Section 5.0

New Codes

Code	Code Description	Similar Codes	Recommended Placement
00100	Anesthesia for procedures on salivary glands, including biopsy	All anesthesia codes are Ancillary	ANCILLARY PROCEDURES
01937	Anesthesia for percutaneous image-guided injection, drainage or aspiration procedures on the spine or spinal cord; cervical or	All anesthesia codes are Ancillary	ANCILLARY PROCEDURES
01938	Anesthesia for percutaneous image-guided injection, drainage or aspiration procedures on the spine or spinal cord; lumbar or sacral	All anesthesia codes are Ancillary	ANCILLARY PROCEDURES
01939	Anesthesia for percutaneous image-guided destruction procedures by neurolytic agent on the spine or spinal cord; cervical or thoracic	All anesthesia codes are Ancillary	ANCILLARY PROCEDURES
01940	Anesthesia for percutaneous image-guided destruction procedures by neurolytic agent on the spine or spinal cord; lumbar or sacral	All anesthesia codes are Ancillary	ANCILLARY PROCEDURES
01941	Anesthesia for percutaneous image-guided neuromodulation or intravertebral procedures (eg, kyphoplasty, vertebroplasty) on the spine or spinal cord; cervical or	All anesthesia codes are Ancillary	ANCILLARY PROCEDURES
01942	Anesthesia for percutaneous image-guided neuromodulation or intravertebral procedures (eg, kyphoplasty, vertebroplasty) on the spine or spinal cord; lumbar or sacral	All anesthesia codes are Ancillary	ANCILLARY PROCEDURES
33509	Harvest of upper extremity artery, 1 segment, for coronary artery bypass procedure, endoscopic	Coronary artery bypass with arterial graft procedures (CPT 33517-33536) are on lines 69,98,189,285	69 ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION 98 CARDIOMYOPATHY 189 CHRONIC ISCHEMIC HEART DISEASE
33894	Endovascular stent repair of coarctation of the ascending, transverse, or descending thoracic or abdominal aorta, involving stent placement; across major side branches	Coarctation of the aorta is on line 44	44 COARCTATION OF THE AORTA

Code	Code Description	Similar Codes	Recommended Placement
33895	Endovascular stent repair of coarctation of the ascending, transverse, or descending thoracic or abdominal aorta, involving stent placement; not crossing major side branches	Coarctation of the aorta is on line 44	44 COARCTATION OF THE AORTA
33897	Percutaneous transluminal angioplasty of native or recurrent coarctation of the aorta	Coarctation of the aorta is on line 44	44 COARCTATION OF THE AORTA

Code	Code Description	Similar Codes	Recommended Placement
63052	Laminectomy, facetectomy, or foraminotomy (unilateral or bilateral with decompression of spinal cord, cauda equina and/or nerve root[s] [eg, spinal or lateral recess stenosis]), during posterior interbody arthrodesis, lumbar; single vertebral segment (List separately in addition to code for primary procedure)	Similar code 63047 (Laminectomy, facetectomy and foraminotomy (unilateral or bilateral with decompression of spinal cord, cauda equina and/or nerve root[s], [eg, spinal or lateral recess stenosis]), single vertebral segment; lumbar) is on line 47,150,254,346,361,529 Posterior interbody arthrodesis (CPT 22630) is on lines 47,150,200,254,346,361,401,478, 529, 558	47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS 150 CERVICAL VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR CLOSED; OTHER VERTEBRAL DISLOCATIONS/FRACTURES, OPEN OR UNSTABLE; SPINAL CORD INJURIES WITH OR WITHOUT EVIDENCE OF VERTEBRAL INJURY 200 CANCER OF BONES 254 CHRONIC OSTEOMYELITIS 346 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS 361 SCOLIOSIS 478 CLOSED DISLOCATIONS/FRACTURES OF NON-CERVICAL VERTEBRAL COLUMN WITHOUT NEUROLOGIC INJURY OR STRUCTURAL INSTABILITY 529 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS

Code	Code Description	Similar Codes	Recommended Placement
63053	Laminectomy, facetectomy, or foraminotomy (unilateral or bilateral with decompression of spinal cord, cauda equina and/or nerve root[s] [eg, spinal or lateral recess stenosis]), during posterior interbody arthrodesis, lumbar; each additional segment (List separately in addition to code for primary procedure)	See above	47,150,200,254,346,361,401,478, 529, 558
66989	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1-stage procedure), manual or mechanical technique (eg, irrigation and aspiration or phacoemulsification), complex, requiring devices or techniques not generally used in routine cataract surgery (eg, iris expansion device, suture support for intraocular lens, or primary posterior capsulorrhexis) or performed on patients in the amblyogenic developmental stage; with insertion of intraocular (eg, trabecular meshwork, supraciliary, suprachoroidal) anterior segment aqueous drainage device, without extraocular reservoir, internal approach, one or more	Both cataract removal codes (CPT 66982-66988) and the code for insertion of anterior segment aqueous drainage devices (CPT 66183) are on line 139 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE	139 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE

Code	Code Description	Similar Codes	Recommended Placement
66991	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1 stage procedure), manual or mechanical technique (eg, irrigation and aspiration or phacoemulsification); with insertion of intraocular (eg, trabecular meshwork, supraciliary, suprachoroidal) anterior segment aqueous drainage device, without extraocular reservoir, internal approach, one or more	Both cataract removal codes (CPT 66982-66988) and the code for insertion of anterior segment aqueous drainage devices (CPT 66183) are on line 139 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE	139 GLAUCOMA, OTHER THAN PRIMARY ANGLE-CLOSURE
69716	Implantation, osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor	Similar codes 69714 and 69715 (Implantation, osseointegrated implant, temporal bone, with percutaneous attachment to external speech processor/cochlear stimulator; with/without mastoidectomy) are on lines 311 and 445	311 HEARING LOSS - AGE 5 OR UNDER 446 HEARING LOSS - OVER AGE OF FIVE
69719	Revision or replacement (including removal of existing device), osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor	See above	311, 446
69726	Removal, osseointegrated implant, skull; with percutaneous attachment to external speech processor	See above	285 COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT 311, 446
69727	Removal, osseointegrated implant, skull; with magnetic transcutaneous attachment to external speech processor	See above	285, 311, 446
80220	Hydroxychloroquine	Drug level	DIAGNOSTIC PROCEDURES

Code	Code Description	Similar Codes	Recommended Placement
80503	Pathology clinical consultation; for a clinical problem, with limited review of patient's history and medical records and straightforward medical decision making When using time for code selection, 5-20 minutes of total time is spent on the date of the consultation.		DIAGNOSTIC PROCEDURES
80504	Pathology clinical consultation; for a moderately complex clinical problem, with review of patient's history and medical records and moderate level of medical decision making When using time for code selection, 21-40 minutes of total time is spent on the date of the consultation.		DIAGNOSTIC PROCEDURES
80505	Pathology clinical consultation; for a highly complex clinical problem, with comprehensive review of patient's history and medical records and high level of medical decision making When using time for code selection, 41-60 minutes of total time is spent on the date of the consultation.		DIAGNOSTIC PROCEDURES
80506	Pathology clinical consultation; prolonged service, each additional 30 minutes (List separately in addition to code for primary procedure)		DIAGNOSTIC PROCEDURES

Code	Code Description	Similar Codes	Recommended Placement
91303	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5x1010 viral particles/0.5 mL dosage, for intramuscular use	Already placed on line 3 in January 2021 Represents the Janssen (J&J) vaccine	3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS

Code	Code Description	Similar Codes	Recommended Placement
93593	Right heart catheterization for congenital heart defect(s) including imaging guidance by the proceduralist to advance the catheter to the target zone; normal native connections	Congenital heart disease lines 45, 67, 70, 76, 84, 85, 88, 89, 104, 105, 110, 118, 128, 130, 134, 138, 176, 188, 232, 264, 653	45 CORONARY ARTERY ANOMALY 67 VENTRICULAR SEPTAL DEFECT 70 CONGENITAL PULMONARY VALVE ANOMALIES 76 PATENT DUCTUS ARTERIOSUS; AORTIC PULMONARY FISTULA/WINDOW 84 ENDOCARDIAL CUSHION DEFECTS 85 CONGENITAL PULMONARY VALVE ATRESIA 88 DISCORDANT CARDIOVASCULAR CONNECTIONS 89 CONGENITAL MITRAL VALVE STENOSIS/INSUFFICIENCY 104 TETRALOGY OF FALLOT (TOF); CONGENITAL VENOUS ABNORMALITIES 105 CONGENITAL STENOSIS AND INSUFFICIENCY OF AORTIC VALVE 110 CONGENITAL HEART BLOCK; OTHER OBSTRUCTIVE ANOMALIES OF HEART 118 ATRIAL SEPTAL DEFECT, SECUNDUM 128 COMMON TRUNCUS 130 TOTAL ANOMALOUS
93594	Right heart catheterization for congenital heart defect(s) including imaging guidance by the proceduralist to advance the catheter to the target zone; abnormal native connections	See above	45, 67, 70, 76, 84, 85, 88, 89, 104, 105, 110, 118, 128, 130, 134, 138, 176, 188, 232, 264, 653

Code	Code Description	Similar Codes	Recommended Placement
93595	Left heart catheterization for congenital heart defect(s) including imaging guidance by the proceduralist to advance the catheter to the target zone, normal or abnormal native connections	See above	45, 67, 70, 76, 84, 85, 88, 89, 104, 105, 110, 118, 128, 130, 134, 138, 176, 188, 232, 264, 653
93596	Right and left heart catheterization for congenital heart defect(s) including imaging guidance by the proceduralist to advance the catheter to the target zone(s); normal native connections	See above	45, 67, 70, 76, 84, 85, 88, 89, 104, 105, 110, 118, 128, 130, 134, 138, 176, 188, 232, 264, 653
93597	Right and left heart catheterization for congenital heart defect(s) including imaging guidance by the proceduralist to advance the catheter to the target zone(s); abnormal native connections	See above	45, 67, 70, 76, 84, 85, 88, 89, 104, 105, 110, 118, 128, 130, 134, 138, 176, 188, 232, 264, 653
93598	Cardiac output measurement(s), thermodilution or other indicator dilution method, performed during cardiac catheterization for the evaluation of congenital heart defects (List separately in addition to code for primary procedure)	See above	45, 67, 70, 76, 84, 85, 88, 89, 104, 105, 110, 118, 128, 130, 134, 138, 176, 188, 232, 264, 653

Code	Code Description	Similar Codes	Recommended Placement
99424	Principal care management services, for a single high-risk disease, with the following required elements: one complex chronic condition expected to last at least 3 months, and that places the patient at significant risk of hospitalization, acute exacerbation/decompensation, functional decline, or death, the condition requires development, monitoring, or revision of disease-specific care plan, the condition requires frequent adjustments in the medication regimen and/or the management of the condition is unusually complex due to comorbidities, ongoing communication and care coordination between relevant practitioners furnishing care; first 30 minutes provided personally by a physician or other qualified health care professional, per calendar month.	Similar codes G2064 and G2065 (Comprehensive care management services) are on all lines with E&M codes	All lines with E&M codes

Code	Code Description	Similar Codes	Recommended Placement
99425	Principal care management services, for a single high-risk disease, with the following required elements: one complex chronic condition expected to last at least 3 months, and that places the patient at significant risk of hospitalization, acute exacerbation/decompensation, functional decline, or death, the condition requires development, monitoring, or revision of disease-specific care plan, the condition requires frequent adjustments in the medication regimen and/or the management of the condition is unusually complex due to comorbidities, ongoing communication and care coordination between relevant practitioners furnishing care; each additional 30 minutes provided personally by a physician or other qualified health care professional, per calendar month (List separately in addition to code for primary procedure)	See above	All lines with E&M codes

Code	Code Description	Similar Codes	Recommended Placement
99426	Principal care management services, for a single high-risk disease, with the following required elements: one complex chronic condition expected to last at least 3 months, and that places the patient at significant risk of hospitalization, acute exacerbation/decompensation, functional decline, or death, the condition requires development, monitoring, or revision of disease-specific care plan, the condition requires frequent adjustments in the medication regimen and/or the management of the condition is unusually complex due to comorbidities, ongoing communication and care coordination between relevant practitioners furnishing care; first 30 minutes of clinical staff time directed by physician or other qualified health care professional, per calendar month.	See above	All lines with E&M codes

Code	Code Description	Similar Codes	Recommended Placement
99427	Principal care management services, for a single high-risk disease, with the following required elements: one complex chronic condition expected to last at least 3 months, and that places the patient at significant risk of hospitalization, acute exacerbation/decompensation, functional decline, or death, the condition requires development, monitoring, or revision of disease-specific care plan, the condition requires frequent adjustments in the medication regimen and/or the management of the condition is unusually complex due to comorbidities, ongoing communication and care coordination between relevant practitioners furnishing care; each additional 30 minutes of clinical staff time directed by a physician or other qualified health care professional, per calendar month (List separately in addition to code for primary procedure)	See above	All lines with E&M codes

Code	Code Description	Similar Codes	Recommended Placement
99437	Chronic care management services with the following required elements: multiple (two or more) chronic conditions expected to last at least 12 months, or until the death of the patient, chronic conditions that place the patient at significant risk of death, acute exacerbation/decompensation, or functional decline, comprehensive care plan established, implemented, revised, or monitored; each additional 30 minutes by a physician or other qualified health care professional, per calendar month (List separately in addition to code for primary procedure)	Similar chronic care management codes (CPT 99490-99491) are on all lines with E&M codes	All lines with E&M codes

1) **81523** Oncology (breast), mRNA, next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis
    a. Per the oncology genetic counselor on GAP, this code represents a form of Mammaprint, which is a covered test in GN148
        i. Mammaprint is also coded with CPT 81521 (Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis) or HCPCS S3854 (Gene expression profiling panel for use in the management of breast cancer treatment)
        ii. These codes are both on line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
    b. Next generation sequencing is the use of ultra-high throughput massively parallel RNA sequencing. The advantage of NGS compared to microarrays is that is does not require the probes used for microarray testing and reduces cross-hybridization.
    c. HERC staff recommendations:
        i. Place CPT 81523 on line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER
        ii. Update GN148 as shown below

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE

Lines 157,184,191,229,262,271,329

The use of tissue of origin testing (e.g. CPT 81504) is included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For early stage breast cancer, the following breast cancer genome profile tests are included on Line 191 when the listed criteria are met. One test per primary breast cancer is covered when the patient is willing to use the test results in a shared decision-making process regarding adjuvant chemotherapy. Lymph nodes with micrometastases less than 2 mm in size are considered node negative.

- Oncotype DX Breast Recurrence Score (CPT 81519) for breast tumors that are estrogen receptor positive, HER2 negative, and either lymph node negative, or lymph node positive with 1-3 involved nodes.
- EndoPredict (CPT 81522) and Prosigna (CPT 81520 or PLA 0008M) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative.
- MammaPrint (using CPT 81521, 81523 or HCPCS S3854) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk.

For early stage breast cancer that is estrogen receptor positive, HER2 negative, and either lymph node negative or lymph node positive with 1-3 involved nodes, Breast Cancer Index (CPT 81518) is included on Line 191 when the patient is willing to use the test results in a shared decision-making process regarding prolonged adjuvant endocrine therapy.

EndoPredict, Prosigna, and MammaPrint are not included on Line 191 for early stage breast cancer with involved axillary lymph nodes. Oncotype DX Breast Recurrence Score is not included on Line 191 for breast cancer involving four or more axillary lymph nodes or more extensive metastatic disease.

Oncotype DX Breast DCIS Score (CPT 81479) is included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For melanoma, BRAF gene mutation testing (CPT 81210) is included on Line 229. DecisionDx-Melanoma (CPT 81529) is included on Line 662.

For lung cancer, epidermal growth factor receptor (EGFR) gene mutation testing (CPT 81235) is included on Line 262 only for non-small cell lung cancer. KRAS gene mutation testing (CPT 81275) is not included on this line.

For colorectal cancer, KRAS gene mutation testing (CPT 81275) is included on Line 157. BRAF (CPT 81210) and Oncotype DX are not included on this line. Microsatellite instability (MSI) is included on the Line 662.

For bladder cancer, Urovysion testing is included on Line 662.

For prostate cancer, Oncotype DX Genomic Prostate Score, Prolaris Score Assay (CPT 81541), and Decipher Prostate RP (CPT 81542) are included on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For thyroid cancer, Afirma gene expression classifier (CPT 81546) is included on Line 662.

The development of this guideline note was informed by a HERC coverage guidance on Biomarkers Tests of Cancer Tissue for Prognosis and Potential Response to Treatment; the prostate-related portion of that coverage guidance was superseded by a Coverage Guidance on Gene Expression Profiling for Prostate Cancer. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

2) 91113 Gastrointestinal tract imaging, intraluminal (eg, capsule endoscopy), colon
    a. VBBS/HERC reviewed in October 2021 and reaffirmed lack of coverage
    b. Staff summary from the October review: Major evidence sources (NICE, AHRQ) and specialty society guidelines (ASGE) do not find strong evidence for use of wireless capsule endoscopy for evaluation of gastroparesis or intestinal motility issues. The American Society for Gastrointestinal Endoscopy finds limited application for the use of capsule endoscopy in the esophagus or colon.
    c. HERC staff recommendations:
        i. Place CPT 91113 on line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
        ii. Update the GN173 as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 662
The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
91113	Gastrointestinal tract imaging, intraluminal (eg, capsule endoscopy), colon	Insufficient evidence of effectiveness	November 2021

3) **93319** 3D echocardiographic imaging and postprocessing during transesophageal echocardiography, or during transthoracic echocardiography for congenital cardiac anomalies, for the assessment of cardiac structure(s) (eg, cardiac chambers and valves, left atrial appendage, interatrial septum, interventricular septum) and function, when performed
    a. Similar codes:
        i. On line 662/Gn173
            1. 76376: 3D rendering with interpretation and reporting of computed tomography, magnetic resonance imaging, ultrasound, or other tomographic modality with image postprocessing under concurrent supervision; not requiring image postprocessing on an independent workstation
            2. 76377: 3D rendering with interpretation and reporting of computed tomography, magnetic resonance imaging, ultrasound, or other tomographic modality with image postprocessing under concurrent supervision; requiring image postprocessing on an independent workstation
            3. Note: per CMS, these codes are to be added to the ECHO CPT code to represent to work in 3D rendering and interpretation
    b. Other codes
        i. 93355: Echocardiography, transesophageal (TEE) for guidance of a transcatheter intracardiac or great vessel(s) structural intervention(s) (eg, TAVR, transcatheter pulmonary valve replacement, mitral valve repair, paravalvular regurgitation repair, left atrial appendage occlusion/closure, ventricular septal defect closure)

(peri-and intra-procedural), real-time image acquisition and documentation, guidance with quantitative measurements, probe manipulation, interpretation, and report, including diagnostic transesophageal echocardiography and, when performed, administration of ultrasound contrast, Doppler, color flow, and 3D

c. HERC staff summary: no other 3D rendering codes are currently covered on the Prioritized List. 3D is listed as one aspect of CPT 93355
d. HERC staff recommendation:
    i. Place CPT 99319 on line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    ii. Update the GN173 entry for 3D image rendering as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 662
The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
76376-76377 99319	3D rendering of imaging studies	No additional proven benefit beyond the standard study, therefore not reimbursed separately	~~November 2019~~ November 2021

4) **94625** Physician or other qualified health care professional services for outpatient pulmonary rehabilitation; without continuous oximetry monitoring (per session) and **94626** Physician or other qualified health care professional services for outpatient pulmonary rehabilitation; with continuous oximetry monitoring (per session)
    a. Similar code: HCPCS G0424 (Pulmonary rehabilitation, including exercise (includes monitoring), one hour, per session, up to two sessions per day) is on lines 9,58,222,233,240,283
    b. COVID and long term post-COVID conditions are on line 399
    c. HERC staff recommendation:
        i. Add CPT 94625 and 94626 to the lines below
            1. 9 ASTHMA
            2. 58 BRONCHIECTASIS
            3. 222 OCCUPATIONAL LUNG DISEASES
            4. 233 ADULT RESPIRATORY DISTRESS SYNDROME; ACUTE RESPIRATORY FAILURE; RESPIRATORY CONDITIONS DUE TO PHYSICAL AND CHEMICAL AGENTS
            5. 240 CONDITIONS REQUIRING HEART-LUNG AND LUNG TRANSPLANTATION
            6. 283 CHRONIC OBSTRUCTIVE PULMONARY DISEASE; CHRONIC RESPIRATORY FAILURE
            7. 399 INFLUENZA, NOVEL RESPIRATORY VIRUSES
        ii. Add HCPCS G0424 (Pulmonary rehab) to line 399 INFLUENZA, NOVEL RESPIRATORY VIRUSES

2022 CPT Code Review

Exclusion of Left Atrial Appendage

Codes: **33267, 33268, 33269** Exclusion of left atrial appendage

1) **33267:** Exclusion of left atrial appendage, open, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)
2) **33268**: Exclusion of left atrial appendage, open, performed at the time of other sternotomy or thoracotomy procedure(s), any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)
3) **33269**: Exclusion of left atrial appendage, thoracoscopic, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)

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

This code was reviewed in 2016 as part of the 2017 CPT code review. Based on a 2012 and a 2016 systematic review as well as a 2014 NICE review, this procedure was determined to be experimental and added to line 662/GN173.

