%, Pa=83%). The positive predictive values of 43% (R) and 38% (Pa) were unsatisfactory, whereas the negative predictive values were 96% for both parameters. The authors concluded that Pa, as well as R, in whole-body BIA can be used to rule out a developing edema of the upper limb. This study is limited by lack of a control and small sample size.

Smoot et al. (2011) compared diagnostic accuracy of measures of breast cancer-related lymphedema (BCRL). Cross-sectional design comparing clinical measures with the criterion standard of previous diagnosis of BCRL. Sensitivity, specificity, receiver operator characteristic curve and area under the curve (AUC) were used to evaluate accuracy. A total of 141 women were categorized as having (n=70) or not having (n=71) BCRL based on past diagnosis by a health care provider, which was used as the reference standard. Analyses of ROC curves for the continuous outcomes yielded AUC of .68 to .88; of the physical measures bioimpedance spectroscopy yielded the highest accuracy with an AUC of .88 for women whose dominant arm was the affected arm. The lowest accuracy was found using the 2-cm diagnostic cutoff score to identify previously diagnosed BCRL (AUC, .54-.65). The authors concluded that these findings support the use of bioimpedance spectroscopy in the assessment of existing BCRL; however, further investigation is warranted.

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).

Reference(s)


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<tr>
<td>93799</td>
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<tr>
<td>94799</td>
<td>Unlisted pulmonary service or procedure [when used to report inert gas rebreathing]</td>
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</table>

The use of inert gas rebreathing 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

This technique is based on the observation that the absorption and disappearance of a blood-soluble gas is proportional to cardiac blood flow. The patient is asked to breathe and rebreathe from a rebreathing bag filled with oxygen mixed with a fixed proportion of two inert gases; typically nitrous oxide and sulfur hexafluoride. The nitrous oxide is soluble in blood and is therefore absorbed during the blood’s passage through the lungs at a rate that is proportional to the blood flow. The sulfur hexafluoride is insoluble in blood and therefore stays in the gas phase and is used to determine the lung volume from which the soluble gas is removed. These gases and carbon dioxide are measured continuously and simultaneously at the mouthpiece.

A Hayes report on noninvasive hemodynamic monitoring concluded that the evidence was insufficient to assess the safety and/or impact on health outcomes or patient management using the Innocor system of inert gas rebreathing in children with cardiac disease (Hayes, 2014).
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 bioimpedance. 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 New York Heart Association (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 important 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.

Jakovljevic et al. (2008) compared cardiac output determined by different rebreathing methods at rest and at peak exercise. The aims of the study were threefold: first, to compare values for resting Q (T) produced by the equilibrium-CO(2), exponential-CO(2) and inert gas-N(2)O rebreathing methods and, second, to evaluate the reproducibility of these three methods at rest. The third aim was to assess the agreement between estimates of peak exercise Q (T) derived from the exponential and inert gas rebreathing methods. A total of 18 healthy subjects visited the exercise laboratory on different days. Two more exercise tests were used to measure Q (T) at peak exercise using the IGR method. The exponential method produced significantly higher estimates at rest (averaging 10.9 l min(-1)) compared with the equilibrium method (averaging 6.6 l min(-1)) and the inert gas rebreathing method (averaging 5.1 l min(-1); P < 0.01). All methods were highly reproducible with the exponential method having the largest coefficient of variation (5.3%). At peak exercise, there were non-significant differences between the exponential and inert gas rebreathing methods (P = 0.14). The limits of agreement were -0.49 to 0.79 l min(-1). Due to the ability to evaluate the degree of gas mixing and to estimate intra-pulmonary shunt, we believe that the inert gas rebreathing method has the potential to measure Q (T) more precisely than either of the CO(2) rebreathing methods used in this study. At peak exercise, the exponential and inert gas rebreathing methods both showed acceptable limits of agreement.

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 Innocor 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 Innocor 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)**


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

**Spirometry** and other pulmonary function tests are unproven and not medically necessary in children under the age of three due to insufficient evidence of safety and/or efficacy 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 2009 guideline, published jointly with the European Respiratory Society, the American Thoracic Society (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)**


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<td>96902</td>
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**Clinical Evidence**

Trichograms are the microscopic examination of hair and identifies hair growth rate and anagen (hair growth) and 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 reference(s). 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)**


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<tr>
<td>97139</td>
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**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 telogen (hair resting phase) ratio. Alopecia is the most common indication for completing this test.

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.