Description: The left atrial appendix (LAA) is the most common place of thrombosis in patients with atrial fibrillation, and it can be excluded from the systemic circulation at the time of cardiac surgery by excision, ligation, suturing, or stapling. LAA exclusion has been proposed as a method to reduce stroke risk in patients with atrial fibrillation, as an alternative to anti-coagulation medications.

Evidence

Percutaneous closure devices

1) **MED 2017:** percutaneous transcatheter closure of the left atrial appendage with endocardial implant (CPT Code 33340)
    1. There are data on the efficacy of the WATCHMAN, the only implanted device currently approved by the Food and Drug Administration (FDA) for percutaneous closure of the left atrial appendage, from two randomized controlled trials (RCTs):
        a. WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT AF)
        b. Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation (PREVAIL)
    2. The risk of ischemic strokes appears to be similar for those undergoing WATCHMAN placement or continuing with anticoagulation with warfarin, according to direct comparisons.
    3. Indirect comparisons through the use of network meta-analysis estimate a similar risk of ischemic stroke with novel oral anticoagulants (e.g., direct thrombin inhibitors, factor Xa inhibitors).
    4. The first RCT of the WATCHMAN device observed increased risk of serious procedural harms, notably pericardial tamponade necessitating percutaneous drainage or surgery and periprocedural stroke. Subsequent RCTs and clinical registries demonstrate decreased rates of these events compared to the original studies, possibly resulting from increased operator experience.

5. Conclusions: Estimates of the effect of the WATCHMAN device for percutaneous left atrial appendage closure demonstrate non-inferiority to warfarin therapy for ischemic stroke, mortality, and major bleeding. Current studies have not been designed to provide information of superiority for any of these outcomes. The data providing the estimates from meta-analyses arise from two RCTs with a total of 1,114 individuals. The older study, PROTECT AF, found increased rates of procedure-related complications that appeared to improve in the more recent PREVAIL study, but still include potential for significant morbidity and mortality from complications such as procedure-related stroke and pericardial effusion/tamponade requiring surgery or prolonged hospitalization. Procedure-related risks are balanced by the potential for major bleeding events caused by warfarin or other novel oral anticoagulants. Direct comparisons between the WATCHMAN, warfarin, and newer agents do not exist in the literature, but several network meta-analyses estimated similar risk of major bleeding for WATCHMAN, warfarin, and novel oral anticoagulant agents.

2) **Ontario Health Technology Assessment 2017:** Left atrial appendage closure device with delivery system
    1. N=2 studies comparing the LAAC device with warfarin
        a. PREVAIL and PROTECT AF trials (7000+ patients each)
    2. LAAC device was comparable to novel oral anticoagulants in reducing stroke (odds ratio [OR] 0.85; credible interval [Cr.I] 0.63–1.05). Similarly, the reduction in the risk of all-cause mortality was comparable between the LAAC device and novel oral anticoagulants (OR 0.71; Cr.I 0.49–1.22). The LAAC device was found to be superior to novel oral anticoagulants in preventing hemorrhagic stroke (OR 0.45; Cr.I 0.29–0.79), whereas novel oral anticoagulants were found to be superior to the LAAC device in preventing ischemic stroke (OR 0.67; Cr.I 0.24–1.64).
    3. The body of clinical evidence was found to be of moderate quality as assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria
    4. Results from the economic evaluation indicate that the LAAC device is cost-effective compared with aspirin in patients with contraindications to oral anticoagulants. In patients without contraindications to oral anticoagulants, we found that the LAAC device is not cost-effective compared with novel oral anticoagulants.

Peri-operative closure

3) **Mohamed 2021**, meta-analysis of surgical left atrial appendage occlusion during cardiac surgery
    1. N=5 RCTs (2,580 patients randomized to LAAO and 2,548 patients randomized to conservative management
        a. Median follow up 3.7 yrs
    2. Patients who underwent S-LAAO had significantly lower rates of thromboembolic events after surgery compared to the control group (RR 0.67, 95% CI [0.53, 0.84]; p <0.01;
    3. All-cause mortality, major bleeding/blood transfusion, and myocardial infarction were all similar between the groups (RR 1.0, 95% CI [0.9, 1.11]; p = 0.97), (RR 0.93, 95% CI [0.79, 1.10]; p = 0.41), and (RR 0.88, 95% CI [0.61, 1.28]; p = 0.51), respectively
    4. No adverse events related to the procedure were reported
4) **Kheiri 2020**, meta-analysis of left atrial appendage closure vs anticoagulation in patients with atrial fibrillation
    1. N=2 RCTs (1516 patients) of oral anticoagulation vs LAAO

2. Early procedural complications (within 7 days) included 3.1% pericardial effusion, 0.6% device embolization 0.5% major bleeding, 0.5% stroke, and 0.1% death (combined risk of serious complications 5.0%).
3. Compared with OAC, LAAC was associated with a statistically significant reduction of all-cause death (incident- rate-ratio = 0.74, 95% CI 0.56 to 0.99, p = 0.02; HR 0.73, 95% CI 0.56 to 0.97, p = 0.03; absolute-risk-difference = 2.6%) and cardiovascular death (HR 0.63, 95% CI 0.42 to 0.94, p = 0.02). There were no significant differences between groups in terms of all stroke or systemic embolism (HR 0.99, 95% CI 0.65 to 1.50, p = 0.96) or overall bleeding (HR 0.88, 95% CI 0.65 to 1.20, p = 0.43).
4. Although serious early procedure related complications were not infrequent (5.0%) these complications occurred predominantly in earlier RCTs, with more contemporary data demonstrating a lower complication risks and higher success rates, perhaps due in part to improvements in patient selection and/or operator experience

5) **Whitlock 2021,** RCT of left atrial appendage occlusion during cardiac surgery to prevent stroke
    1. N=2379 patients in the occlusion group and N=2391 patients in the no-occlusion group
        i. Patients scheduled to undergo cardiac surgery for another indication with atrial fibrillation and at least a score of 2 on the CHADS-VASc scale
        ii. Follow up 3.8 years
    2. Ischemic stroke or systemic embolism occurred in 114 participants (4.8%) in the occlusion group and in 168 (7.0%) in the no-occlusion group (hazard ratio, 0.67; 95% confidence interval, 0.53 to 0.85; P = 0.001). The incidence of perioperative bleeding, heart failure, or death did not differ significantly between the trial groups.
    3. No difference seen in hospitalization for heart failure, myocardial infarction, or death between groups
    4. Adverse events: Re-exploration for bleeding within the first 48 hours after surgery occurred in 94 participants (4.0%) in the occlusion group and in 95 (4.0%) in the no-occlusion group. The 30-day mortality was 3.7% in the occlusion group and 4.0% in the no-occlusion group.
    5. At hospital discharge, 83.4% of the participants in the occlusion group and 81.0% of those in the no-occlusion group were receiving oral anticoagulation, and the corresponding values were 79.6% and 78.9% at the 1-year visit and 75.3% and 78.2% at the 3-year visit.
    6. Conclusion: Among participants with atrial fibrillation who had undergone cardiac surgery, most of whom continued to receive ongoing antithrombotic therapy, the risk of ischemic stroke or systemic embolism was lower with concomitant left atrial appendage occlusion performed during the surgery than without it.

6) **Friedman 2018**, retrospective cohort study of left atrial appendage occlusion during concomitant cardiac surgery with readmission for thromboembolism
    1. N=10,524 patients (3,892 underwent LAAO)
        a. Mean follow up 2.6 yrs
        b. Claims data study with no clinical verification
    2. S-LAAO, compared with no S-LAAO, was associated with lower unadjusted rates of thromboembolism (4.2% vs 6.2%), all-cause mortality (17.3% vs 23.9%), and the composite end point (thromboembolisms, hemorrhagic stroke and all cause mortality at 3 years) (20.5% vs 28.7%) but no significant difference in rates of hemorrhagic stroke (0.9% vs 0.9%). After inverse probability–weighted adjustment, S-LAAO was

associated with a significantly lower rate of thromboembolism (subdistribution hazard ratio [HR], 0.67; 95% CI, 0.56-0.81; P < .001), all-cause mortality (HR, 0.88; 95% CI, 0.79-0.97; P = .001), and the composite end point (HR, 0.83; 95% CI, 0.76-0.91; P < .001) but not hemorrhagic stroke (subdistribution HR, 0.84; 95% CI, 0.53-1.32; P = .44). S-LAAO, compared with no S-LAAO, was associated with a lower risk of thromboembolism among patients discharged without anticoagulation (unadjusted rate, 4.2% vs 6.0%; adjusted subdistribution HR, 0.26; 95% CI, 0.17-0.40; P < .001), but not among patients discharged with anticoagulation (unadjusted rate, 4.1% vs 6.3%; adjusted subdistribution HR, 0.88; 95% CI, 0.56-1.39; P = .59).

3. Conclusions: Among older patients with AF undergoing concomitant cardiac surgery, S-LAAO, compared with no S-LAAO, was associated with a lower risk of readmission for thromboembolism over 3 years. These findings support the use of S-LAAO, but randomized trials are necessary to provide definitive evidence.

Expert guidelines

1) **ACC/AHA 2019,** management of patients with atrial fibrillation https://reader.elsevier.com/reader/sd/pii/S0735109719302098?token=E9BC269822C4EAEAE6973C13F2F98F1B173251DB348D095EBBDEDAF974274746737A4A65ABEC446C168E350A9CF7740D&originRegion=us-east-1&originCreation=20211014142627
    a. Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation
        i. Level of evidence B-NR (moderate quality evidence from 1 or more well designed, well executed non-randomized studies, observations studies or registry studies)
        ii. Strength of recommendation: IIB (weak)
        iii. Noted to be a focus of ongoing research
    b. Surgical occlusion of the LAA may be considered in patients with AF undergoing cardiac surgery, as a component of an overall heart team approach to the management of AF.
        i. Level of evidence B-NR (moderate quality evidence from 1 or more well designed, well executed non-randomized studies, observations studies or registry studies)
        ii. Strength of recommendation: IIB (weak)
        iii. New recommendation based on the Friedman article above

Other policies

1) **NICE 2021,** management of atrial fibrillation https://www.nice.org.uk/guidance/ng196/resources/atrial-fibrillation-diagnosis-and-management-pdf-66142085507269
    a. Consider left atrial appendage occlusion (LAAO) if anticoagulation is contraindicated or not tolerated and discuss the benefits and risks of LAAO with the person
        i. This is device occlusion, not surgical occlusion
    b. Do not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated.
    c. No recommendation/policy found on operative LAAO
2) **CMS**
    a. Only covers left atrial appendage occlusion devices as part of a study
    b. No policy found on operative LAAO

Other payer policies

1) **Aetna 2020:**
    a. No policy was found on left atrial appendage occlusion during other cardiac surgery
    b. Aetna considers left atrial appendage closure (LAAC) devices medically necessary for non-valvular atrial fibrillation (NVAF) when the device has received U.S. Food and Drug Administration (FDA) Premarket Approval (PMA) for that device's FDA-approved indication and meet all of the conditions specified below
    c. The member must have: A CHADS2 score ≥ 2
    d. Shared decision making documented
    e. suitability for short-term warfarin (i.e., the member is able to take short-term warfarin) and long-term aspirin but deemed unable to take long term oral anticoagulation due to
        i. Member has thromboembolism while on an oral anticoagulant (i.e., while INR is in therapeutic range); *or*
        ii. Member has major bleed (intracranial bleed, significant gastrointestinal bleeding (not just guaiac positive stools) while on an oral anticoagulant (i.e., while INR is in therapeutic range); *or*
        iii. Member has elevated risk of bleeding on oral anticoagulant with a HAS-BLED score of 3 or more; *or*
        iv. Member has other absolute contraindication to long-term anticoagulation;
    f. The member (preoperatively and postoperatively) is under the care of a cohesive, multidisciplinary team (MDT) of medical professionals; *and*
    g. The procedure must be furnished in a hospital with an established structural heart disease (SHD) and/or electrophysiology (EP) program; *and*
    h. The procedure must be performed by an interventional cardiologist(s), electrophysiologst(s) or cardiovascular surgeon(s) that meet certain criteria

2) Cigna 2020
    a. Percutaneous transcatheter closure of the left atrial appendage (CPT code 33340) for non-valvular atrial fibrillation using a U.S. Food and Drug Administration (FDA) approved device is considered medically necessary for the prevention of stroke when ALL of the following criteria are met:
        i. There is an increased risk of stroke and systemic embolism based on CHADS2* ≥ 2 or CHA2DS2-VASc** score ≥ 3 and systemic anticoagulation therapy is recommended.
        ii. Attestation that for this individual the long-term risk of systemic anticoagulation outweighs the risk of the device implantation.
    b. Surgical closure of the left atrial appendage, including use of a clip, (CPT code 33999) for the prevention of stroke in conjunction with other cardiac surgical procedures is considered experimental, investigational or unproven.

Exclusion of Left Atrial Appendage

HERC staff summary: Left atrial appendage occlusion, either with a device or with surgical closure as part of another cardiac surgery, is an active area of investigation for preventing stroke in patients with atrial fibrillation.

In regard to percutaneous LAAO procedures, no significant new data has been published since the 2016 EGBS review which found them to be experimental. Private payers and the UK health system appear to cover the transcatheter closure device, and Medicare covers it with evidence development for patients who are not candidates for long term anticoagulation.

In regard to surgical occlusion of the left atrial appendage during other cardiac surgery, this procedure is thought to be non-inferior to anticoagulation but has a significant rate of complications based on limited evidence. The studies on surgical occlusion are confounded by the fact that most studies appear to have patients continue anticoagulation, making the effect of surgical LAA occlusion difficult to discern. Private payers do not cover surgical LAAO and no policies were found for NICE or CMS.

Expert guidelines say that both types of procedures "may be considered" as a weak recommendation.

Overall, both procedures appear to be experimental. The LAAO procedure during other cardiac procedures may be reasonable to coverage for patients who have contraindications to anticoagulation.

HERC staff recommendations:

1) Update date of last review in GN173 to November 2021 regardless of which option below is selected
2) Add the codes below to Line 662 and make the updates to the GN173 entry shown below
    a. **33267:** Exclusion of left atrial appendage, open, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)
    b. **33268**: Exclusion of left atrial appendage, open, performed at the time of other sternotomy or thoracotomy procedure(s), any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)
    c. **33269**: Exclusion of left atrial appendage, thoracoscopic, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
33267, 33268, 33269 33340	Exclusion of left atrial appendage Percutaneous transcatheter closure of the left atrial appendage with endocardial implant	Insufficient evidence of effectiveness	~~November, 2016~~ November 2021

Health Quality Ontario

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ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Left Atrial Appendage Closure Device With Delivery System: A Health Technology Assessment

KEY MESSAGES

Atrial fibrillation is a common heart disease involving electrical disturbances in the atria (the top two chambers) of the heart, which can reduce the heart's ability to pump blood efficiently. Nonvalvular atrial fibrillation (atrial fibrillation that does not involve the heart valves) is the most common form of atrial fibrillation and can lead to stroke. To prevent stroke, people with nonvalvular atrial fibrillation often take oral anticoagulants (medications that prevent the blood from clotting) daily for life. However, on occasion, patients may be unable to take these medications owing to side effects. A new device, the left atrial appendage closure device with delivery system (LAAC device), may be able to prevent stroke in people with nonvalvular atrial fibrillation without the need for lifelong treatment with oral anticoagulants.

In this health technology assessment, we compared the effectiveness and cost-effectiveness of the LAAC device versus novel oral anticoagulants and oral antiplatelet medications in patients with nonvalvular atrial fibrillation.

We found moderate-quality evidence suggesting that the LAAC device and novel oral anticoagulants are similarly effective in preventing stroke. To date, no randomized controlled evidence is available regarding the effectiveness of the device in people with nonvalvular atrial fibrillation with contraindications to oral anticoagulants. However, some evidence suggests that the device may be effective in this patient population; if so, our results indicate that the device would be cost-effective in this patient population. People with nonvalvular atrial fibrillation with whom we spoke reported positive support for the LAAC device and reported valuing having access to the LAAC device if it were shown to be safe, effective, and recommended by their health care providers.

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ABSTRACT

Background

Atrial fibrillation is a common cardiac arrhythmia, and 15% to 20% of those who have experienced stroke have atrial fibrillation. Treatment options to prevent stroke in people with atrial fibrillation include pharmacological agents such as novel oral anticoagulants or nonpharmacological devices such as the left atrial appendage closure device with delivery system (LAAC device). The objectives of this health technology assessment were to assess the clinical effectiveness and cost-effectiveness of the LAAC device versus novel oral anticoagulants in patients without contraindications to oral anticoagulants and versus antiplatelet agents in patients with contraindications to oral anticoagulants.

Methods

We performed a systematic review and network meta-analysis. We also conducted an economic literature review, economic evaluation, and budget impact analysis to assess the cost-effectiveness and budget impact of the LAAC device compared with novel oral anticoagulants and oral antiplatelet agents (e.g., aspirin). We also spoke with patients to better understand their preferences, perspectives, and values.

Results

Seven randomized controlled studies met the inclusion criteria for indirect comparison. Five studies assessed the effectiveness of novel oral anticoagulants versus warfarin, and two studies compared the LAAC device with warfarin. No studies were identified that compared the LAAC device with aspirin in patients in whom oral anticoagulants were contraindicated. Using the random effects model, we found that the LAAC device was comparable to novel oral anticoagulants in reducing stroke (odds ratio [OR] 0.85; credible interval [Cr.I] 0.63–1.05). Similarly, the reduction in the risk of all-cause mortality was comparable between the LAAC device and novel oral anticoagulants (OR 0.71; Cr.I 0.49–1.22). The LAAC device was found to be superior to novel oral anticoagulants in preventing hemorrhagic stroke (OR 0.45; Cr.I 0.29–0.79), whereas novel oral anticoagulants were found to be superior to the LAAC device in preventing ischemic stroke (OR 0.67; Cr.I 0.24–1.64). The body of clinical evidence was found to be of moderate quality as assed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. Results from the economic evaluation indicate that the LAAC device is cost-effective compared with aspirin in patients with contraindications to oral anticoagulants. In patients without contraindications to oral anticoagulants, we found that the LAAC device is not cost-effective compared with novel oral anticoagulants. Publicly funding the LAAC device in patients with nonvalvular atrial fibrillation with contraindications to oral anticoagulants could result in additional funding of $1.1 million to $7.7 million over the first five years. Patients interviewed reported on the impact of living with nonvalvular atrial fibrillation and were supportive of the LAAC device as a treatment option.

Conclusions

Moderate-quality evidence suggests that the LAAC device is as effective as novel oral anticoagulants in preventing stroke in people with nonvalvular atrial fibrillation. However, our results indicate that the LAAC device is cost-effective only in patients with contraindications to oral anticoagulants. People with nonvalvular atrial fibrillation with whom we spoke reported positive support for the LAAC device.

Meta-analysis of Surgical Left Atrial Appendage Occlusion During Cardiac Surgery

Atrial fibrillation (AF) is a common arrhythmia in the elderly population and represents a significant risk for cardio-embolic stroke secondary to thrombi originating from the left atrial appendage.[1,2] Although oral anticoagulation is considered the standard of care, numerous concerns exist. Patient noncompliance, intolerance, and subtherapeutic drug levels are examples.[3] Moreover, the risk of bleeding poses a significant problem, especially in elderly, frail patients. Surgical-left atrial appendage occlusion (S-LAAO) has been considered an alternative strategy to reduce the risk of future cardioembolic events. Patients undergoing cardiac surgery are usually frail with other comorbidities and a high prevalence of AF.[3] It was assumed that S-LAAO at the time of non-AF cardiac surgery might be protective from future thromboembolic events.[1−5] However, until recently, data from randomized controlled trials (RCTs)were limited. We conducted a meta-analysis of RCTs comparing S-LAAO in non-AF cardiac surgery versus conservative management.

We performed a comprehensive search of the electronic databases for RCTs comparing S-LAAO versus conservative management among patients undergoing non-AF cardiac surgery. The primary outcome of interest is long-term thrombo-embolic events, defined as stroke, transient ischemic attack, or systemic embolization. Secondary outcomes included all-cause mortality, major bleeding/or requirement of blood transfusion, myocardial infarction, and cross-clamp time (min). We calculated risk ratios (RRs) and mean differences with their 95% confidence intervals (CIs) for dichotomous and continuous data, respectively. All analysis was conducted with RevMan 5.4 software using a random-effects model.

We identified 5 RCTs[1−5] with 2,580 patients randomized to S-LAAO and 2,548 patients randomized to conservative management. The median follow-up was 3.7 years, the mean age was 71 ± 8.4 years, 32% were females, 81% had hypertension, 31% had diabetes, and the mean CHA_2 DS_2-VASc score was 4.1±1.5. Patients who underwent S-LAAO had significantly lower rates of thromboembolic events after surgery compared to the control group (RR 0.67, 95% CI [0.53, 0.84]; p <0.01; Figure 1). All-cause mortality, major

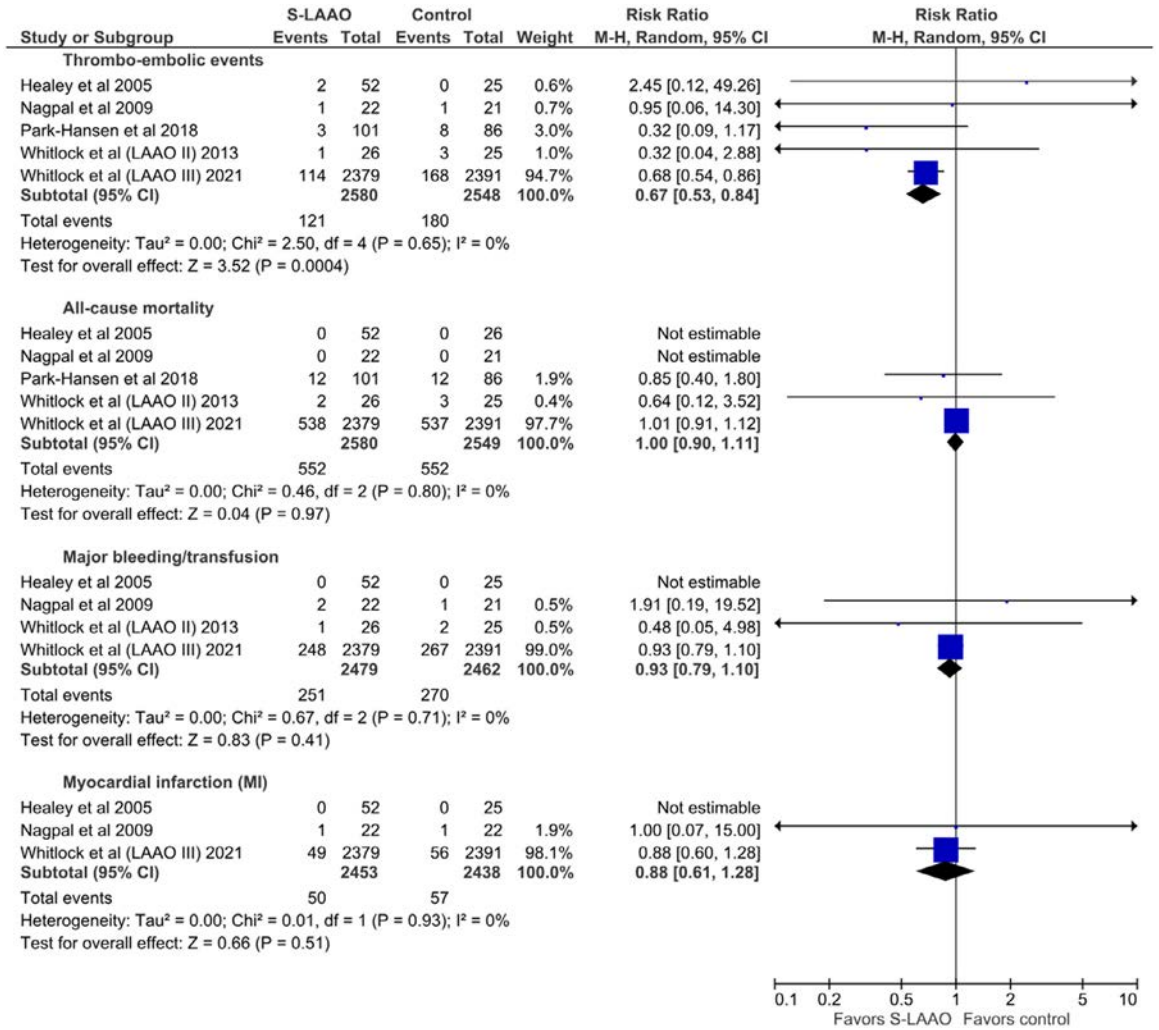

Figure 1. Forest plot comparing the clinical outcomes among patients who received surgical left atrial appendage occlusions during cardiac surgery.

bleeding/blood transfusion, and myocardial infarction were all similar between the groups (RR 1.0, 95% CI [0.9, 1.11]; p = 0.97), (RR 0.93, 95% CI [0.79, 1.10]; p = 0.41), and (RR 0.88, 95% CI [0.61, 1.28]; p = 0.51), respectively (Figure 1).

In conclusion, in patients with known AF, S-LAAO at the time of non-AF cardiac surgery significantly reduces future thromboembolic events than conservative management.

Disclosures

The authors have no conflicts of interest to report.

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23 May 2021
2 June 2021

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The Effect of Clinical Depression on Post-TAVI All-Cause Mortality

The effect of diagnosed clinical depression is still poorly understood when it comes to outcomes post-transcatheter aortic valve implantation (TAVI).[1] To understand this potential issue, we examined TAVI cases with a confirmed diagnosis of depression post-TAVI. The purpose of this study was to investigate the potential all-cause mortality over a period of 1,825 days (5-year period).

To understand the potential impact of confirmed clinical depression, we queried the TriNetx database (Research Network) for cases between January 1, 2015 and January 11, 2021. We identified 2,049 cases with confirmed clinical depression using the International Classification of Diseases 10 codes (F33.1, F33.0, F32, F32.1, F33, F32.0, F33.41, F34.1, and F33.2). We also identified 13,274 patients treated during the same period who did not have a specified confirmed clinical depression post-TAVI. We compared all-cause mortality between propensity-matched cohorts. We used descriptive statistics to measure association and employed a Kaplan-Meier survival curve to assess the endpoints of mortality. A propensity score matching of 1:1 was performed using the covariates (age, gender, hypertension, coronary artery disease, chronic heart failure, diabetes, smoking history, chronic obstructive pulmonary disease, and body mass index >30 kg/m^2). We then conducted propensity score matching to reduce possible differences and created well-matched cohorts (2,049/2,049) over a period of 1,825 days (5 years).

Of the 15,323 patients who were included, 2,049 (13%) were confirmed clinical depression, and 13,274 (87%) were not. Patients in the TAVI + depression group were younger (76.8 ± 9.53 vs 78.3 ± 8.9 p <0.001) and more likely to be female (55.3% vs 41.5% p <0.001). In the PSM cohorts, all-cause mortality occurred in (439/2,049) (21.4%) and (346/2,049) (16.8%) patients in the TAVI + depression versus no TAVI + depression, respectively (risk difference 4.53% (2.133% to 6.945%, p <0.002). A Kaplan-Meier survival analysis confirmed a statistically significant association between the TAVI + depression versus no TAVI + depression (log-rank test p = 0.002; Figure 1).

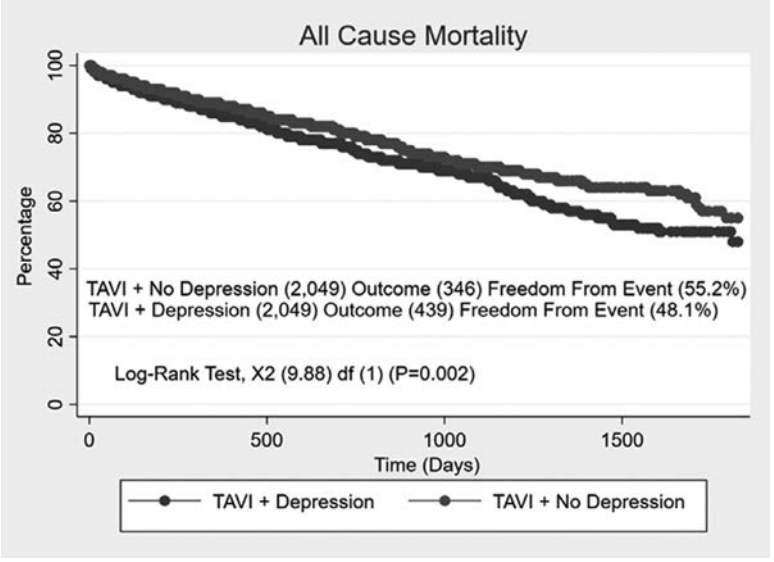

Figure 1. TAVI (depression) versus TAVI (no depression) (Matched).

Study Locations: Charleston Area Medical Center, 3100 McCorkle Ave SE, Charleston, WV, 25302 and Charleston Area Medical Center Research Institute and Center for Clinical Sciences Research, 3200 McCorkle Ave SE, Charleston, WV, 25302.

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https://doi.org/10.1016/j.amjcard.2020.07.021

Meta-analysis of Left Atrial Appendage Closure Versus Anticoagulation in Patients With Atrial Fibrillation

Oral anticoagulation (OAC) (vitamin-K-antagonists or direct oral anticoagulants) is the standard-of-care to prevent systemic thromboembolism in patients with atrial fibrillation (AF). However, a growing number of patients have a contraindication or are deemed inappropriate for long-term OAC therapy[1] and therefore an alternative mechanical strategy to prevent left atrial appendage (LAA) thrombus migration has emerged to treat this population. We conducted a meta-analysis of all randomized clinical trials (RCTs) to assess the safety and efficacy of LAA closure (LAAC) versus anticoagulation in high-risk AF patients.

We performed a comprehensive electronic databases search for RCTs. Two authors extracted and analyzed the data using R v3.3.1 and STATA v15.1 software. The primary outcome was all-cause death. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) to account for differences in follow-up duration using a random-effects model. A unique Kaplan-Meier curve for all-cause death was reconstructed from the included trials and a Cox proportional-hazards model was calculated. The proportional-hazards assumption was tested using the residual Schoenfeld test.

We identified 3 RCTs with 1,516 total patients (age 73.0 ± 8.1 years; females 31%), randomizing 5,038.9 patient-years of follow-up.[2,3] The mean CHA2DS2-VASc score was 4.0 ± 1.5 and 31.1% of the patients had permanent AF. Successful device deployment was achieved in 91.9% of the study participants. Early procedural complications (within 7 days) included 3.1% pericardial effusion, 0.6% device embolization, 0.5% major bleeding, 0.5% stroke, and 0.1% death (combined risk of serious complications 5.0%).

Compared with OAC, LAAC was associated with a statistically significant reduction of all-cause death (incident-rate-ratio = 0.74, 95% CI 0.56 to 0.99, p = 0.02; HR 0.73, 95% CI 0.56 to 0.97, p = 0.03; absolute-risk-difference = 2.6%) and cardiovascular death (HR 0.63, 95% CI 0.42 to 0.94, p = 0.02). There were no significant differences between groups in terms of all stroke or systemic embolism (HR 0.99, 95% CI 0.65 to 1.50, p = 0.96) or overall bleeding (HR 0.88, 95% CI 0.65 to 1.20, p = 0.43). However, LAAC was associated with a significant reduction of nonprocedural bleeding compared with OAC (HR 0.49; 95% CI 0.35 to 0.70; p <0.01) (Figure 1). Subgroup analysis of all-cause mortality based on the type of anticoagulants (vitamin-K-antagonists vs direct oral anticoagulants) showed no significant interaction.

This investigation demonstrated for the first time that LAAC was associated with a significant reduction of all-cause death. LAAC was also associated with a significant reduction in cardiovascular death and nonprocedural related bleeding.

The observation of lower mortality in the LAAC group is paramount considering 2/3 of the enrolled population were above 75 years which may impose significant competing mortality risks in this population. The primary driver for the lower mortality could be explained by the significant reduction in bleeding.

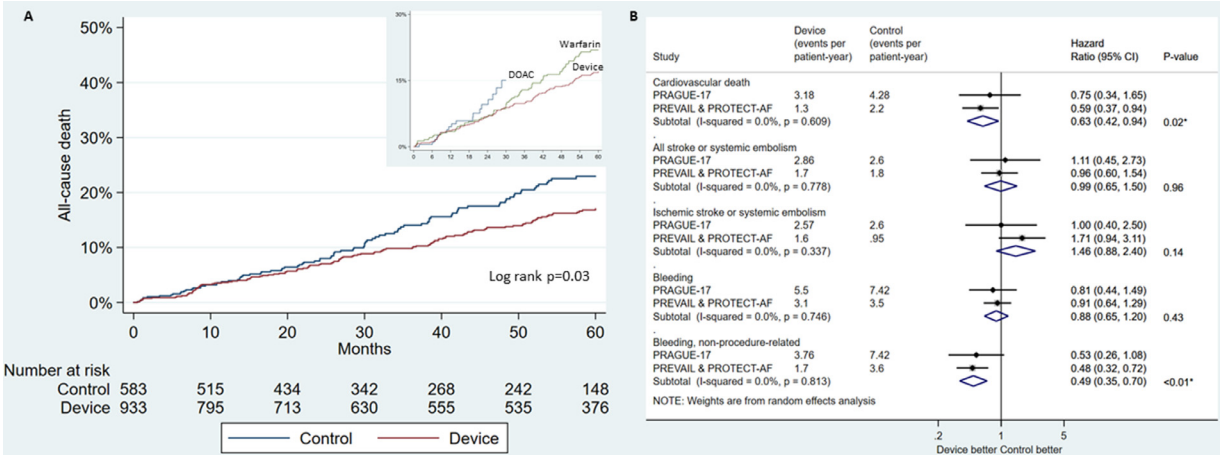

Figure 1. Kaplan Meier curve for all-cause death *(A)* and forest plot for clinical outcomes *(B)*. DOAC = direct oral anticoagulants; PRAUGE-17 = Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation; PREVAIL = Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy; PROTECT AF = WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation.

The divergence of mortality curves is notable beyond follow-up duration of 1 year − the time where most of the LAAC arm discontinued anticoagulant therapy. It is noteworthy in the PRAGUE-17 trial, the LAAC group did not require anticoagulation (only 13.8% of the patients received apixaban for 3 months).[3] This observation might indeed favor lower bleeding in the device arm, and therefore conferred a lower mortality.

The nonstatistically significant trend toward higher ischemic stroke or systemic embolism in the LAAC arm warrants further investigation. This observation is mainly derived from the lower-than-expected ischemic stroke events in the warfarin group of the PREVAIL trial at a rate of 0.73%. This rate could be partially explained by the relatively high appropriate time-in-therapeutic range for warfarin (68%) and/or low sample size, which is reflected by the wide confidence interval in our analysis.[2]

Although serious early procedure-related complications were not infrequent (5.0%) these complications occurred predominantly in earlier RCTs, with more contemporary data demonstrating a lower complication risks and higher success rates, perhaps due in part to improvements in patient selection and/or operator experience.[4] Nevertheless, the decision of LAAC should be individualized in a shared decision-making process with appropriately selected patients, considering the short-term procedural complications, long-term thromboembolism risk absent therapy, and bleeding risks while on anticoagulation.

In conclusion, in selected patients with nonvalvular AF, LAAC is associated with lower all-cause and cardiovascular death, and nonprocedural bleeding without increased ischemic events. Further long-term adequately powered trials assessing ischemic endpoints are needed.

Disclosures

The authors have no conflicts of interest to disclose.

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Letter to the Editor in Response to Nous et al 2020

Dear Editor,—

We were interested to read Nous et al's[1] recent article which described the prognostic benefits of using coronary computed tomography angiography (CCTA) to identify subclinical coronary artery disease (CAD) in patients with atrial fibrillation (AF). The addition of the calcium score and CCTA resulted in the re-classification of 47 patients' cardiovascular risk stratification score. Twenty-eight of these moved up in classification with 8 becoming very high-risk due to obstructive CAD. Initiation of secondary prevention (statin therapy) in these patients was concluded to be beneficial.[2]

Dunleavy et al[3] investigated patients undergoing computed tomography of the pulmonary veins prior to AF ablation therapies. They identified 131 patients with undiagnosed coronary artery calcification, yet none of these patients were prescribed a statin upon discharge. Thus, whilst CCTA may enhance risk stratification of AF patients it is apparent that this does not always translate to a change in clinical practice.

Nous et al[1] also states that the observed radiation dose of CCTA was high, limiting its use in asymptomatic patients. Cori et al[4] noted that in symptomatic patients undergoing radiofrequency ablation the use of CT compared to no CT resulted in a significantly higher effective radiation dose with no improvements in clinical outcomes for AF. Whilst it is worth noting that Nous et al[1] identified benefit in stratification for cardiovascular risk, it raises the point as to whether the benefits of routine CT in all AF patients would justify the radiation exposure.

Despite these limitations, the authors introduce a novel way in which CT in AF could be of prognostic benefit.[1] As the identification and management of CAD to improve AF burden is already recommended in the international guidelines,[5] this approach may be useful prior to catheter ablation given that patients are likely to undergo a CT. The true impact CT scans could have on stratifying the medical management of AF patients requires further investigation with larger sample sizes.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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2 July 2020

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Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke

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ABSTRACT

BACKGROUND

Surgical occlusion of the left atrial appendage has been hypothesized to prevent ischemic stroke in patients with atrial fibrillation, but this has not been proved. The procedure can be performed during cardiac surgery undertaken for other reasons.

METHODS

We conducted a multicenter, randomized trial involving participants with atrial fibrillation and a CHA_2DS_2-VASc score of at least 2 (on a scale from 0 to 9, with higher scores indicating greater risk of stroke) who were scheduled to undergo cardiac surgery for another indication. The participants were randomly assigned to undergo or not undergo occlusion of the left atrial appendage during surgery; all the participants were expected to receive usual care, including oral anticoagulation, during follow-up. The primary outcome was the occurrence of ischemic stroke (including transient ischemic attack with positive neuroimaging) or systemic embolism. The participants, research personnel, and primary care physicians (other than the surgeons) were unaware of the trial-group assignments.

RESULTS

The primary analysis population included 2379 participants in the occlusion group and 2391 in the no-occlusion group, with a mean age of 71 years and a mean CHA_2DS_2-VASc score of 4.2. The participants were followed for a mean of 3.8 years. A total of 92.1% of the participants received the assigned procedure, and at 3 years, 76.8% of the participants continued to receive oral anticoagulation. Stroke or systemic embolism occurred in 114 participants (4.8%) in the occlusion group and in 168 (7.0%) in the no-occlusion group (hazard ratio, 0.67; 95% confidence interval, 0.53 to 0.85; P=0.001). The incidence of perioperative bleeding, heart failure, or death did not differ significantly between the trial groups.