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.

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.

Martinez-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 byVAS, 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 tendonitis 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.

Reference(s)
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.

Lajeunesse et al. (2015) conducted a literature review to evaluate the exoskeletons’ (Rewalk™, Mina, Indego® and Rex®) design and usefulness for functional mobility by people with spinal cord injury. The authors noted exoskeleton use is effective for walking in a laboratory but there are no training protocols to modify identified outcomes over the term usage (Rewalk™: 3 months, Mina: 2 months and Indego®: 1 session). Levels of evidence of selected papers were low. The authors concluded applicability and effectiveness of lower limb exoskeletons as assistive devices in the community have not been demonstrated. More research is needed on walking performance with these exoskeletons compared to other mobility devices and other training contexts in the community.

ECRI (2016) conducted an evidence review of medical literature to evaluate powered wearable exoskeletons in the rehabilitation and community settings. The evidence for powered wearable exoskeleton use by patients with SCI was limited to 10 short-term noncomparative studies: 7 assessed the ReWalk, 1 assessed the Ekso GT, and 2 assessed the Indego. These studies included outcomes data on only 129 patients with SCI who underwent exoskeleton training in rehabilitation centers: 60 using a ReWalk exoskeleton, 7 using an Ekso GT exoskeleton, and 56 using an Indego exoskeleton. The authors concluded with a low level of confidence that after ReWalk training, some patients with SCI who were unable to walk can walk unassisted for a short distance at a slow rate of speed in a rehabilitation setting, and that a few of those who learned to walk also learned to ascend and descend stairs with assistance in that setting. The authors also concluded with low confidence that with minimal assistance some patients with SCI who were unable to walk or had difficulty walking can walk for a short distance at a slow rate of speed and walk on outdoor surfaces, ramps, and grass wearing an Indego exoskeleton in a rehabilitation setting. 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. There were no studies reported on powered exoskeleton use for ongoing therapeutic exercise in a rehabilitation setting, and no studies compared the safety and efficacy of powered exoskeletons with those of conventional rehabilitative strategies.

In addition, ECRI (2016) noted that although three powered exoskeletons are commercially available for personal use, no studies assess short- or long-term safety and efficacy of these devices in the home/community setting. Thus, 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 (QOL) compared with other assistive devices used to enable standing or mobility is not possible at this time. Patients with SCI likely require continued, long-term use of a powered exoskeleton in a home/community setting to maintain any potential improvements in health and QOL achieved during training, so long-term comparative studies that assess pain, spasticity, bowel/bladder function, skin integrity, degree of independence in performing activities of daily living, and potential device-related adverse events are needed.

Buesing et al. (2015) completed a study which compared the effects of the Stride Management Assist (SMA®) System, a new wearable robotic device developed by Honda R&D Corporation, Japan, with functional task specific training (FTST) on spatiotemporal gait parameters in stroke survivors. SMA and FTST interventions provided similar, significant improvements in spatiotemporal gait parameters; however, the SMA group showed additional improvements across more parameters at various time points. These results indicate that the SMA® device could be a useful therapeutic tool to improve spatiotemporal parameters and contribute to improved functional mobility in stroke survivors. Further research is needed to determine the feasibility of using this device in a home setting versus a clinic setting, and whether such home use provides continued benefits.

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<th>Code</th>
<th>Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with remote analysis and report</th>
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<tbody>
<tr>
<td>99174</td>
<td>Instrument-based ocular screening (e.g., photoscreening, automated-refraction), bilateral; with on-site analysis</td>
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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, 2014) 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).

Yanovitch et al. (2010) evaluated the sensitivity, specificity, and positive and negative predictive values of photoscreening in detecting treatable ocular conditions in children with Down syndrome (DS). Photoscreening and complete ophthalmologic evaluations were performed in 50 consecutive 3- to 10-year-old children with DS. Most children were able to complete photoscreening (94% with Medical Technology and Innovations [MTI] and 90% with Visiscreen OSS-C [VR]). Many children had an identified diagnosis on ophthalmologic examination (n = 46, 92%). Of these, approximately one-half (n = 27, 54%) had one or more condition(s) requiring treatment. Both the MTI and VR photoscreening devices had a sensitivity of 93% (95% confidence interval 0.76-0.99) for detecting treatable ocular conditions. The specificities for the MTI and VR photoscreening were 0.35 (0.18-0.57) and 0.55 (0.34-0.74), respectively. The authors concluded that photoscreening is sensitive but less specific at detecting treatable ocular conditions in children with DS. In specific instances, the use of photoscreening in the DS population has the potential to save time and expense related to routine eye examinations, particularly in children with a normal baseline comprehensive examination.

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%.

In an Agency for Healthcare Research and Quality (AHRQ) Evidence Synthesis for Screening for Visual Impairment in Children, Chou, et al. (2011) identified 15 studies (13 fair-quality and 2 poor-quality) that evaluated the diagnostic accuracy of photoscreeners. According to the authors of this report, there is good evidence that commonly used visual acuity tests, stereoaucuity tests, cover-uncover tests, autorefractors, and photoscreeners are useful for screening, though differences among studies in the populations evaluated, screening tests evaluated, screening thresholds applied, and target conditions sought make it difficult to reach strong conclusions about how they compare with one another. Screening tests were generally associated with a high rate of false-positives in low-prevalence populations which could result in unnecessary prescription of eyeglasses. The authors stated that evidence on when to initiate preschool screening remains limited. The authors concluded that direct evidence on effectiveness of preschool vision screening for improving visual acuity or other clinical outcomes remains very limited and does not adequately address the question of whether screening is more effective than no screening. However, good evidence on diagnostic accuracy and treatments suggest that preschool vision screening could lead to increased detection of visual impairment and greater improvement in visual outcomes than if children were never screened. According to the authors, additional studies are needed to better understand effects of screening compared with no screening, to clarify the risk for potential unintended harms from screening (such as use of unnecessary treatments), and to define optimal time at which to initiate screening during the preschool years.

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 autorefractor.
      - For visual acuity testing, appropriately scaled (logMAR) single crowded HOTV letters or LEA Symbols surrounded by crowding bars at a 5-ft (1.5-m) test distance with the child matching or reading the optotypes aloud should be used. A passing score is the correct identification of three of three or three of four optotypes with each eye at the 20/50 level for children aged 36 through 47 months and at the 20/40 level for children aged 48 to younger than 72 months. Acceptable practices are to use the HOTV or LEA Symbols calibrated for a 10-ft (3-m) test distance or to use a single line of these optotypes surrounded by a rectangular crowding bar on all four sides. Other optotypes like Allen pictures and the Tumbling E should not be used.
      - The other best practice vision screening method is instrument-based screening using either the Retinomax autorefractor or the SureSight Vision Screener set in child mode and programmed with the VIP Study pass/fail criteria software for 90% specificity (version 2.24 or 2.25) in minus cylinder form. Using the Plusoptix photoscreener is considered acceptable practice, as is adding the PASS stereoacuity test as a supplement to one of the best practice screening methods.
- Vision screening requires training and certification of screening personnel, acquiring sufficient and appropriate space, obtaining and maintaining equipment and supplies, as well as recording and reporting the screening results to the family, primary care provider/medical home, and when indicated the school or appropriate state agency.
- A best practice for children who fail vision screening includes documentation of the referral to and subsequent comprehensive eye examination by an optometrist or ophthalmologist.

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)

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<tr>
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<th>Description</th>
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<tr>
<td>L3999</td>
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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/](http://www.myopro.com/). (Accessed May 18, 2016)

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.

**Reference(s)**

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

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); whiles only 5 control patients were able to walk independently. At the 2-month follow-up, the participants used...
their VASS prostheses for 62 hours a week, which was significantly longer than the control group using the standard prosthesis for 5 hours per week (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.

In a randomized, cross-over study, Klute et al (2011) evaluated the effect of a VASS system compared with pin suspension in patients with lower extremity amputations (n=20). Interventions included total surface-bearing socket with a VASS, and modified patellar tendon-bearing socket with a pin lock suspension system. Study results suggest that patient activity levels were significantly lower with the VASS system compared with the pin suspension (P=0.0056). In addition, residual limb positioning was significantly less with the VASS system compared with the pin suspension (P=0.00210). Subjectively, patients reported better overall outcomes with the pin suspension system than VASS. The study authors observed that the VASS resulted in a significantly improved socket fit (measured by limb movement) compared with the prosthetic socket; however, the clinical relevance of this improvement is not clear. The study was limited by the lack of patient- and clinically-relevant functional outcomes to properly assess the effect of VASS and pin suspension systems in amputees.

No professional society guidelines addressing this technology were identified.