CONCLUSIONS

Among participants with atrial fibrillation who had undergone cardiac surgery, most of whom continued to receive ongoing antithrombotic therapy, the risk of ischemic stroke or systemic embolism was lower with concomitant left atrial appendage occlusion performed during the surgery than without it. (Funded by the Canadian Institutes of Health Research and others; LAAOS III ClinicalTrials.gov number, NCT01561651.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Whitlock at the David Braley Research Institute, Hamilton General Hospital, 237 Barton St. E, Hamilton, ON L8L 2X2, Canada, or at richard.whitlock@phri.ca.

*A full list of the LAAOS III Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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JAMA | Original Investigation

Association Between Left Atrial Appendage Occlusion and Readmission for Thromboembolism Among Patients With Atrial Fibrillation Undergoing Concomitant Cardiac Surgery

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IMPORTANCE The left atrial appendage is a key site of thrombus formation in atrial fibrillation (AF) and can be occluded or removed at the time of cardiac surgery. There is limited evidence regarding the effectiveness of surgical left atrial appendage occlusion (S-LAAO) for reducing the risk of thromboembolism.

OBJECTIVE To evaluate the association of S-LAAO vs no receipt of S-LAAO with the risk of thromboembolism among older patients undergoing cardiac surgery.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of a nationally representative Medicare-linked cohort from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (2011-2012). Patients aged 65 years and older with AF undergoing cardiac surgery (coronary artery bypass grafting [CABG], mitral valve surgery with or without CABG, or aortic valve surgery with or without CABG) with and without concomitant S-LAAO were followed up until December 31, 2014.

EXPOSURES S-LAAO vs no S-LAAO.

MAIN OUTCOMES AND MEASURES The primary outcome was readmission for thromboembolism (stroke, transient ischemic attack, or systemic embolism) at up to 3 years of follow-up, as defined by Medicare claims data. Secondary end points included hemorrhagic stroke, all-cause mortality, and a composite end point (thromboembolism, hemorrhagic stroke, or all-cause mortality).

RESULTS Among 10 524 patients undergoing surgery (median age, 76 years; 39% female; median CHA_2DS_2-VASc score, 4), 3892 (37%) underwent S-LAAO. Overall, at a mean follow-up of 2.6 years, thromboembolism occurred in 5.4%, hemorrhagic stroke in 0.9%, all-cause mortality in 21.5%, and the composite end point in 25.7%. S-LAAO, compared with no S-LAAO, was associated with lower unadjusted rates of thromboembolism (4.2% vs 6.2%), all-cause mortality (17.3% vs 23.9%), and the composite end point (20.5% vs 28.7%) but no significant difference in rates of hemorrhagic stroke (0.9% vs 0.9%). After inverse probability–weighted adjustment, S-LAAO was associated with a significantly lower rate of thromboembolism (subdistribution hazard ratio [HR], 0.67; 95% CI, 0.56-0.81; $P < .001$), all-cause mortality (HR, 0.88; 95% CI, 0.79-0.97; $P = .001$), and the composite end point (HR, 0.83; 95% CI, 0.76-0.91; $P < .001$) but not hemorrhagic stroke (subdistribution HR, 0.84; 95% CI, 0.53-1.32; $P = .44$). S-LAAO, compared with no S-LAAO, was associated with a lower risk of thromboembolism among patients discharged without anticoagulation (unadjusted rate, 4.2% vs 6.0%; adjusted subdistribution HR, 0.26; 95% CI, 0.17-0.40; $P < .001$), but not among patients discharged with anticoagulation (unadjusted rate, 4.1% vs 6.3%; adjusted subdistribution HR, 0.88; 95% CI, 0.56-1.39; $P = .59$).

CONCLUSIONS AND RELEVANCE Among older patients with AF undergoing concomitant cardiac surgery, S-LAAO, compared with no S-LAAO, was associated with a lower risk of readmission for thromboembolism over 3 years. These findings support the use of S-LAAO, but randomized trials are necessary to provide definitive evidence.

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Editorial page 345

Supplemental content

CME Quiz at jamanetwork.com/learning

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NCA - Percutaneous Left Atrial Appendage (LAA) Closure Therapy (CAG-00445N) - Decision Memo

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

The Centers for Medicare & Medicaid Services (CMS) covers percutaneous left atrial appendage closure (LAAC) for non-valvular atrial fibrillation (NVAF) through Coverage with Evidence Development (CED) under 1862(a)(1)(E) of the Social Security Act with the following conditions:

A. Left Atrial Appendage Closure devices are covered when the device has received Food and Drug Administration (FDA) Premarket Approval (PMA) for that device's FDA-approved indication and meet all of the conditions specified below:

- *The patient must have:*
  - *A CHADS2 score ≥ 2 (Congestive heart failure, Hypertension, Age >75, Diabetes, Stroke/transient ischemia attack/thromboembolism) or CHA2DS2-VASc score ≥ 3 (Congestive heart failure, Hypertension, Age ≥ 65, Diabetes, Stroke/transient ischemia attack/thromboembolism, Vascular disease, Sex category)*
  - *A formal shared decision making interaction with an independent non-interventional physician using an evidence-based decision tool on oral anticoagulation in patients with NVAF prior to LAAC. Additionally, the shared decision making interaction must be documented in the medical record.*
  - *A suitability for short-term warfarin but deemed unable to take long term oral anticoagulation following the conclusion of shared decision making, as LAAC is only covered as a second line therapy to oral anticoagulants.The patient (preoperatively and postoperatively) is under the care of a cohesive, multidisciplinary team (MDT) of medical professionals. The procedure must be furnished in a hospital with an established structural heart disease (SHD) and/or electrophysiology (EP) program.*
  - *The procedure must be performed by an interventional cardiologist(s), electrophysiologst(s) or cardiovascular surgeon (s) that meet the following criteria:*
    - *Has received training prescribed by the manufacturer on the safe and effective use of the device prior to performing LAAC; and*
    - *Has performed ≥ 25 interventional cardiac procedures that involve transeptal puncture through an intact septum; and*
    - *Continues to perform ≥ 25 interventional cardiac procedures that involve transeptal puncture through an intact septum, of which at least 12 are LAAC, over a two year period.*
- *The patient is enrolled in, and the MDT and hospital must participate in a prospective, national, audited registry that: 1) consecutively enrolls LAAC patients and 2) tracks the following annual outcomes for each patient for a period of at least four years from the time of the LAAC:*
  - *Operator-specific complications*
  - *Device-specific complications including device thrombosis*
  - *Stroke, adjudicated, by type*
  - *Transient Ischemic Attack (TIA)*
  - *Systemic embolism*
  - *Death*
  - *Major bleeding, by site and severity*

The registry must be designed to permit identification and analysis of patient, practitioner and facility level factors that predict patient risk for these outcomes. The registry must collect all data necessary to conduct analyses adjusted for relevant confounders and have a written executable analysis plan in place to address the following

2022 CPT Code Review

Cerebral Embolic Protection Devices

Code**: 33370** Transcatheter placement and subsequent removal of cerebral embolic protection device(s), including arterial access, catheterization, imaging, and radiological supervision and interpretation, percutaneous

Similar codes: None

Description: Cerebral embolic protection devices are filters designed to capture or deflect emboli traveling to the brain during transcatheter aortic valve replacement procedures in order to protect the supra-aortic vessels from embolic debris. These filters are normally positioned across the origin of supra-aortic vessels before the advancement of the TAVR system across the aortic valve and is retrieved at the end of the procedure. If emboli can be deflected using these devices, then stroke could be reduced as a complication of this type of procedure. There are several such devices on the market, including the Embrella, Claret, and Triguard devices.

Evidence

1) **Lansky 2021**, REFLECT I trial
    1. Triguard device
    2. Prospective single-blind study 2:1 randomization (N=141 device vs N=63 control, plus 54 "roll in" patient)
    a. Roll in patients defined as proctored cases performed when investigators did not have prior experience with the device
    b. Patients undergoing transcatheter aortic valve replacement
    c. Study stopped early by the data safety monitoring board
    3. The primary safety outcome (defined as composite of all-cause death, stroke, life-threatening or disabling bleeding, stage 2–3 acute kidney injury (AKI), coronary artery obstruction requiring intervention, major vascular complications, and valve-related dysfunction requiring repeat procedure) at 30 days occurred in 21.8% (95% CI 15.1–29.8%) of subjects in the TG group, meeting the primary safety endpoint compared with the pre-specified performance goal of 34.4% (P<0.001)
    4. The primary hierarchical efficacy endpoint was not significantly different between groups, with a mean score (higher is better) of -5.3± 99.8 for TG and 11.8± 96.4 for controls (P= 0.314)
2) **Nazif 2021**, REFLECT II trial
    1. TriGuard 3 device
    2. Prospective single-blind study 2:1 randomization (N=121 device vs N=58 control, plus 41 "roll in" patient)
    a. Roll in patients defined as proctored cases performed when investigators did not have prior experience with the device
    b. Patients undergoing transcatheter aortic valve replacement
    c. Study stopped early by the data safety monitoring board
    d. primary hierarchical composite efficacy endpoint (including death or stroke at 30 days, National Institutes of Health Stroke Scale score worsening in hospital, and cerebral ischemic lesions on diffusion weighted magnetic resonance imaging at 2 to 5 days)
    e. The trial met its primary safety endpoint compared with the PG (15.9% vs. 34.4% ($p < 0.0001$). The primary hierarchal efficacy endpoint at 30 days was not met (mean scores [higher is better]: -8.58 TG3 vs. 8.08 control; $p = 0.857$).

3) **Butala 2020**, Transcatheter valve therapy registry study
    1. Cohort registry study using the Society for Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry.
    2. N=126,186 patients from 599 sites
    3. In our primary analysis using the instrumental variable model, there was no association between EPD use and in-hospital stroke (adjusted relative risk, 0.90 [95% CI, 0.68–1.13]; absolute risk difference, −0.15% [95% CI, −0.49 to 0.20]). However, in our secondary analysis using the propensity score–based model, EPD use was associated with 18% lower odds of in-hospital stroke (adjusted odds ratio, 0.82 [95% CI, 0.69–0.97]; absolute risk difference, −0.28% [95% CI, −0.52 to −0.03]).
    4. CONCLUSIONS: In this nationally representative observational study, we did not find an association between EPD use for TAVR and in-hospital stroke in our primary instrumental variable analysis, and found only a modestly lower risk of in-hospital stroke in our secondary propensity-weighted analysis. These findings provide a strong basis for large-scale randomized, controlled trials to test whether EPDs provide meaningful clinical benefit for patients undergoing TAVR.

HERC staff summary: Cerebral embolic protection devices are actively being studied as a way to reduce the risk of stroke during transcatheter aortic valve replacement surgeries. However, the studies to date have not found a reduction in stroke, death, or other important outcomes.

HERC staff recommendation:

1) Place CPT 33370 (Transcatheter placement and subsequent removal of cerebral embolic protection device(s), including arterial access, catheterization, imaging, and radiological supervision and interpretation, percutaneous) on line 662 and place entry in GN173 as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
33370	Transcatheter placement and subsequent removal of cerebral embolic protection device(s)	Insufficient evidence of effectiveness	November 2021

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 2670–2679
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CLINICAL RESEARCH
Interventional cardiology

A randomized evaluation of the TriGuard™ HDH cerebral embolic protection device to Reduce the Impact of Cerebral Embolic LEsions after TransCatheter Aortic Valve ImplanTation: the REFLECT I trial

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See page 2680 for the editorial comment on this article (doi:10.1093/eurheartj/ehab212)

Aims The REFLECT I trial investigated the safety and effectiveness of the TriGuard™ HDH (TG) cerebral embolic deflection device in patients undergoing transcatheter aortic valve replacement (TAVR).

Methods and results This prospective, multicentre, single-blind, 2:1 randomized (TG vs. no TG) study aimed to enrol up to 375 patients, including up to 90 roll-in patients. The primary combined safety endpoint (VARC-2 defined early safety) at 30 days was compared with a performance goal. The primary efficacy endpoint was a hierarchical composite of (i) all-cause mortality or any stroke at 30 days, (ii) National Institutes of Health Stroke Scale (NIHSS) worsening at 2–5 days or Montreal Cognitive Assessment worsening at 30 days, and (iii) total volume of cerebral ischaemic lesions detected by diffusion-weighted magnetic resonance imaging at 2–5 days. Cumulative scores were compared between treatment groups using the Finkelstein–Schoenfeld method. A total of 258 of the planned, 375 patients (68.8%) were enrolled (54 roll-in and 204 randomized). The primary safety outcome was met compared with the performance goal (21.8% vs. 35%, $P < 0.0001$). The primary hierarchical efficacy endpoint was not met (mean efficacy score, higher is better: -5.3 ± 99.8 TG vs. 11.8 ± 96.4 control, $P = 0.31$). Covert central nervous system injury was numerically lower with TG both in-hospital (46.1% vs. 60.3%, $P = 0.0698$) and at 5 days (61.7 vs. 76.2%, $P = 0.054$) compared with controls.

Conclusion REFLECT I demonstrated that TG cerebral protection during TAVR was safe in comparison with historical TAVR data but did not meet the predefined effectiveness endpoint compared with unprotected TAVR controls.

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Randomized Evaluation of TriGuard 3 Cerebral Embolic Protection After Transcatheter Aortic Valve Replacement

REFLECT II

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ABSTRACT

OBJECTIVES The REFLECT II (Randomized Evaluation of TriGuard 3 Cerebral Embolic Protection After Transcatheter Aortic Valve Implantation) trial was designed to investigate the safety and efficacy of the TriGUARD 3 (TG3) cerebral embolic protection in patients undergoing transcatheter aortic valve replacement.

BACKGROUND Cerebral embolization occurs frequently following transcatheter aortic valve replacement and procedure-related ischemic stroke occurs in 2% to 6% of patients at 30 days. Whether cerebral protection with TriGuard 3 is safe and effective in reducing procedure-related cerebral injury is not known.

METHODS This prospective, multicenter, single-blind, 2:1 randomized (TG3 vs. no TG3) study was designed to enroll up to 345 patients. The primary 30-day safety endpoint (Valve Academic Research Consortium-2 defined) was compared with a performance goal (PG). The primary hierarchical composite efficacy endpoint (including death or stroke at 30 days, National Institutes of Health Stroke Scale score worsening in hospital, and cerebral ischemic lesions on diffusion-weighted magnetic resonance imaging at 2 to 5 days) was compared using the Finkelstein-Schoenfeld method.

RESULTS REFLECT II enrolled 220 of the planned 345 patients (63.8%), including 41 roll-in and 179 randomized patients (121 TG3 and 58 control subjects) at 18 US sites. The sponsor closed the study early after the U.S. Food and Drug Administration recommended enrollment suspension for unblinded safety data review. The trial met its primary safety endpoint compared with the PG (15.9% vs. 34.4% ($p < 0.0001$). The primary hierarchal efficacy endpoint at 30 days was not met (mean scores [higher is better]: −8.58 TG3 vs. 8.08 control; $p = 0.857$). A post hoc diffusion-weighted magnetic resonance imaging analysis of per-patient total lesion volume above incremental thresholds showed numeric reductions in total lesion volume >500 mm^3 (−9.7%) and >1,000 mm^3 (−44.5%) in the TG3 group, which were more pronounced among patients with full TG3 coverage: −51.1% (>500 mm^3) and −82.9% (>1,000 mm^3).

CONCLUSIONS The REFLECT II trial demonstrated that the TG3 was safe compared with a historical PG but did not meet its pre-specified primary superiority efficacy endpoint. (J Am Coll Cardiol Intv 2021;14:515–27)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Circulation

ORIGINAL RESEARCH ARTICLE

Cerebral Embolic Protection and Outcomes of Transcatheter Aortic Valve Replacement

Results From the Transcatheter Valve Therapy Registry

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BACKGROUND: Stroke remains a devastating complication of transcatheter aortic valve replacement (TAVR), which has persisted despite refinements in technique and increased operator experience. While cerebral embolic protection devices (EPDs) have been developed to mitigate this risk, data regarding their impact on stroke and other outcomes after TAVR are limited.

METHODS: We performed an observational study using data from the Society for Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Patients were included if they underwent elective or urgent transfemoral TAVR between January 2018 and December 2019. The primary outcome was in-hospital stroke. To adjust for confounding, the association between EPD use and clinical outcomes was evaluated using instrumental variable analysis, a technique designed to support causal inference from observational data, with site-level preference for EPD use within the same quarter of the procedure as the instrument. We also performed a propensity score–based secondary analysis using overlap weights.

RESULTS: Our analytic sample included 123 186 patients from 599 sites. The use of EPD during TAVR increased over time, reaching 28% of sites and 13% of TAVR procedures by December 2019. There was wide variation in EPD use across hospitals, with 8% of sites performing >50% of TAVR procedures with an EPD and 72% performing no procedures with an EPD in the last quarter of 2019. In our primary analysis using the instrumental variable model, there was no association between EPD use and in-hospital stroke (adjusted relative risk, 0.90 [95% CI, 0.68–1.13]; absolute risk difference, −0.15% [95% CI, −0.49 to 0.20]). However, in our secondary analysis using the propensity score–based model, EPD use was associated with 18% lower odds of in-hospital stroke (adjusted odds ratio, 0.82 [95% CI, 0.69–0.97]; absolute risk difference, −0.28% [95% CI, −0.52 to −0.03]). Results were generally consistent across the secondary end points, as well as subgroup analyses.

CONCLUSIONS: In this nationally representative observational study, we did not find an association between EPD use for TAVR and in-hospital stroke in our primary instrumental variable analysis, and found only a modestly lower risk of in-hospital stroke in our secondary propensity-weighted analysis. These findings provide a strong basis for large-scale randomized, controlled trials to test whether EPDs provide meaningful clinical benefit for patients undergoing TAVR.

Key Words: embolic protection devices ■ registries ■ stroke ■ transcatheter valve aortic replacement

Editorial, see p 2241

During the past decade, transcatheter aortic valve replacement (TAVR) has transformed the treatment of aortic stenosis.[1] Although technological improvements, refinements in technique, and increased operator experience have led to progressive reductions in most complications, periprocedural stroke continues to occur in ≈2% of patients after TAVR.[2] Many of these are attributed to embolic events during the procedure and can lead

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2022 CPT Code Review
Drug-Induced Sleep Endoscopy

Code: **42975** Drug-induced sleep endoscopy, with dynamic evaluation of velum, pharynx, tongue base, and larynx for evaluation of sleep-disordered breathing, flexible, diagnostic

Similar codes: none

Description: Drug-induced sleep endoscopy (DISE), also known as sleep nasoendoscopy or nasopharyngoscopy, is an upper airway evaluation technique which uses a flexible fiberoptic endoscope to examine the site of airway obstruction while individuals are in a sedative-induced sleep designed to mimic the natural sleep state. The purpose of DISE is to determine what causes site of airway obstruction during sleep and help surgeons determine and plan appropriate surgical procedures for their patients with OSA who have failed, or were unable to tolerate, positive airway pressure (e.g., CPAP or BIPAP).

The DISE procedure is currently listed as one of the criteria for evaluation of medical necessity for the FDA-approved hypoglossal nerve neurostimulation. Note: hypoglossal nerve stimulation is not a covered therapy for OSA on the Prioritized List

Evidence

1) **Cheong 2021**, review of drug-induced sleep endoscopy for management of obstructive sleep apnea
    a. Utilization for determining possible benefit from mandibular advancement devices (MAD)
        i. Many of the published studies on DISE and MAD are retrospective. Selection bias is also a major issue as those recruited for MAD tended to have less severe OSA, and patients deemed not likely to benefit were not recruited for MAD use in the first place. Nonetheless, based on the currently available information, it appears that most patients who have improved airway dimensions with mandibular advancement during DISE will benefit from an MAD. Conclusion: More studies are required to demonstrate the efficacy of DISE in the management of OSA.
    b. Utilization in prescribing positional therapy
        i. Positional maneuvers during DISE can assess the feasibility of combination therapy (e.g., MAD or limited surgery with positional therapy) for multilevel collapse, potentially reducing the number of invasive interventions required
    c. Role in planning surgical intervention
        i. Further multicenter prospective randomized trials with control groups who do not undergo DISE are sorely needed to investigate the true clinical impact of DISE in patients undergoing OSA surgery.
    d. Role in planning upper airway stimulation (e.g. hypoglossal nerve stimulation)
        i. DISE was incorporated as a mandatory screening investigation in the landmark Stimulation Therapy for Apnea Reduction (STAR) trial following earlier studies that showed CCCp during DISE to be associated with poor results after upper airway stimulation
    e. Conclusions: High-quality clinical evidence supporting the value of DISE in guiding alternative treatments for OSA is limited

2022 CPT Code Review
Drug-Induced Sleep Endoscopy

Other payer policies

1) **Aetna 2021**
    a. *Drug-Induced Sleep Endoscopy (DISE):* Aetna considers the use of DISE medically necessary to evaluate appropriateness of FDA-approved hypoglossal nerve stimulation when all of the criteria for hypoglossal nerve stimulation are met. Aetna considers DISE experimental and investigational for all other indications because of insufficient evidence in the peer-reviewed published medical literature of its safety and effectiveness
2) **Cigna 2021** only covers DISE for evaluation for hypoglossal nerve stimulation

HERC staff summary

Drug induce sleep endoscopy appears to be an experimental procedure. It is only covered by private payers when used for evaluation for hypoglossal nerve stimulation, which is not a covered procedure on the Prioritized List. Please see discussion on hypoglossal nerve stimulation later in the 2022 CPT code review.