Reference(s)

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<tbody>
<tr>
<td>0377T</td>
<td>Anoscopy with directed submucosal injection of bulking agent for fecal incontinence</td>
</tr>
<tr>
<td>L8605</td>
<td>Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, anal canal</td>
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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 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 gastrourolgy use) and not a drug. Solesta Injectable Gel (Salix Pharmaceuticals Inc.) received FDA premarket approval (PMA) on May 27, 2011 (P100014). See the following website for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=p100014. (Accessed May 18, 2016)

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, October 2014. Updated October 2015.)

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.

Danielson 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. The authors stated that the treatment has a potential to improve QoL. According to the authors, a 75% decrease in incontinence episodes may be a more accurate threshold to indicate a successful incontinence treatment than the more commonly used 50%. Study limitations include the lack of controls and a small study population.

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

In a 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.
Reference(s)

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<th>Description</th>
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<tr>
<td>P2031</td>
<td>Hair analysis (excluding arsenic)</td>
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Laboratory analysis of hair for content of environmental substances of concern for exposure assessment and health interpretation of the results is unproven and not medically necessary 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 disorders such as mineral or protein deficiency or mineral toxicity. Hair analysis has not been proven to be effective in ascertaining mineral or metabolic imbalances or IgE-mediated allergic diseases. Hair analysis has also not been proven to be of use in either the diagnosis or treatment of conditions such as autism, schizophrenia, and mood disorders.

Wolowiec et al. (2013) conducted a systematic review on the relation between the mineral composition of hair and physical or mental disorders. Sixty-six studies were included in the review. Most of the authors 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.

While hair analysis is useful during a forensic exam, its use 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 reference(s). Interpretation is 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).

Hirano et al. (2011) evaluated hair shaft abnormalities in 65 individuals with ectodermal dysplasia (ED) syndromes using light microscopy and compared findings with those in 41 unaffected controls. Light microscopy identified various pathologic hair shaft abnormalities in each type of ED, although none of the findings were statistically significantly different from those of the control group. According to the authors, light microscopy is a poor adjuvant tool in the diagnosis of ED syndromes. Most findings are nonspecific and not sufficiently sensitive.

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.

Several guidelines provide a discussion of hair analysis, 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

Reference(s)
American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and
American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology. Bernstein IL, Li JT,
diagnosis of autism: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Child Neurology
UK: NICE; February 2011.
National Institute of Allergy and Infectious Diseases (NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, et al.
Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J
Niggemann B, Gruber C. Unproven diagnostic procedures in IgE-mediated allergic diseases. Allergy. 2004;59(8):806-808
Passalacqua G, Compalati E, Schiappoli M, Senna G. Complementary and alternative medicine for the treatment and diagnosis of
Tamburo E, Varrica D, Dongarrà G, et al. Trace elements in scalp hair samples from patients with relapsing-remitting multiple
10.1016/j.cca.2013.02.001.
Younge JO, Wester VL, van Rossum EF, et al. Cortisol levels in scalp hair of patients with structural heart disease. Int J Cardiol. 2015
Feb 10;184C:71-78.

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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>P2033</td>
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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)
U.S. Department of Health and Human Services, Center for Medicare & Medicaid Services (CMS). Obsolete or unreliable diagnostic

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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)
Radiesse is proven and medically necessary and reconstructive for treating the following:

- Facial defects due to facial lipidatrophy in persons with human immunodeficiency virus (HIV)
- 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) categorizes Radiesse and Sculptra as medical devices (injectable implants).

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 lipidatrophy, 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 May 3, 2016)

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 May 3, 2016)

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 bilateral defects. 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).

Reference(s)


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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®
- Amnioband
- AmnioExcel™ or Biodexcel™
- AmnioGen-A™, AmnioGen-C™, AmnioGen-45™, or AmnioGen-200™
- Amnionmatrix™ or Biodmatrix™
- AmnioPro™, BioRenew™, BioSkin™, or WoundEx™
- AmnioPro™ Flow, BioRenew™ Flow, BioSkin™ Flow, or WoundEx™ Flow
• Architect Extracellular Matrix®
• Artacent®
• Bio-ConneKt®
• Biodfence™ or Biodfence Dryflex™
• Biovance®
• Clarixflo®
• Cygnus™
• Cytal™
• Dermapure™
• Dermavest® or Plurivest
• Epicord™
• Epifix®
• Excellagen®
• Ez-derm®
• Grafix®
• Guardian
• Helicoll™
• Hmatrix®
• Interfyl™
• Keramatrix®
• Marigen™
• Mediskin™
• Miroderm™
• Neox®
• Neoxflo®
• Nushield
• PalinGen® Amniotic Tissue Allograft and PalinGen® Flow products
• ProMatrX™
• PuraPly™ or PuraPly™ Antimicrobial
• Repriza®
• Revitalon®
• Tensix®
• Truskin™
• 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 (AlloSource) 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 (allofibroblasts 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.