HERC staff recommendations:

1) Place **42975 (**Drug-induced sleep endoscopy, with dynamic evaluation of velum, pharynx, tongue base, and larynx for evaluation of sleep-disordered breathing, flexible, diagnostic) on line 662 and add an entry to GN173 as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
42975	Drug-induced sleep endoscopy, with dynamic evaluation of velum, pharynx, tongue base, and larynx for evaluation of sleep-disordered breathing, flexible, diagnostic	Insufficient evidence of effectiveness	November 2021

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Review

The Emerging Role of Drug-Induced Sleep Endoscopy in the Management of Obstructive Sleep Apnea

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Obstructive sleep apnea is a prevalent sleep disorder characterized by partial or complete obstruction of the upper airway. Continuous positive airway pressure is the first-line therapy for most patients, but adherence is often poor. Alternative treatment options such as mandibular advancement devices, positional therapy, and surgical interventions including upper airway stimulation target different levels and patterns of obstruction with varying degrees of success. Drug-induced sleep endoscopy enables the visualization of upper airway obstruction under conditions mimicking sleep. In the era of precision medicine, this additional information may facilitate better decision-making when prescribing alternative treatment modalities, with the hope of achieving better adherence and/or success rates. This review discusses the current knowledge and evidence on the role of drug-induced sleep endoscopy in the non-positive airway pressure management of obstructive sleep apnea.

Keywords. *Surgery; Mandibular Advancement Device; Obstructive Sleep Apnea; Endoscopy*

INTRODUCTION

Obstructive sleep apnea (OSA) affects nearly one billion people worldwide based on statistics published in 2019, with a prevalence exceeding 50% in some countries [1]. While snoring and excessive daytime sleepiness are the commonest and most emphatic complaints of patients, it is the resultant cardiovascular sequelae that have the direst consequences on health [2-4]. Continuous positive airway pressure (CPAP) has long been commonly accepted as the first-line treatment for OSA. However, it is well-known for having low levels of acceptance and poor adherence [5]. Alternative treatments such as mandibular advancement devices (MADs), positional therapy, and upper airway surgery (including upper airway stimulation) may be considered for patients who cannot tolerate or accept CPAP [6-8].

OSA therapy is traditionally guided by the results of a sleep study that determines the severity of OSA by calculating the average number of respiratory events per hour of sleep, otherwise known as the apnea-hypopnea index (AHI). The AHI, however, does not reflect the complicated pathophysiology behind OSA; it merely reflects the resultant respiratory compromise. Drilling down to the contributory roles of various anatomical and/or non-anatomical pathophysiological mechanisms behind OSA in each patient is useful in order to better select appropriate treatment methods [9]. Various algorithms utilizing metrics apart from the AHI that are reported during routine clinical polysomnography (PSG) have been created to do this [10-12], but they are still not widely employed in the clinical setting. Analysis of inspiratory flow shape during PSG may help to pinpoint the specific site of obstruction, particularly in cases with an isolated collapsing pharyngeal structure [13], but obstruction often occurs at multiple levels in OSA [14,15]. Sleep studies therefore play a limited role in determining the suitability of alternative treatments at the individual level.

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Table 1. Summary of potential roles of DISE in determining treatment options for OSA

Alternative treatment for OSA	Potential role of DISE
Mandibular advancement device	Retrolingual collapse during DISE and expansion of the retrolingual space with mandibular advancement are predictive of treatment success. A simulation bite may mimic the actual effects of a mandibular advancement device more accurately than a jaw thrust.
Positional therapy	Improvement in collapse when the patient is in the lateral (compared to supine) position is predictive of success. Obstruction at the level of the tongue base and epiglottis will change most significantly with position.
Surgery	To select an appropriate surgical technique for the site of obstruction. DISE findings may alter the initial surgical plan. Retrolingual obstruction may suggest lower success rates with uvulopalatopharyngoplasty alone. DISE findings may not be predictive of success for certain soft tissue surgical procedures (e.g., tongue base surgery) and may not improve the overall surgical success rate. Oropharyngeal wall obstruction may suggest a higher success rate with maxillomandibular advancement than soft tissue surgery. Pediatric patients at high risk of persistent OSA may benefit from DISE even before undergoing tonsillectomy and adenoidectomy.
Upper airway stimulation	To determine hypoglossal nerve stimulator candidacy, as complete concentric collapse of the palate has been associated with poorer outcomes.

DISE, drug-induced sleep endoscopy; OSA, obstructive sleep apnea.

Drug-induced sleep endoscopy (DISE) has emerged as a safe and useful technique that allows direct visualization of the anatomy and collapsibility of the upper airway via nasoendoscopy while the patient is sedated [16-18]. It is a relatively simple procedure, and complications such as central apnea and deep desaturation requiring intubation are infrequent [19]. Since it was first described in 1991 [20], anecdotal reports, case series, and prospective registries on DISE have been published. Propofol, midazolam, and dexmedetomidine are the most commonly employed anesthetic drugs. Administration techniques vary across centers, ranging from bolus doses to regular injection doses and continuous infusions. Clinical assessments of unconsciousness with vocal and/or tactile stimulation, as well as indices such as the bispectral index score, help determine the appropriate level of sedation. The variation in techniques worldwide reflects limitations in the realm of DISE; specifically, no drug currently achieves or mimics natural sleep perfectly, and there is no established "best" way at present to perform DISE despite many recommendations. Multiple classification systems have been devised over the years to report endoscopic findings accurately and succinctly, but none has been universally adopted [21,22]. As CPAP functions by splinting the entire length of the upper airway open, patients on CPAP therapy do not usually undergo DISE to determine the exact sites of obstruction, but may benefit from a more precise evaluation if it is necessary to troubleshoot the mechanism of CPAP failure [23]. This review provides an overview of the current knowledge and evidence on the role of DISE in non-CPAP management alternatives for OSA. Many studies in the current literature are retrospective, non-randomized, and heterogeneous, making it challenging to conduct head-to-head comparisons or wide-scale validation of specific techniques. We discuss some unique studies that reveal different perspectives in this field, and summarize what DISE can offer in the management of OSA (Table 1).

HIGHLIGHTS

- Drug-induced sleep endoscopy (DISE) allows visualization of upper airway collapsibility for non-continuous positive airway pressure therapy of obstructive sleep apnea (OSA).
- Jaw thrust or simulation bite predicts benefits from a mandibular advancement device.
- Positional maneuvers during DISE assess the potential utility of positional therapy.
- Knowledge of collapse levels and configurations enables customization of the surgical plan.
- More studies are required to demonstrate the efficacy of DISE in the management of OSA.

ROLE OF DISE IN PRESCRIBING MADs

The MAD is an oral appliance recommended for adult OSA patients who are intolerant of CPAP or prefer an MAD [24]. By mechanically advancing the mandible, MADs enlarge the upper airway laterally, predominantly at the velopharynx, due to stretching of the soft tissue connecting the mandibular rami, tongue, soft palate and lateral walls [25,26]. The tongue muscles are shifted forward [25,27], and the airway becomes less collapsible. It is effective in reducing breathing disturbances, AHI, and excessive daytime sleepiness. Compared to CPAP, MADs achieve similar health-related outcomes, but have better acceptance and tolerance rates [28].

Being able to accurately predict whether an MAD will be beneficial is advantageous, as device and follow-up costs can be sizable. To simulate wearing an MAD, the mandible is manually advanced by 5–10 mm during DISE. If the upper airway caliber

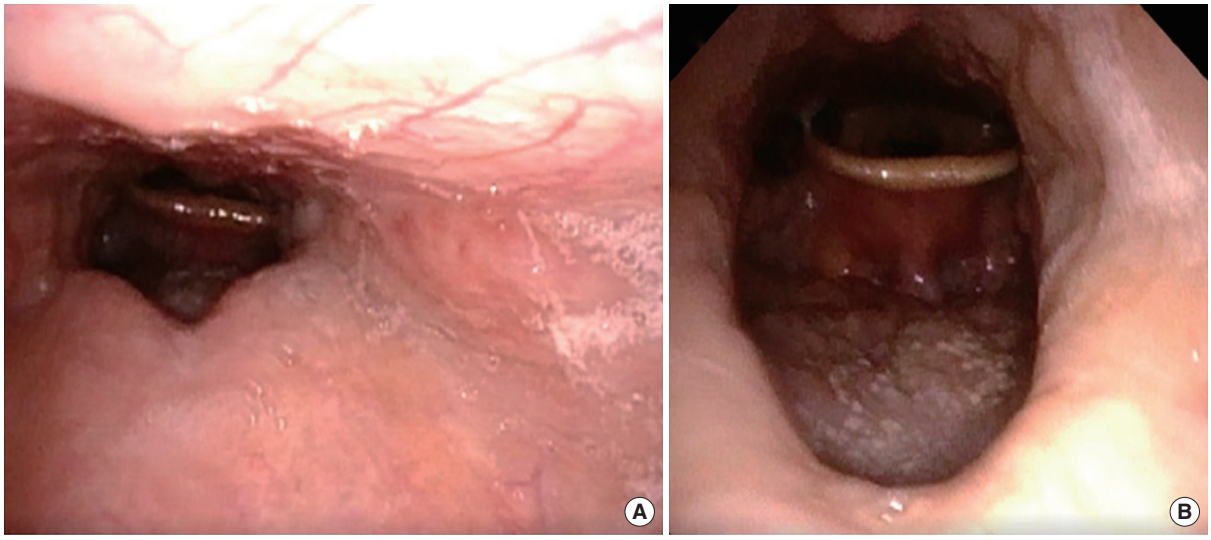

Fig. 1. The narrow retropalatal and retrolingual spaces seen during drug-induced sleep endoscopy (A) expand when a jaw thrust maneuver is performed (B).

increases significantly in response to manual advancement of the mandible, it can be predicted that MAD therapy will be helpful (Fig. 1).

One of the earliest accounts of DISE being able to predict successful MAD therapy was published in 2005 [29]. The study described 19 patients who underwent MAD therapy after diagnostic DISE revealed multilevel obstruction (n=18) or isolated tongue base obstruction (n=1). Gentle mandibular advancement was performed in 17 of these patients, improving airway patency and snoring in all. Follow-up DISE with an MAD after 8–25 months showed the following: three patients had a clear airway without snoring, eight had marked subjective improvements in both the airway and snoring, five improved but had residual palatal snoring, and one did not demonstrate any change. The patient with no change subsequently experienced symptom resolution after further advancement of his MAD, indicating that it had not been titrated adequately. PSG done at least 2 months after subjectively successful MAD use showed an overall decrease in the median AHI from 28 (range, 14–62) to 6 (range, 0.3–17) events/hr. Treatment success (defined as AHI <10 events/hr) was achieved in 74% of the patients. The authors suggested that DISE could serve as a diagnostic test to identify patients with obstruction configurations that would benefit from an MAD, and as a prognostic indicator for MAD therapy.

More recently, a non-randomized retrospective case control study compared the MAD treatment outcomes of 20 OSA patients who had undergone DISE before using an MAD (DISE group) versus 20 who had not (non-DISE group) [30]. The DISE and non-DISE cohorts were matched for age, body mass index, and pre-MAD PSG characteristics. The DISE group was selected for MAD therapy because of the observation that the jaw thrust maneuver during DISE led to significant improvement in the retrolingual and retropalatal airspace. The DISE group was found to have a higher rate of treatment success, defined as a post-treatment AHI <20 events/hr with a 50% improvement (75% of DISE patients vs. 50% of non-DISE patients; $P=0.09$), and a larger proportion dropped to <5 events/hr (45% of DISE patients vs. 15% of non-DISE patients; $P=0.04$). There was a significantly greater decrease in the AHI in the DISE group than in the non-DISE group (31.54±23.19 to 7.93±6.03 events/hr vs. 29.81±19.36 to 14.67±12.23 events/hr, respectively; $P=0.04$). Although limitations include small sample size, lack of randomization, and varying levels of sleep studies used in post-treatment evaluation, this study suggests that enlargement of the retrolingual and retropalatal airway during a jaw thrust is associated with effective MAD treatment.

To determine whether manually pulling the mandible forward or using a simulation bite was more accurate at predicting MAD outcomes, a center performed DISE on 200 patients with sleep-disordered breathing who were considering MAD treatment [31]. Multilevel obstruction was predominantly seen (87.2%), with combined palatal and tongue base collapse (34.4%) being the most common pattern. The upper airway was assessed first with a simulation bite *in situ*. The simulation bite was then removed to return the patient to baseline, and finally the patient was evaluated using a chin-lift maneuver to achieve maximal protrusion of the mandible. After review by a dental sleep professional who was blinded to the DISE findings, 110 OSA patients (of whom 53.6% had mild OSA) eventually completed MAD titration and a repeat PSG with MAD *in situ*. Unfortunately, this study did not have a control group. Positive treatment response, defined as a reduction in AHI of ≥50%, was achieved in 69% of patients. After adjusting for sex, age, body mass index, AHI, and positional dependency, a complete absence of collapse while wearing the

simulation bite during DISE was independently associated with a positive treatment response (P=0.007). The presence of palatal collapse (P=0.02) and absence of hypopharyngeal collapse (P=0.03) during baseline DISE were also independent predictors of positive treatment response. The use of a simulation bite during DISE to predict the treatment outcome showed a sensitivity of 91%, a specificity of 53%, a positive likelihood ratio of 1.96, and a negative likelihood ratio of 0.16. Interestingly, the chin-lift maneuver was not found to have a statistically significant association with upper airway caliber or treatment response. The authors postulated that the simulation bite was a significant predictor because it added a certain amount of vertical opening, which also occurs with an MAD, but not with a chin-tilt or jaw thrust. Another study reported only slight to moderate agreement in the degree of obstruction and configuration of the upper airway between a jaw thrust and a boil-and-bite MAD during DISE [32]. Some have pointed out that the discomfort from a jaw thrust can awaken or reduce the depth of sedation of the patient, which may play a part in improving the degree of obstruction [33,34].

A recent study investigated the use of collapse patterns seen during DISE as a means of prognosticating MAD success and failure [35]. This study analyzed 72 patients who were prescribed an MAD, completed baseline DISE, and underwent a 3-month follow-up PSG. The presence of tongue base collapse during DISE was associated with a 3.69 times higher odds ratio (P=0.013) for achieving response, defined as a decrease in AHI of ≥50%. Complete concentric collapse at the palate (CCCp) and complete laterolateral oropharyngeal collapse resulted in 5.32 (P=0.234) and 6.62 (P=0.033) times higher odds of worsening baseline AHI (treatment deterioration) respectively, after adjusting for AHI and body mass index. In a retrospective analysis, the authors noted that using tongue base collapse and CCCp configurations to advise for and against MAD prescription in their subgroup of moderate to severe OSA patients would have increased the proportion of patients who responded and reduced the proportion of patients who deteriorated by approximately 50%, respectively.

Many of the published studies on DISE and MAD are retrospective. Selection bias is also a major issue as those recruited for MAD tended to have less severe OSA, and patients deemed not likely to benefit were not recruited for MAD use in the first place. Nonetheless, based on the currently available information, it appears that most patients who have improved airway dimensions with mandibular advancement during DISE will benefit from an MAD. Application of a custom-made simulation bite in preadjusted maximum comfortable protrusion when clinically feasible may improve predictive accuracy.

ROLE OF DISE IN PRESCRIBING POSITIONAL THERAPY

A large proportion of OSA patients have positional OSA because gravitational forces worsen upper airway collapse when they are supine [36-38]. Positional therapy works by preventing supine sleep; techniques include special pillows and binders, positional alarms, vests, and the older method of sewing tennis balls into a pocket on the back of a shirt. Although equally effective at reducing respiratory indices in patients with mild OSA, the more cost-effective tennis ball technique has lower adherence and poorer quality of life outcomes than sleep position trainers [39].

Turning the patient to the lateral position during DISE can simulate the possible effect of positional therapy. It has been suggested that turning both the head and trunk lateral is more

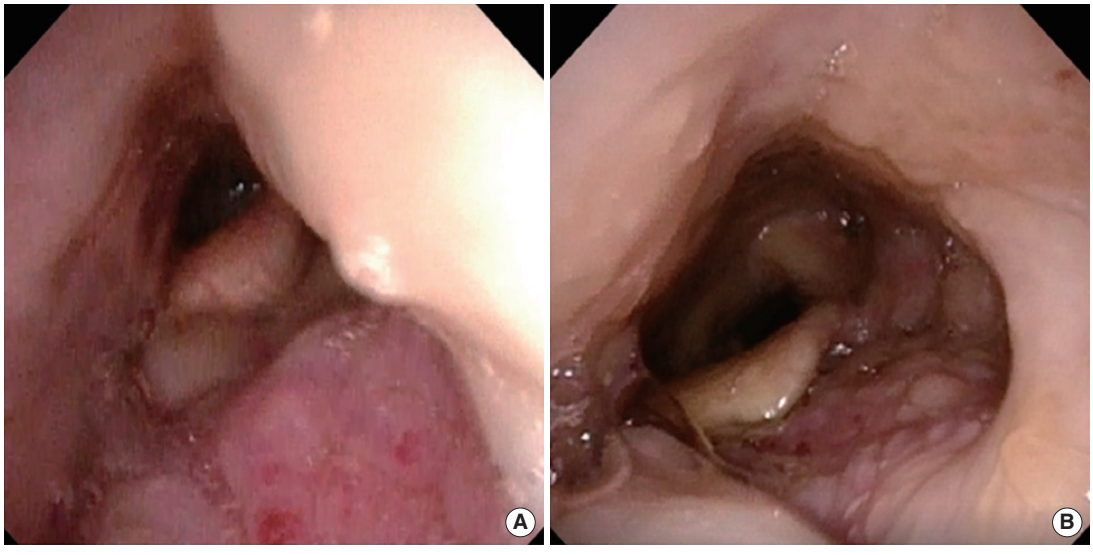

Fig. 2. The tongue base collapse seen in supine position (A) during drug-induced sleep endoscopy improves with head turning (B). The effect of palatal coupling is also visible in (B).

representative of non-supine sleep positioning in patients with positional OSA than turning the head alone [40]. Improvement in collapse is highly marked in positional OSA patients, with up to 91% of positional OSA patients demonstrating at least partial improvement when lateral instead of supine [41,42], suggesting that DISE frequently confirms the positional findings on PSG. DISE may be useful in situations where a patient is certain that his/her non-supine sleep is subjectively better than when supine, but PSG reports inadequate non-supine sleep time. Tongue base and epiglottic collapse improve most with positional change (Fig. 2) [42,43].

A randomized controlled study conducted on patients with residual positional OSA despite MAD treatment showed that the additional use of a sleep position trainer with an MAD resulted in higher therapeutic efficacy, as proven on PSG, than using either of the treatment modalities alone [44]. Positional maneuvers during DISE can assess the feasibility of combination therapy (e.g., MAD or limited surgery with positional therapy) for multilevel collapse, potentially reducing the number of invasive interventions required [40].