**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 matrices 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 wounds (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.

**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 processed from human amniotic and placental tissues.

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.

**AmnioPro, BioRenew, BioSkin, WoundEx**

AmnioPro, BioRenew, BioSkin, and WoundEx are wound coverings, surgically applied to the skin in the treatment of chronic acute and surgical wounds. These are made of decellularized human amniotic membrane.

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

**AmnioPro Flow, BioRenew Flow, BioSkin Flow, WoundEx Flow**

AmnioPro Flow, BioRenew Flow, BioSkin Flow, and WoundEx Flow are for use in difficult to reach, irregularly shaped or tunneled wounds. They are made of decellularized particulate placental connective tissue matrix.

There are few published studies addressing the use of AmnioPro Flow, BioRenew Flow, BioSkin Flow, or WoundEx Flow for wound treatment. Therefore, it is not possible to conclude whether AmnioPro Flow, BioRenew Flow, BioSkin Flow, or WoundEx Flow have 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.
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.

Clarixflo
Clarixflo 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. See the following

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

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 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 introducing bias in the reporting of outcomes. Three of the authors had 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.

In a prospective, randomized, controlled, parallel group, multi-center clinical trial, Zelen et al. (2014c) compared the healing effectiveness of treatment of chronic lower extremity diabetic ulcers with either weekly applications of Apligraf®, EpiFix®, or standard wound care with collagen-alginate dressing. Patient inclusion criteria included ulcer
duration of ≥4 weeks, unresponsive to standard wound care and no clinical signs of infection. 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, at 2.15 grafts at a cost of $1669 versus 6.2 grafts at a cost of $9216, respectively. The authors concluded that 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. According to the authors, the study was limited because 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. According to the authors, 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. 

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. 

In a prospective, randomized, single-center clinical trial, Zelen et al. (2013) compared healing characteristics of diabetic foot ulcers treated with dehydrated human amnion 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. 

Zelan 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 multicenter clinical trials and long-term follow-up data to validate the durability of healed wounds.

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).

**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 paediatric 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.

**Grafix**

Grafix is a living skin substitute allograft comprised of a biologic membrane with native mesenchymal stem cells.

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.
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.

Marigen
Marigen is a processed fish dermal matrix composed of fish collagen that is intended to treat chronic wounds due to diabetes or other circulatory problems.

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

Baldursson 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.

Neox
Neox Wound Matrix is used as a wound covering for dermal ulcers and defects. It is made from cryopreserved human amniotic membrane.

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.

NeoxFlo
NeoxFlo 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 NeoxFlo 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 completed. 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 $2.2 \pm 17.4$ points for controls versus $38.7 \pm 11.4$ points for those receiving 0.5 cc mDHACM and $33.7 \pm 14.0$ points for those receiving 1.25 cc mDHACM. By week 8 AOFAS Hindfoot scores increased by a mean of $12.9 \pm 16.9$ points for controls versus $51.6 \pm 10.1$ and $53.3 \pm 9.4$ 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 in patients with refractory plantar fasciitis, mDHACM is a viable treatment option. Study limitations include lack of a power analysis, small sample size, limited follow-up, lack of an active comparator, and lack of blinding of outcome assessors.

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.

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.

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.

**XCM Biologic**

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

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

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) 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)**


### POLICY HISTORY/REVISION INFORMATION

<table>
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<th>Date</th>
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| 07/01/2017 | Revised coverage rationale:  
|           |   - Added language to indicate:  
|           |     ▪ **Retinal birefringence scanning/retinal polarization scanning (CPT code 0469T)** is unproven and not medically necessary for the detection of eye misalignment or strabismus  
|           |     ▪ **Optical coherence tomography (OCT) (CPT codes 0470T and 0471T)** is unproven and not medically necessary for diagnosing and treating skin conditions  
|           |   - Updated list of applicable CPT codes for the use of retinal prosthetic devices for treating retinal disease; added 0472T and 0473T  
|           |   - Updated supporting information to reflect the most current clinical evidence and references  
|           |   - Archived previous policy version 2017T0535PP |