ROLE OF DISE IN PLANNING SURGICAL INTERVENTION

OSA surgery aims to improve upper airway patency by removing structures that cause obstructions, stiffening collapsible areas, and expanding the luminal dimensions [45]. Surgical interventions carry inherent risks, so it is critical that the procedures and patients are appropriately selected to maximize the success rate. Although an awake endoscopic examination is informative and easily performed by otolaryngologists, DISE confers additional information about collapse configurations under sedation. Some surgeons supplement the static clinical examination with the Müller maneuver, but this maneuver is effort-dependent and has been criticized for flaws such as inaccuracy at predicting retrolingual collapse during sedation or sleep (Figs. 3 and 4) [46,47].

Identifying the main contributor(s) of collapse guides decision-making. Lateral pharyngeal wall collapse, for instance, is notoriously difficult to address with soft tissue surgery. Maxillomandibular advancement advances the bony framework of the upper and lower jaws, is highly successful at reducing upper airway collapsibility (especially at the lateral walls), and produces excellent outcomes [48,49]. Although it is arguably more major surgery, it is justifiable to propose maxillomandibular advancement surgery as the primary procedure in cases where DISE reveals significant lateral pharyngeal collapse.

Several studies have also investigated the utility of DISE in predicting the likelihood of success following specific surgical procedures. One study found that different patterns of airway obstruction seen on DISE predicted different outcomes after tonsillectomy and uvulopalatopharyngoplasty [50]. Twenty OSA patients with soft palate obstruction identified during the Müller maneuver underwent DISE before surgery. The levels of obstruction seen during DISE were categorized into upper airway ob-

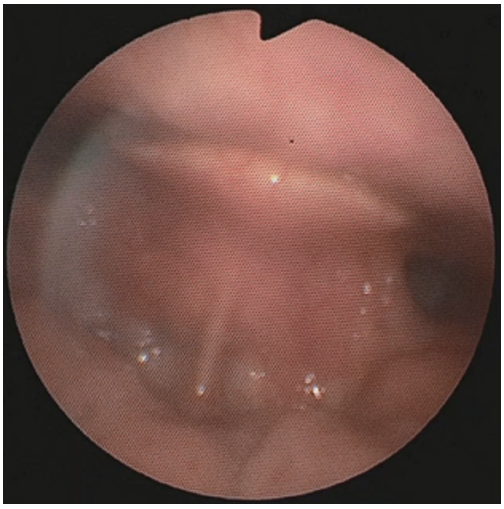

Fig. 4. Rhythmic complete anteroposterior collapse of the epiglottis was seen during drug-induced sleep endoscopy. This did not occur during the clinical examination while the patient was awake, even during the Müller maneuver.

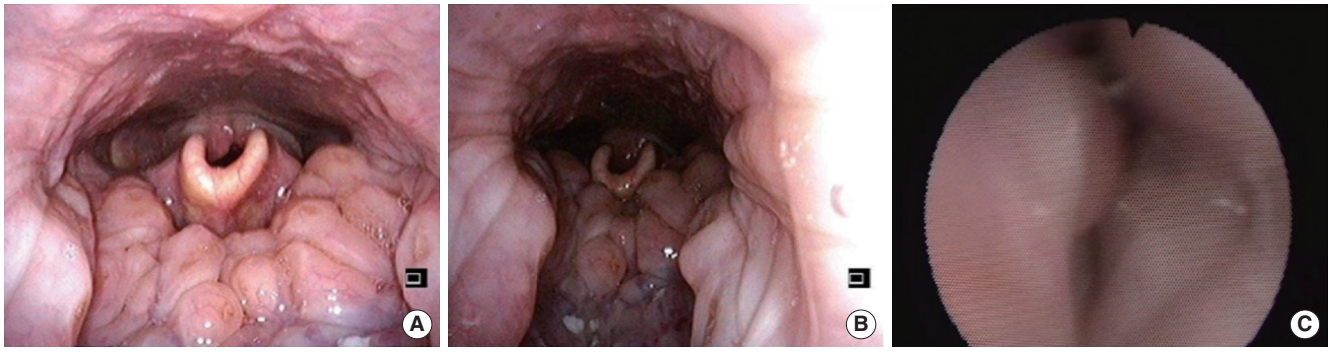

Fig. 3. (A) Endoscopic view of the upper airway at rest. (B) The lateral oropharyngeal walls collapsed partially during the Müller maneuver. (C) However, complete collapse was seen during drug-induced sleep endoscopy.

struction (i.e., originating from the uvula, soft palate, and/or tonsils) and lower airway obstruction (i.e., originating from the tongue base and/or epiglottis). Surgical success was defined as a decrease in the respiratory disturbance index to <5 events/hr or by ≥50%. A higher surgical success rate was reported in the group with upper airway obstruction during DISE ($P<0.05$). All 14 successful cases displayed upper airway obstruction. The group with lower airway obstruction had a lower success rate ($P<0.01$).

However, the outcomes of other surgical procedures, such as tongue base surgery, are not as predictable. A retrospective case series of 101 patients who underwent transoral robotic surgery found that preoperative DISE findings were not predictive of success or cure, although patients without oropharyngeal lateral wall collapse were more likely to demonstrate improvement [51]. Similarly, a recently published single-center retrospective study reported the surgical outcomes of 95 patients who had undergone tongue base surgery as part of multilevel surgery [52]. No significant difference was found between the group that only underwent a preoperative awake endoscopic examination with the Müller maneuver and the group that underwent DISE in addition to the Müller maneuver, both in terms of percentage of AHI improvement (47.0%±32.0% vs. 48.3%±35.4%, respectively, $P=0.852$) and surgical success (42.6% vs. 45.8%, respectively, $P=0.748$), defined as a postoperative AHI <20 events/hr with ≥50% improvement in AHI.

A recent multicenter retrospective study involving 275 patients (59% had severe OSA) highlighted the utility of DISE in prognosticating pharyngeal surgery outcomes in general [53]. All patients underwent preoperative DISE. The distribution of primary structure collapse was as follows: velum, 35%; oropharyngeal lateral walls, 24%; tongue, 39%; and epiglottis, 2%. The overwhelming majority (93%) underwent palate surgery, and 60% underwent tongue surgery. Overall, 41% achieved a surgical response (defined as an AHI decrease of ≥50% and <15 events/hr), and the AHI improved from 41±24 to 21±20 events/hr ($P<0.001$). A greater AHI decrease was seen for complete than partial velum-related obstruction in patients who underwent palate and tongue resection procedures, but there was no difference in the postoperative AHI (22.0±17.4 vs. 18.6±17.0 events/hr, $P=0.44$). In adjusted analyses, the surgical success rate was approximately 50% lower for any oropharyngeal lateral wall-related obstruction among all patients, in those with moderate to severe OSA, and in those who underwent isolated palate surgery. Complete tongue-related obstruction was also associated with a lower surgical success rate in patients with moderate to severe OSA. This study found that velum and epiglottis-related obstructions were not clearly associated with surgical outcomes. The differing conclusion found for velum-related obstructions in this paper may be attributed to tonsillar hypertrophy being an exclusion criterion.

Other issues when considering the potential usefulness of DISE include whether the surgical plan is altered based on information gathered from DISE, and whether such alterations increase success rates. Several studies have shown that the surgical plan can be changed in up to 64% of cases after DISE is performed [54-58].

In the pediatric population, DISE is traditionally performed if adenotonsillectomy, the classical first-line surgical treatment, is ineffective [59]. Patients at high risk of persistent OSA after adenotonsillectomy (e.g., those with small tonsils and adenoids, obesity, age >7 years, severe OSA, African-American ethnicity, Down syndrome, craniofacial anomalies, and neuromuscular disorders) may benefit from DISE even before initial surgery [60], as one study showed that 58% of patients ended up undergoing surgery other than adenotonsillectomy [61]. A DISE-directed intervention at the time of initial surgery in children has been shown to produce symptomatic and objective improvement on repeat PSG [61,62]. Occult or late-onset laryngomalacia, a condition where the arytenoids prolapse into the laryngeal inlet only during sleep, has been reported in children older than those who experience infantile laryngomalacia. This finding would only be obvious during DISE, since it only occurs during sleep. A study of 22 pediatric patients who underwent supraglottoplasty for this finding demonstrated an AHI reduction from 15.4 to 5.4 events/hr ($P<0.001$), with comparable reductions in AHI for those who had undergone supraglottoplasty alone or in combination with other interventions [63]. Several other studies have also reported successful clinical outcomes of supraglottoplasty, but did not obtain postoperative PSG due to the dramatic clinical improvement noted [64,65].

There are conflicting conclusions regarding the impact of DISE on surgical outcomes. Some studies have suggested that DISE improves success rates, possibly because it aids selection of an appropriate operative technique. A study of 136 patients who underwent uvulopalatopharyngoplasty after demonstrating at least retropalatal obstruction on DISE reported surgical outcomes that were better than historical data [66]. A single-center retrospective analysis of 87 patients found that multiple procedures for multilevel obstruction were performed less frequently in those who underwent DISE than in those who did not (8% vs. 60%, $P<0.001$) [67]. Nonetheless, the mean postoperative AHI was lower in the DISE group than in the non-DISE group (10 vs. 19 events/hr, $P=0.052$). Surgical success (decline in AHI by ≥50% and to ≤20 events/hr) also occurred more frequently in the DISE group than in the non-DISE group (86% vs. 51%, $P<0.001$). However, other authors have reported that DISE made no difference in outcomes [56,57]. A conflicting report was recently published detailing the experience of 326 patients from nine centers across seven countries [68]. The investigators did not find any benefit in the DISE group (170 patients) compared to the non-DISE (156 patients) group that would support preoperative DISE. In fact, some outcome parameters favored the non-DISE group. While the strengths of this study include generalizability (It is generalizable because the samples are from multiple centers and numerous) because of its multicenter nature and rela-

tively large sample size, its results need to be interpreted with caution. The study was not randomized. Instead patients were put into the two groups based on whether DISE had been performed, which was dependent on protocols that differed across countries and even from surgeon to surgeon. There could therefore have been selection bias, as DISE may not have been performed in patients perceived to be good surgical candidates based on other clinical parameters, and the surgical procedures performed were decided upon by individual surgeons without a common treatment algorithm. The results may reflect the standard of care and effectiveness of OSA surgery between countries, rather than truly revealing the utility—or lack thereof—of DISE.

Although DISE equips a surgeon with knowledge of obstruction patterns, an interesting study found that similar postoperative success rates and AHI could be achieved in patients with unilevel and multilevel obstruction seen on DISE after unilevel (pharyngoplasty) surgery alone. The authors suggested that multilevel surgery may not always be necessary at first, even in patients who demonstrate multilevel obstruction during DISE [69]. However, it is unknown whether the patients with multilevel obstruction would have had even better outcomes if multilevel surgery had been performed. Further multicenter prospective randomized trials with control groups who do not undergo DISE are sorely needed to investigate the true clinical impact of DISE in patients undergoing OSA surgery.

ROLE OF DISE IN PLANNING UPPER AIRWAY STIMULATION

Upper airway stimulation is a surgical technique that has emerged in recent years. Implantation of the stimulation system reduces upper airway collapsibility by stimulating the hypoglossal nerve to cause tongue protrusion and opening of the upper airway. Inspire (Inspire Medical Systems Inc., Maple Grove, MN, USA), an implantable pacemaker-like pulse-generator with sensing and stimulation leads, was the first device of its kind approved by the U.S. Food and Drug Administration in 2014 [70,71]. Medium-term data on safety and efficacy have been promising [72]. Since then, a few similar systems have been developed and evaluated [73,74]. In recent individual patient-level data from four cohorts comprising 584 adults with OSA implanted with the Inspire hypoglossal nerve stimulator, treatment success (defined as a decrease in AHI by >50% and to <20 events/hr) was observed in 77.1% of patients [75].

DISE was incorporated as a mandatory screening investigation in the landmark Stimulation Therapy for Apnea Reduction (STAR) trial following earlier studies that showed CCCp during DISE to be associated with poor results after upper airway stimulation [76,77]. One of these studies analyzed 21 CPAP-intolerant moderate to severe OSA patients who underwent DISE before implantation [76]. Five of the patients (23.8%) demonstrated CCCp, of whom none achieved success or a significant change in the AHI (41.5±13.8 vs. 48.1±18.7 events/hr, P=0.44) 6 months post-implantation. Conversely, 81% of those without CCCp achieved success (defined as AHI <20 events/hr and a reduction of ≥50%). As the technology undergoes further refinement and becomes more affordable, upper airway stimulation will continue to revolutionize the treatment of OSA, and the role that DISE plays in the patient selection protocol will continue to evolve.

In the event of poor treatment response after implantation despite multiple settings and titration attempts, DISE can be performed to troubleshoot the reason for failure. Palatoglossal coupling is one of the main mechanisms by which protrusion of the genioglossus increases both retrolingual and retropalatal dimensions. However, patients with persistent soft palate obstruction seen on DISE may benefit from uvulopalatopharyngoplasty with tonsillectomy [78]. Similarly, DISE can help to evaluate any residual areas of obstruction in OSA surgery non-responders [79].

CONCLUSION

High-quality clinical evidence supporting the value of DISE in guiding alternative treatments for OSA is limited. The heterogeneous and retrospective nature of many studies, as well as issues of inherent bias, has produced a bag of mixed conclusions. As a result, adoption and utilization of DISE is varied across the globe, and it is often not understood or considered relevant by many nonsurgical sleep practitioners. However, this disenchantment should be addressed because OSA is a multidisciplinary condition with complex pathophysiology and profound cardiometabolic consequences. The paradigm of OSA treatment has shifted—its objectives have gone beyond improving snoring and sleepiness alone, and now encompass bettering blood pressure control and cardiovascular outcomes. Pivotal multicenter clinical trials of CPAP therapy have thus far highlighted the high prevalence of poor adherence and the neutral effect of CPAP on cardiovascular outcomes [80,81]. DISE has the advantage of providing an increased understanding of a patient's upper airway mechanics via a low-risk procedure, with the possibility of using the knowledge gained to make guided prescriptions of treatment alternatives that may increase the frequency of positive outcomes. DISE has the potential to be the main driver behind the next level of care for OSA in this era of precision medicine.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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2022 CPT Code Review
Per-oral Endoscopic Myotomy

Code: **43497** Lower esophageal myotomy, transoral (ie, peroral endoscopic myotomy [POEM])

Similar code: this procedure was previously billed with CPT 43499 Unlisted procedure, esophagus

Description: Peroral endoscopic myotomy (POEM) is a procedure in which a scope is passed through the mouth and into the esophagus. Part of the muscle layer of the lower part of the esophagus, the sphincter, and the upper part of the stomach is removed. POEM has been proposed as a treatment for a variety of esophageal and gastric conditions, including achalasia, diverticula, gastroparesis, and congenital hypertrophic pyloric stenosis.

Achalasia is a rare condition in which the lower esophageal sphincter loses inhibitory neural input making it fail to relax after swallowing. Treatments include Botox injections, laparoscopic Heller myotomy, and pneumatic dilation.

Gastroparesis is a condition in which the stomach does not empty normally. It is commonly associated with diabetes. Treatments for gastroparesis include medications, better diabetic control, and lifestyle changes such as eating small frequent meals.

Diverticula of the esophagus are pouches that form because the muscles of the esophagus fail to relax after swallowing. This can cause pain, and food can be caught in the diverticula. Serious cases are treated with various types of surgery.

Evidence

Achalasia

1) **Zhong 2021,** systematic review and meta-analysis of peroral endoscopic myotomy for achalasia in children
    a. N=11 studies (389 children)
        i. 3 prospective cohort, 8 retrospective cohort
        ii. Clinical success was defined as a decrease in Eckardt score to ≤3 during follow-up.
    b. Pooled clinical success was achieved in 343 children (92.4%; 95% CI, 89.0%–94.8%, I2 =0%)
    c. After POEM, the Eckardt score was significantly decreased by 6.76 points (95% CI, 6.18–7.34, *P*<0.00001, I2 =84%), and the LES pressure was significantly reduced by 19.38 mmHg (95% CI, 17.54–21.22, *P*<0.00001, I2 =33%)
    d. The pooled major adverse events rate was 12.8% (95% CI, 4.5%– 31.5%, I2 =87%). Specifically, the pooled occurrence rate of mucosal injury was 4.6% (95% CI, 1.9%–10.5%, I2 =48%), the rate of pneumothorax was 3.0% (95% CI, 1.4%–6.3%, I2 =0%), the rate of pneumonitis was 4.4% (95% CI, 1.1%–16.6%, I2 =80%), and the rate of pneumoperitoneum was 5.3% (95% CI, 2.1%–13.1%, I2 =56%)
    e. Conclusion: Our current study demonstrated that the POEM was an effective and safe technique for treating achalasia in children. Further randomized comparative studies of POEM and other therapeutic methods are warranted to determine the most effective treatment modality for achalasia in children.

2) **Zhong 2020,** systematic review and meta-analysis of peroral endoscopic myotomy vs pneumatic dilation for achalasia
    a. N=7 studies (619 patients: 298 POEM and 321 pneumatic dilation)
        i. Follow-up 2 to 70 months
        ii. "clinical success" was not defined
    b. At 3 months' follow-up, the clinical success was achieved in 151 of 155 patients (96.9%, 95% CI, 92.3–98.7%) in the POEM group, while in 136 of 155 patients (80.8%, 95% CI, 73.5–86.5%) in the pneumatic dilation group, giving a risk ratio of 1.13 (95% CI, 0.99–1.28, $P = 0.06$, $I2 = 67\%$). At 6 months' follow-up, the clinical success was achieved in 122 of 127 patients (95.6%, 95% CI, 90.3–98.1%) in the POEM group compared to 198 of 236 patients (83.8%, 95% CI, 78.5–88.0%) in the pneumatic dilation group, with a risk ratio of 1.14 (95% CI, 1.06–1.22, $P = 0.0002$, $I2 = 0\%$) At 12 months' follow-up, treatment success was achieved in 202 of 212 patients (94.9%, 95% CI, 90.9–97.2%) in the POEM group compared to 246 of 340 patients (71.9%, 95% CI, 66.8–76.5%) in the pneumatic dilation group, with a risk ratio of 1.34 (95% CI, 1.24–1.45, $P < 0.00001$, $I2 = 17\%$) (Fig. 2c). At 24 months' follow-up, the clinical success was achieved in 161 of 175 patients (91.7%, 95% CI, 86.5–95.0%) in the POEM group compared to 194 of 297 patients (63.8%, 95% CI, 52.4–73.9%) in the pneumatic dilation group, with a risk ratio of 1.35 (95% CI, 1.10–1.65, $P = 0.004$, $I2 = 70\%$)
    c. The posttreatment mean Eckardt scores was significantly different in patients undergoing POEM (1.166, 95% CI, 0.709–1.622) versus those receiving pneumatic dilation (2.024, 95% CI, 1.518–12.531), with a mean difference of −0.88 (95% CI, −1.54 to −0.23, $P = 0.008$, $I2 = 93\%$)
    d. The gastroesophageal reflux (GER) rate for POEM was significantly higher than pneumatic dilation, with a risk ratio of 4.17 (95% CI, 1.52–11.45, $P = 0.006$, $I2 = 61\%$)
    e. other complications in the POEM group, such as subcutaneous emphysema, mucosal injuries and bleeding, were significantly higher than in the pneumatic dilation group, with a risk ratio of 3.78 (95% CI, 1.41–10.16, $P = 0.008$, $I2 = 0\%$)
    f. Conclusion: The long-term efficacy of POEM was superior to that of pneumatic dilation, but accompanied by higher complications. More randomized controlled studies are warranted to determine the optimal method for achalasia in the future
3) **Tan 2020,** systematic review and meta-analysis of peroral endoscopic myotomy in achalasia in patients with failed previous interventions
    a. N=15 studies (2,276 patients)
        i. All cohort studies, 6 prospective, 9 retrospective
        ii. 1261 patients had undergone previous procedures, 1015 patients were treatment naïve
        iii. Clinical success was defined as an Eckardt score ≤3 during the study follow-up period
    b. Ten studies with 1,095 patients reported the clinical success of POEM for patients with prior endoscopic or/ and surgical treatment. Clinical success was achieved in 999 patients (91.2%) at 3-month follow-up. The pooled clinical success in patients with greater than three months' follow-up was 90.8% (95% CI, 88.8% to 92.4%).
    c. Four studies reported clinical success with 1-year follow-up. Two studies reported 2- and 3-year follow-ups. The pooled results of clinical success rates for 1-, 2-, and 3-year followups were 89.9% (95% CI, 86.9% to 92.3%), 85.8% (95% CI, 81.7% to 89.1%) and 81.2% (95% CI, 76.2% to 85.4%), respectively

d. Fourteen studies with 1,195 patients reported the adverse events of POEM for patients with prior endoscopic or/and surgical treatment. A total of 83 (6.9%) adverse events occurred. The pooled adverse events rate was 10.3% (95% CI, 6.6% to 15.8%)
    i. Major adverse events included mediastinitis, esophageal leak, pneumothorax, pleural effusion, bleeding requiring transfusion or re-intervention, hydrothorax, mucosal tear
e. Conclusion: POEM appears to be a safe, effective and feasible treatment for those who have undergone previous failed endoscopic or surgical intervention. It has similar outcomes in previously treated and treatment-naive achalasia patients. It may be an attractive option for the treatment of patients with this difficult condition. However, further studies with a long-term follow-up to determine the durability of rescue POEM are still warranted.

4) **Awaiz 2017,** systematic review and meta-analysis of peroral endoscopy myotomy and laparoscopic Heller myotomy for achalasia
    a. N=7 trials comparing laparoscopic Heller myotomy (LHM) to peroral endoscopic myotomy (POEM) reported in 20 publications
        i. N=250 patients undergoing LHM, 233 patients undergoing POEM
        ii. All grades and subtypes of achalasia were included
        iii. No requirement for prior treatment with pneumatic balloon dilation, Botox injection or other treatment
    b. There was a comparable overall complication rate (OR, 1.25; 95% CI, 0.56-2.77; P=0.59), postoperative GERD rate (OR, 1.27; 95% CI, 0.70-2.30; P=0.44), length of hospital stay (WMD, 0.30; 95% CI, -0.24 to 0.85; P=0.28), postoperative pain score (WMD, -0.26; 95% CI, -1.58 to 1.06; P=0.70), and long-term GERD (WMD, 1.06; 95% CI, 0.27-4.1; P=0.08) for both procedures. There was a significantly higher short-term clinical treatment failure rate for LHM (OR, 9.82; 95% CI, 2.06-46.80; P<0.01).
    c. Conclusions: POEM compares favorably to LHM for achalasia treatment in short-term perioperative outcomes. However, there was a significantly higher clinical treatment failure rate for LHM on short-term postoperative follow-up. Presently long-term postoperative follow-up data for POEM beyond 1 year are unavailable and eagerly awaited.

Gastroparesis

1) **Li 2021**, meta analysis of gastric per-oral endoscopy myotomy for refractory gastroparesis
    a. N=8 studies (272 patients)
        i. 2 prospective and 6 retrospective cohort studies
    b. The pooled clinical response rate was 84% (95% CI, 77–89%). The gastric emptying scintigraphy (GES) improvement rate and GES normal rate were also analyzed, and the results were 84% (95% CI, 77–90%) and 53% (95% CI, 39–66%), respectively. Finally, the pooled adverse events rate was 12% (95% CI, 6–19%).
        i. “Clinical response rate” was defined as whatever the article used for response rate
    c. Conclusion: POEM was shown to be feasible and safe for the treatment of gastroparesis with various etiologies, which could be a potential first-line therapy for certain patients. Future studies are needed to investigate the appropriate patients for POEM to explore the “most beneficial” subgroup of patients.

Esophageal diverticula

1) **Facciorusso 2021**, systematic review and meta-analysis of peroral endoscopic myotomy for the treatment of esophageal diverticula
    a. N=12 studies (300 patients) with Zenker's diverticulum (ZD) or epiphrenic diverticula
        i. 4 studies were retrospective case-control studies comparing POEM to flexible endoscopic treatment
        ii. 7 studies were retrospective cohort studies
        iii. 1 study was a prospective case series
    b. Pooled rate of technical success was 95.9% (93.4%-98.3%) in ZD patients and 95.1% (88.8%-100%) in patients with epiphrenic diverticula. Pooled rate of treatment success was similar for ZD (90.6%, 87.1%-94.1%) and epiphrenic diverticula (94.2%, 87.3%-100%). Rates of treatment success were maintained at 1 year (90%, 86.4%-97.4%) and 2 years (89.6%, 82.2%-96.9%) in ZD patients. Pooled rate of symptom recurrence was 2.6% (0.9%-4.4%) in ZD patients and 0% in patients with epiphrenic diverticula. Pooled rates of adverse events and severe adverse events were 10.6% (4.6%- 16.6%) and 3.5% (0%-7.4%) in ZD and 8.4% (0%-16.8%) and 8.4% (0%-16.8%) in epiphrenic diverticula, respectively.
    c. Conclusion: POEM represents an effective and safe therapy for the treatment of esophageal diverticula.

<u>Expert guidelines</u>

1) **Society of American Gastrointestinal and Endoscopic Surgeons (SAGE) 2021**, guidelines for the use of peroral endoscopic myotomy for the treatment of achalasia
    a. POEM vs Heller myotomy
        i. The Guideline panel suggests that adult and pediatric patients with type I and II achalasia may be treated with either POEM or laparoscopic Heller myotomy based on surgeon and patient's shared decision-making (conditional recommendation, very low certainty evidence).
        ii. Based on their collective experience, the panel suggests POEM over laparoscopic Heller myotomy for type III adult or pediatric achalasia. (expert opinion)
    b. POEM vs pneumatic dilation
        i. The Guideline panel recommends peroral endoscopic myotomy over pneumatic dilatation in patients with achalasia (strong recommendation, moderate certainty evidence)
        ii. For the subgroup of patients who are particularly concerned about the continued use of PPI post-operatively, the panel suggests that either POEM or pneumatic dilatation can be used based on joint patient and surgeon decision-making (conditional recommendation, very low certainty evidence).
1) **American College of Gastroenterology (AGC) 2020,** guideline on the diagnosis and management of achalasia
    a. Based on current data, we recommend tailored POEM or laparoscopic Heller myotomy (LHM) for type III achalasia
        i. Moderate level of evidence, strong recommendation
    b. POEM compared with LHM with fundoplication or pneumatic dilation is associated with a higher incidence of GERD.
    c. We recommend that POEM or pneumatic dilation result in comparable symptomatic improvement in patients with types I or II achalasia

i. Low level of evidence, conditional recommendation

d. We recommend that POEM and LHM result in comparable symptomatic improvement in patients with achalasia
    i. Moderate level of evidence, strong recommendation

Other payer policies

1) **Aetna 2021**:
    a. Aetna considers per-oral endoscopic myotomy (POEM) medically necessary for the treatment of type III (spastic) achalasia. Aetna considers POEM experimental and investigational for other types of achalasia.
    b. Aetna considers gastric per-oral endoscopic myotomy (G-POEM) experimental and investigational for the following indications because its effectiveness for these indications has not been established (not an all-inclusive list):
        i. Treatment of congenital hypertrophic pyloric stenosis
        ii. Treatment of gastroparesis.
        iii. Aetna considers diverticular peroral endoscopic myotomy (D-POEM) experimental and investigational for the treatment of esophageal diverticulum because its effectiveness has not been established.
        iv. Aetna considers Zenker per-oral endoscopic myotomy (Z-POEM) diverticulotomy experimental and investigational for closing defect due to Zenker's diverticulum because its effectiveness has not been established.

2) **CMS NCD 2021**
    a. POEM may be considered medically necessary for treatment of symptomatic, monometrically proven primary idiopathic achalasia, types I, II, or III.

3) **Premara BCBS 2021**
    a. POEM is investigational. More and larger studies are needed to compare POEM with standard surgery to treat esophageal achalasia

4) **PacificSource 2020**
    a. PacificSource considers the POEM procedure medically necessary when ALL the following criteria are met:
        i. A diagnosis of esophageal achalasia type III (spastic) is established by the following:
            1. Twenty percent (20%) or more of swallows have premature spastic contractions as indicated by esophageal manometry; and
            2. Non-relaxing lower esophageal sphincter pressure (LES) indicated by a barium esophagogram with fluoroscopy and esophageal manometry.
        ii. Failure of a previous treatment for achalasia (e.g. Botox, pneumatic dilation); and
        iii. None of the following contraindications are present:
            1. Severe pulmonary disease; or
            2. Esophageal irradiation; or
            3. Esophageal malignancy; or
            4. Bleeding disorder, including coagulopathy; or
            5. Recent esophageal surgery; and endoscopic intervention

Current Prioritized List status

ICD-10-CM K22.0 (Achalasia of cardia) is on line 378 ESOPHAGEAL STRICTURE; ACHALASIA

Line 378 includes CPT codes for pneumatic dilation of the esophagus, and CPT 43279 (Laparoscopy, surgical, esophagomyotomy (Heller type), with fundoplasty, when performed)

HERC staff summary

Peroral endoscopic myotomy [POEM]) is a relatively established procedure that has been studied as treatment for a variety of conditions of the stomach and esophagus, including achalasia, esophageal diverticula, and gastroparesis. The literature to date on POEM as a treatment for esophageal diverticula and gastroparesis consists of small cohort studies. There is a more robust literature on POEM for treatment of achalasia, with trials comparing POEM to laparoscopic Heller myotomy (LHM) and multiple cohort studies comparing POEM to pneumatic dilation. Studies tend to be small as achalasia is a rare condition. POEM appears to have similar outcomes to LHM for achalasia for improvement of achalasia symptoms at least in the short term, but has some significant adverse events including pneumothorax, esophageal rupture, and significant bleeding, as well as increased rates of GERD. The ACG expert recommendation is for POEM as one option for treatment of achalasia of all types. SAGE recommends POEM over LHM only for type III achalasia (expert recommendation), and private payers and CMS appear to generally align with this recommendation. Achalasia is a rare condition which currently is paired with multiple treatments, including pneumatic dilation and LHM. Staff recommendation for coverage of type III achalasia is based mainly on expert recommendation.

HERC staff recommendations:

1) Add CPT **43497** Lower esophageal myotomy, transoral (ie, peroral endoscopic myotomy [POEM]) to line 378 ESOPHAGEAL STRICTURE; ACHALASIA
2) Adopt a new guideline as shown below for line 378

GUIDELINE NOTE XXX PERORAL ENDOSCOPIC MYOTOMY (POEM)

Line 378

Peroral endoscopic myotomy (POEM; CPT 43497) is included on this line only for treatment of symptomatic, monometrically proven primary idiopathic achalasia, type III.

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DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Systematic Review and Meta-analysis

Clinical outcomes of peroral endoscopic myotomy for achalasia in children: a systematic review and meta-analysis

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SUMMARY. **Peroral endoscopic myotomy (POEM) is a novel minimally invasive intervention, which has shown to be effective and safe for treating achalasia in adults. Presently, POEM was also reported to be effective for achalasia in children. So we conducted this study to explore the clinical outcomes of POEM for pediatric achalasia. A systematic literature search in PubMed, Embase, and Cochrane databases was performed, which covered the period from January 2009 to June 2020. Selecting studies and collecting data was independently by two reviewers according to predefined criteria. The statistical analysis was carried out using Comprehensive Meta-Analysis software version 2 and Review Manager 5.3. A total of 11 studies with 389 children were identified in the final analysis. Pooled technical success of POEM treatment achalasia was achieved in 385 children (97.4%; 95% confidence interval [CI], 94.7%–98.7%), and the pooled clinical success was achieved in 348 children (92.4%; 95% CI, 89.0%–94.8%). After POEM, the Eckardt score was significantly decreased by 6.76 points (95% CI, 6.18–7.34, $P < 0.00001$), and the lower esophageal sphincter pressure was significantly reduced by 19.38 mmHg (95% CI, 17.54–21.22, $P < 0.00001$). The pooled major adverse events rate related to POEM was 12.8% (95% CI, 4.5%–31.5%) and the gastroesophageal reflux rate was 17.8% (95% CI, 14.2%–22.0%). Our current study demonstrated that the POEM was an effective and safe technique for treating achalasia in children. Further randomized comparative studies of POEM and other therapeutic methods are warranted to determine the most effective treatment modality for achalasia in children.**

KEY WORDS: **achalasia, children, meta-analysis, peroral endoscopic myotomy, systematic review.**

BACKGROUND

Achalasia is a primary motor disorder of the esophagus, which is characterized by the loss of esophageal peristalsis and insufficient relaxation of the lower esophageal sphincter (LES), resulting in obstructed bolus transport and stasis of food in the esophagus.[1,2] The most common clinical manifestations for achalasia are dysphagia for both solids and liquids, regurgitation of undigested food, respiratory complications, chest pain, and weight loss.[3] In the pediatric population, it is an extremely uncommon disease, with an estimated annual incidence of 0.02 to 0.31 cases per 100,000 children, nearly 10 times less than that in adults.[4–6] Children with achalasia are usually misdiagnosed and may result in detrimental to a child's growth and development.[7]

Currently, traditional managements of achalasia include drug treatment, botulinum toxin injection, pneumatic dilation (PD), peroral endoscopic myotomy (POEM), and surgical treatment. Laparoscopic Heller' myotomy (LHM) is considered the gold standard for treating achalasia in adults, whereas medical treatments and PDs are often suitable for those older than 45 years or with high surgical risk.[2] In recent years, a novel minimally invasive technique, POEM has been widely accepted for treating achalasia with excellent safety and efficacy in adults.[8–10] So far, some researchers have reported the exciting results of POEM in pediatric patients with achalasia.[11–20]

Lately, Lee *et al.*[21] evaluated the efficacy and safety of POEM in pediatric achalasia in a systematic review and meta-analysis. However, their review was limited by the inclusion of low-quality studies and incomplete pooled analysis, such as lacking pooled technical success rate and adverse events rate. Presently, there are some new studies related to

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Peroral endoscopic myotomy versus pneumatic dilation for achalasia: a systematic review and meta-analysis

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Presently, the primary endoscopic options for the treatment of achalasia are peroral endoscopic myotomy (POEM) and pneumatic dilation. But the clinical outcomes of POEM and pneumatic dilation for achalasia have not yet to be fully evaluated. So, we aimed to compare the clinical outcomes between the two treatment modalities. We searched all the relevant studies published up to September 2019 examining the comparative efficacy between POEM and pneumatic dilation. Outcomes included success rate, Eckardt score, lower esophageal sphincter pressure and adverse events. Outcomes were documented by pooled risk ratios and mean difference with 95% confidence interval (CI) using Review Manager 5.3. Seven studies with a total of 619 patients were identified. There were 298 patients underwent POEM treatment and 321 patients underwent pneumatic dilation treatment. The clinical success rate was higher in the POEM group than that in the pneumatic dilation group at 6, 12 and 24 months' follow-up, with a risk ratio of 1.14 (95% CI, 1.06–1.22, $P=0.0002$, $I^2=0\%$), 1.34 (95% CI, 1.24–1.45, $P<0.00001$, $I^2=17\%$) and 1.35 (95% CI, 1.10–1.65, $P=0.004$, $I^2=70\%$), respectively. The change of Eckardt scores was more obvious in the POEM group than in the pneumatic dilation group, with a mean difference of 1.19 (95% CI, 0.78–1.60, $P<0.00001$, $I^2=70\%$). The rate of gastroesophageal reflux and other complications for POEM was significantly higher than for pneumatic dilation, with a risk ratio of 4.17 (95% CI, 1.52–11.45, $P=0.006$, $I^2=61\%$) and 3.78 (95% CI, 1.41–10.16, $P=0.008$, $I^2=0\%$). Our current evidence suggests that the long-term efficacy of POEM was superior to that of pneumatic dilation, but accompanied by higher complications. Eur J Gastroenterol Hepatol 32: 1413–1421

Introduction

Achalasia is a rare disorder of esophageal motility, with an estimated annual incidence of 1.07–2.2 cases per 100 000 population and the prevalence rates of 10–15.7 per 100 000 population [1]. Its incidence is characterized by no gender difference, and the highest incidence appears in the seventh decade of life [1,2]. The main feature of achalasia is the absence of peristalsis and a failed relaxation of the lower esophageal sphincter (LES), resulting in obstructed bolus transport and stasis of food in the esophagus. The clinical manifestations include dysphagia for both solids and liquids, regurgitation of undigested food, respiratory complications, chest pain, weight loss, and patients often have a reduced quality of life and workforce participation [3,4]. Because the pathogenesis of achalasia is not well understood, a therapeutical approach is aimed to alleviate esophagogastric junction (EGJ) outflow obstruction and subsequently relieve obstructive symptoms [5,6].

Current treatment methods for achalasia included medical treatment, botulinum toxin injection, pneumatic dilation, surgical myotomy and peroral endoscopic myotomy (POEM). The medical therapy and injection of botulinum toxin are limited by short-term efficacy. Laparoscopic Heller myotomy (LHM) is considered the gold standard in achalasia treatment because it can provide superior and long-lasting symptom relief for patients, but elderly patients and patients with multiple comorbidities are not suitable [7–9]. POEM and pneumatic dilation are less invasive endoscopic treatments. Pneumatic dilation is relatively easy to perform, low-cost and does not require special training [2,9]. POEM is a novel technique of minimally invasive method for achalasia, which has been gained popularity worldwide, with the advantages of lack of abdominal incisions, rapid recovery and high efficacy [10,11].

At present, there has been a number of comparative studies of POEM and pneumatic dilation for achalasia [12–18]. Therefore, we aimed to perform a meta-analysis to assess the efficacy and safety between POEM and pneumatic dilation.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for reporting

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Keywords: esophageal achalasia, meta-analysis, peroral endoscopic myotomy, pneumatic dilation, systematic review

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Review Article

Efficacy and Safety of Peroral Endoscopic Myotomy in Achalasia Patients with Failed Previous Intervention: A Systematic Review and Meta-analysis

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Peroral endoscopic myotomy (POEM) has emerged as a rescue treatment for recurrent or persistent achalasia after failed initial management. Therefore, we aimed to investigate the efficacy and safety of POEM in achalasia patients with failed previous intervention. We searched the MEDLINE, Embase, Cochrane, and PubMed databases using the queries "achalasia," "peroral endoscopic myotomy," and related terms in March 2019. Data on technical and clinical success, adverse events, Eckardt score and lower esophageal sphincter (LES) pressure were collected. The pooled event rates, mean differences (MDs) and risk ratios (RR) were calculated. A total of 15 studies with 2,276 achalasia patients were included. Overall, the pooled technical success, clinical success and adverse events rate of rescue POEM were 98.0% (95% confidence interval [CI], 96.6% to 98.8%), 90.8% (95% CI, 88.8% to 92.4%) and 10.3% (95% CI, 6.6% to 15.8%), respectively. Seven studies compared the clinical outcomes of POEM between previous failed treatment and the treatment naïve patients. The RR for technical success, clinical success, and adverse events were 1.00 (95% CI, 0.98 to 1.01), 0.98 (95% CI, 0.92 to 1.04), and 1.17 (95% CI, 0.78 to 1.76), respectively. Overall, there was significant reduction in the pre- and post-Eckardt score (MD, 5.77; p<0.001) and LES pressure (MD, 18.3 mm Hg; p<0.001) for achalasia patients with failed previous intervention after POEM. POEM appears to be a safe, effective and feasible treatment for individuals who have undergone previous failed intervention. It has similar outcomes in previously treated and treatment-naïve achalasia patients. **(Gut Liver 2021;15:153-167)**

Key Words: Esophageal achalasia; Meta-analysis; Pyloromyotomy; Safety; Treatment failure

INTRODUCTION

Achalasia is an esophageal motility disorder, caused by the absence of myenteric neurons and the subsequent impaired lower esophageal sphincter (LES) relaxation. Patients present with dysphagia, regurgitation, chest pain, and weight loss.[1] Treatment options include Heller myotomy (HM), pneumatic balloon dilation (PBD), and botulinum toxin injection (BTI). Although HM is considered the first-line therapy due to its superior long-term outcomes, a failure rate of approximately 10% to 20% is observed.[2,3] Similarly, despite a 90% PBD success rate, recurrence of symptoms occurs post-procedure in 20%, 30%, and 40% of patients in 2, 5 and 10 years, respectively.[4-6] Lastly, BTI is safety and efficacious in the majority of patients; however, symptomatic relief is short term with only 29% of patients reporting continued success during intermediate follow-up.[7] In cases of symptom recurrence after primary intervention, surgical myotomy is often technically challenging. Additionally, a high risk of adverse events is documented. Reported rates of gastrointestinal perforation range from 1.5% to 20% and are typically due to the formation of scars, fibrosis and adhesions resulting from previous surgical or endoscopic interventions.[8-12] PBD and BTI are also rescue management strategies for recurrent achalasia. However, the durability of both interventions is limited. Repeat treat-

Systematic Review and Meta-Analysis of Perioperative Outcomes of Peroral Endoscopic Myotomy (POEM) and Laparoscopic Heller Myotomy (LHM) for Achalasia

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Aims and Objectives: Laparoscopic Heller myotomy (LHM) is the preferred surgical method for treating achalasia. However, peroral endoscopic myotomy (POEM) is providing good short-term results. The objective of this systematic review and meta-analysis was to compare the safety and efficacy of LHM and POEM.

Materials and Methods: A search of PubMed, Cochrane database, Medline, Embase, Science Citation Index, and current contents for English-language articles comparing LHM and POEM between 2007 and 2016 was performed. Variables analyzed included prior endoscopic treatment, prior medical treatment, prior Heller myotomy, operative time, overall complications rate, postoperative gastroesophageal reflux disease (GERD), length of hospital stay, postoperative pain score, and long-term GERD.

Results: Seven trials consisting of 483 (LHM = 250, POEM = 233) patients were analyzed. Preoperative variables, for example, prior endoscopic treatment [odds ratio (OR), 1.32; 95% confidence interval (CI), 0.23-4.61; $P = 0.96$], prior medical treatment [weighted mean difference (WMD), 1.22; 95% CI, 0.52-2.88; $P = 0.65$], and prior Heller myotomy (WMD, 0.47; 95% CI, 0.13-1.67; $P = 0.25$) were comparable. Operative time was 26.28 minutes, nonsignificantly longer for LHM (WMD, 26.28; 95% CI, −11.20 to 63.70; $P = 0.17$). There was a comparable overall complication rate (OR, 1.25; 95% CI, 0.56-2.77; $P = 0.59$), postoperative GERD rate (OR, 1.27; 95% CI, 0.70-2.30; $P = 0.44$), length of hospital stay (WMD, 0.30; 95% CI, −0.24 to 0.85; $P = 0.28$), postoperative pain score (WMD, −0.26; 95% CI, −1.58 to 1.06; $P = 0.70$), and long-term GERD (WMD, 1.06; 95% CI, 0.27-4.1; $P = 0.08$) for both procedures. There was a significantly higher short-term clinical treatment failure rate for LHM (OR, 9.82; 95% CI, 2.06-46.80; $P < 0.01$).

Conclusions: POEM compares favorably to LHM for achalasia treatment in short-term perioperative outcomes. However, there was a significantly higher clinical treatment failure rate for LHM on short-term postoperative follow-up. Presently long-term postoperative follow-up data for POEM beyond 1 year are unavailable and eagerly awaited.

Key Words: achalasia, esophageal dysmotility, laparoscopic methods, Heller myotomy, endoscopic methods, peroral endoscopic myotomy, comparative trials, human, English

(*Surg Laparosc Endosc Percutan Tech* 2017;27:123–131)

Achalasia is a primary incurable esophageal motility disorder that involves a selective loss of inhibitory neural input, resulting in the failure of lower esophageal sphincter (LES) to relax after swallowing. It is accompanied by aperistalsis of the esophageal body, esophageal dilatation, regurgitation, heartburn, weight loss, dysphagia as well as chest pain.[1] There may be some hereditary, neurodegenerative, genetic, and infective contributions to the disease but most commonly it is idiopathic. This disorder is defined accurately by high-resolution impedance manometric criteria in the classic setting of dysphagia. Other diagnostic modalities that have complementary roles include barium swallow and endoscopy.[2]

The conventional approaches used to treat this condition include, but are not limited to, the use of pharmacotherapy, injection of botulinum toxin, endoscopic pneumatic dilatation, and laparoscopic Heller myotomy (LHM). Each treatment modality is associated with risks.[3,4] LHM achieves symptomatic improvement in 89% of patients (range, 77% to 100%). However, the efficacy decreases with long-term follow-up and it typically requires fundoplication to prevent reflux, which occurs in up to 31% of patients.[5]

In recent days, an emerging minimally invasive endoscopic technique of peroral endoscopic myotomy (POEM) is providing an alternate method for treating achalasia with good short-term results. This technique causes less pain and trauma compared with LHM, as no skin incisions are required to gain access to the esophagus.[6] The first experimental porcine model described by Pasricha et al[7] was followed by treatment of a successful case series of 17 achalasia patients by Inoue et al.[8]

Numerous recently published studies aimed at setting up POEM as the standard of care for the management of achalasia. However, because of relatively lower incidence of the disease and smaller sample sizes and follow-up periods of these studies, convincing evidence is still lacking.

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This abstract was presented by Dr Aiman Awaiz, as a poster presentation at the American College of Gastroenterology (ACG) 2016 Scientific Meeting, Program No P1836, October 18, 2016, Las Vegas, NV.

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ORIGINAL ARTICLE

Gastric per-Oral Endoscopic Myotomy for Refractory Gastroparesis: A Meta-Analysis

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Abstract

Background The emerging gastric per-oral endoscopic myotomy (G-POEM) is becoming an alternative treatment method for gastroparesis. This study aimed to evaluate the feasibility and safety of G-POEM for gastroparesis.

Methods Relevant publications were identified through searching PubMed, EMBASE, Cochrane Library, and Web of Science before April 1, 2019. Studies presenting the clinical data of G-POEM for the treatment of gastroparesis were included. Data about effectiveness and safety were extracted, pooled, and analyzed. Forest plots were graphed based on random effects models.

Results A total of 272 patients representing 8 studies were eligible for analysis. The pooled rates of GCSI at preprocedure, 1–3 months, 6 months, and 12 months, were 3.25 (95% CI, 2.75–3.75), 1.80 (95% CI, 1.10–2.49), 1.56 (95% CI, 0.45–2.68), and 1.10 (95% CI, 0.75–1.45), respectively. The pooled results of 4-h GES pre- and post-G-POEM were 41.89% (95% CI, 32.75–51.03%) and 16.48% (95% CI, 9.83–23.14%), respectively. Furthermore, the pooled clinical response rate was 84% (95% CI, 77–89%). The GES improvement rate and GES normal rate were also analyzed, and the results were 84% (95% CI, 77–90%) and 53% (95% CI, 39–66%), respectively. Finally, the pooled adverse events rate was 12% (95% CI, 6–19%).

Conclusions G-POEM was shown to be feasible and safe for the treatment of gastroparesis with various etiologies, which could be a potential first-line therapy for certain patients. Future studies are needed to investigate the appropriate patients for G-POEM to explore the "most beneficial" subgroup of patients.

Keywords Gastric per-oral endoscopic myotomy · G-POEM · Per-oral pyloromyotomy · POP · Gastroparesis

Introduction

Gastroparesis is a chronic debilitating and difficult-to-treat disease, characterized by delayed gastric emptying without mechanical obstruction [1]. The incidence and prevalence of gastroparesis are reported to have increased over the past decade [2]. However, the complex etiology and unclear mechanism of pathophysiology make the treatment of gastroparesis challenging. Presently, the main etiologies include idiopathic, diabetic (Type I and II), and postsurgical (vagal nerve injury), representing 35, 35, and 30% of cases, respectively [3]. Currently, the first-line therapies for treating gastroparesis are lifestyle modification, diet modification, and antiemetic and/or pro-kinetic medications; however, only metoclopramide is approved by the US Food and Drug Administration, and its long-term efficacy was limited with a black-box warning for tardive dyskinesia [4].

Patients who failed to respond to conventional therapy are usually considered to have refractory gastroparesis, and surgical or endoscopic treatment might be an alternative method, such as intrapyloric botulinum injection [5], transpyloric stenting [6], gastric electrical stimulation [7], laparoscopic pyloroplasty or pyloromyotomy [8], and subtotal gastrostomy and Roux-en-Y gastric bypass [9]. Nevertheless, all these interventions have inconsistent or particular indications. The efficacy of intrapyloric injection of botulinum was not confirmed by two recent randomized studies [10]. Migration and long-term effectiveness are the

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Peroral Endoscopic Myotomy for the Treatment of Esophageal Diverticula

A Systematic Review and Meta-analysis

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Background: There is limited evidence on the efficacy of peroral endoscopic myotomy (POEM) in patients with esophageal diverticula.

Aims: This meta-analysis aimed to assess the efficacy and safety profile of POEM in patients with Zenker (ZD) and epiphrenic diverticula.

Methods: With a literature search through August 2020, we identified 12 studies (300 patients) assessing POEM in patients with esophageal diverticula. The primary outcome was treatment success. Results were expressed as pooled rates and 95% confidence intervals.

Results: Pooled rate of technical success was 95.9% (93.4%-98.3%) in ZD patients and 95.1% (88.8%-100%) in patients with epiphrenic diverticula. Pooled rate of treatment success was similar for ZD (90.6%, 87.1%-94.1%) and epiphrenic diverticula (94.2%, 87.3%-100%). Rates of treatment success were maintained at 1 year (90%, 86.4%-97.4%) and 2 years (89.6%, 82.2%-96.9%) in ZD patients. Pooled rate of symptom recurrence was 2.6% (0.9%-4.4%) in ZD patients and 0% in patients with epiphrenic diverticula. Pooled rates of adverse events and severe adverse events were 10.6% (4.6%-16.6%) and 3.5% (0%-7.4%) in ZD and 8.4% (0%-16.8%) and 8.4% (0%-16.8%) in epiphrenic diverticula, respectively.

Conclusion: POEM represents an effective and safe therapy for the treatment of esophageal diverticula.

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A.F., Y.I., and M.A.K.: helped in study concept and design. A.F., Y.I., and D.R.: helped in the acquisition of data. A.F., M.A.K., and R.Y.: helped in analysis and interpretation of data. A.F., Y.I., D.R., V.A., R.Y., and M.A.K.: helped in the drafting of the manuscript. R.Y., M.A.K., V.A., and S.W.: helped in critical revision of the manuscript for important intellectual content; is supported by the Department of Medicine Outstanding Early Scholars Program.

M.A.K. is a consultant for BSCI, Medtronic, Olympus, and GI Supply. R.Y. is a consultant for Medtronic, Ironwood Pharmaceuticals, and Diversatek; received research support from Ironwood Pharmaceuticals; serves on the advisory board at Phatom Pharmaceuticals. S.W. is a consultant for Boston Scientific, Medtronic, Interpace, and Cernostics. The remaining authors declare that they have nothing to disclose.

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Key Words: POEM, septotomy, endoscopy, Zenker

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Esophageal diverticula are rare structural abnormalities which account for < 5% of all patients with dysphagia.[1] Zenker diverticulum (ZD) is the most common type of esophageal diverticula, with a reported prevalence ranging from 0.01% to 0.11%,[2] whereas diverticula located in the distal esophagus, called epiphrenic diverticula, are frequently associated with esophageal motility disorders and have an estimated prevalence of 0.015%.[3] Treatment is recommended for symptomatic patients as esophageal diverticula can lead to complications, such as aspiration and severe dysphagia. Surgical diverticulectomy with myotomy represents the standard surgical treatment, able to provide excellent results (symptom relief: 85% to 100%),[2,3] but with long operation times and high rates of adverse events, including leaks, pulmonary complications, and 0% to 7% risk of mortality.[2,3]

Direct flexible endoscopic septotomy has been routinely practiced but carries a relatively high recurrence rate due to incomplete division of the septum.[4] In contrast, submucosal tunneling septotomy by diverticular peroral endoscopic myotomy (D-POEM) was introduced several years ago. It is performed using a submucosal tunneling approach and, thus, allows complete septum division.[5] Recently this technique was used effectively for septotomy in patients with Zenker[6,7] (where it is called Z-POEM) and epiphrenic diverticula.[8] D-POEM has the potential advantage of allowing a complete septotomy to be performed in a single session and thus potentially reducing recurrence rates.

Given the increasing number of studies testing peroral endoscopic myotomy (POEM) in patients with esophageal diverticula, there is a pressing need to systematically revise the available body of evidence in this field; hence, we performed a meta-analysis to provide a pooled estimate of the efficacy and safety profile of D-POEM. As a secondary analysis, we examined the comparative efficacy of D-POEM with respect to standard flexible endoscopic treatments.

METHODS

Selection Criteria

The literature search strategy was based on the following inclusion criteria: (1) observational or cohort studies assessing POEM in adult patients with esophageal diverticula; (2) studies published in English; (3) articles reporting

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SAGES GUIDELINES

SAGES guidelines for the use of peroral endoscopic myotomy (POEM) for the treatment of achalasia

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Abstract

Background Peroral endoscopic myotomy (POEM) is increasingly used as primary treatment for esophageal achalasia, in place of the options such as Heller myotomy (HM) and pneumatic dilatation (PD)

Objective These evidence-based guidelines from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) intend to support clinicians, patients and others in decisions about the use of POEM for treatment of achalasia.

Results The panel agreed on 4 recommendations for adults and children with achalasia.

Conclusions Strong recommendation for the use of POEM over PD was issued unless the concern of continued postoperative PPI use remains a key decision-making concern to the patient. Conditional recommendations included the option of using either POEM or HM with fundoplication to treat achalasia, and favored POEM over HM for achalasia subtype III.

Keywords Esophageal achalasia · POEM procedure · Heller myotomy · Pneumatic dilatation · Clinical practice guidelines

Abbreviations

POEM	Peroral endoscopic myotomy
HM	Heller myotomy
LHM	Laparoscopic Heller myotomy
PD	Pneumatic dilation
GERD	Gastroesophageal reflux disease
RCT	Randomized controlled trial
RR	Risk ratio
CI	Confidence interval
EtD	Evidence to decision
PPI	Proton pump inhibitor

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ACG Clinical Guidelines: Diagnosis and Management of Achalasia

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Achalasia is an esophageal motility disorder characterized by aberrant peristalsis and insufficient relaxation of the lower esophageal sphincter. Patients most commonly present with dysphagia to solids and liquids, regurgitation, and occasional chest pain with or without weight loss. High-resolution manometry has identified 3 subtypes of achalasia distinguished by pressurization and contraction patterns. Endoscopic findings of retained saliva with puckering of the gastroesophageal junction or esophagram findings of a dilated esophagus with bird beaking are important diagnostic clues. In this American College of Gastroenterology guideline, we used the Grading of Recommendations Assessment, Development and Evaluation process to provide clinical guidance on how best to diagnose and treat patients with achalasia.

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INTRODUCTION

Achalasia is one of the most studied esophageal motility disorders. In this guideline, we address the diagnosis, treatment, and overall management of adult patients with achalasia. This guideline is structured in the format of recommendations, key concepts, and summaries of the evidence. Each recommendation statement has an associated assessment of the quality of evidence and strength of recommendation based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. Key concepts are statements that are not amenable to the GRADE process, either because of the structure of the statement or the available evidence. In some instances, key concepts are based on the extrapolation of evidence and/or expert opinion. The evidence summary for each section provides important definitions and data supporting the recommendations.

METHODS

Each section will provide specific recommendations based on the current literature and a summary of the evidence supporting those recommendations. We used the GRADE process (Table 1) for each of the recommendation statements (Table 2). Two formally trained GRADE methodologists conducted the GRADE process using GRADEPro. This process evaluated the quality of supporting evidence. The quality of the evidence is graded from high to low. "High"-quality evidence indicates that further research is unlikely to change the authors' confidence in the estimate of effect and that we are very confident that the true effect lies close to that of the estimate of the effect. "Moderate"-quality evidence is associated with moderate confidence in the effect estimate, although further research would be likely to have an impact on the confidence of the estimate, whereas "low"-quality evidence indicates that further study would likely have an important impact on the confidence in the estimate of the effect and would likely change the estimate. "Very low"–quality evidence indicates very little confidence in the effect estimate and that the true effect is likely to be substantially different than the estimate of effect. A "strong" recommendation is made when the benefits clearly outweigh the negative, whereas a "conditional" recommendation is used when some uncertainty remains about the balance of benefit and potential harms. Key concepts are statements that are not amenable to the GRADE process, either because of the structure of the statement or because of the available evidence. In some instances, key concepts are based on the extrapolation of evidence and/or expert opinion. Tables 2 and 3 summarize the GRADE recommendations and key concept statements in this guideline.

EPIDEMIOLOGY AND DIAGNOSIS

Achalasia is an esophageal motility disorder with reported global incidence and prevalence ranging from 0.03 to 1.63 per 100,000 persons per year and 1.8 to 12.6 per 100,000 persons per year, respectively (1,2). Achalasia is a rare diagnosis with only 20,000–40,000 affected patients in the United States. It occurs equally in men and women, with no racial predilection. The peak incidence occurs between 30 and 60 years of age. Patients often present with progressive dysphagia to solids and liquids, heartburn, chest pain, regurgitation, and varying degrees of weight loss or nutritional deficiencies (1,3). Diagnosis of achalasia is thus clinically suspected in patients who present with the above-mentioned classic symptoms and then confirmed by objective diagnostic tests discussed below. However, because heartburn may be present in 27%–42% of patients with achalasia, patients are frequently initially misdiagnosed as having gastroesophageal reflux disease (GERD) and are treated with proton pump inhibitors (PPI) (4).

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2022 CPT Code Review
Periurethral Transperinenal Adjustable Balloon Continence Device

Codes

1) **53451**: Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance
2) **53452**: Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance
3) **53453**: Periurethral transperineal adjustable balloon continence device; removal, each balloon
4) **53454**: Periurethral transperineal adjustable balloon continence device; percutaneous adjustment of balloon(s) fluid volume

Description: The periurethral transperinenal adjustable balloon continence devices consists of two small, adjustable, silicone balloons each connected with tubing to a port. The balloons are placed where the prostate was removed or resected. The fluid-filled balloons apply pressure to and support the bladder neck, which helps prevent accidental leakage of urine. The only device currently on the market is the ProACT device from Uromedica.

Many other devices and procedures exist for treatment of post-prostate treatment urinary incontinence. These include artificial urinary sphincters, sling procedures, and injection of bulking agents.

Evidence

1) **Larson 2019,** systematic review and meta-analysis of ProACT for the treatment of male stress urinary incontinence
    a. N=19 studies (1264 patients)
        i. Mean follow up 3.6 years
        ii. Postprostatectomy incontinence in 92.3% of patients
        iii. All cohort studies
        iv. 10 good quality, 7 fair quality, and 2 poor quality studies
    b. At baseline, patients on average were using 4.0 pads per day (PPD) (95% confidence interval [CI]: 2.6-5.4), which was reduced to an average of 1.1 PPD (95% CI: 0.5-1.7) after

ProACT implantation. The number of patients that were considered "dry" was 60.2% (95% CI: 54.2%-65.9%) and the number of patients who were found to be either "dry" or improved greater than 50% was 81.9% (95% CI: 74%-87.8%).

c. The meta-analysis estimate for intraoperative perforation of the bladder or urethra is 5.3% (95% CI: 3.4%-8%). Estimates for infection and urinary retention were 2.2% (95% CI: 1.1%-4.3%) and 1.5% (95% CI: 0.7%-3.4%), respectively. The estimated overall revision rate for all causes is 22.2% (95% CI: 15.2%-31.2%) with a mean followup of 3.6 years (range 12-118 months).

a. Conclusions: Implantation of adjustable balloon devices is efficacious and safe for the treatment of male SUI. Given the minimal invasiveness of the therapy, adjustable balloon devices may be a serious option as a first-line treatment in nonirradiated patients with SUI who are not ideal candidates for the artificial urinary sphincter.

Expert guidelines

1) **American Urologic Association 2019,** guideline on incontinence after prostate treatment
    a. Adjustable balloon devices may be offered to patients with mild stress urinary incontinence after prostate treatment. (Moderate Recommendation; Evidence Level: Grade B)
        i. While the adjustable balloon devices have been shown to improve incontinence, providers should be aware of an increased incidence of intraoperative complications and need for explanation within the first two years compared to the male sling and AUS. Given the limited clinical experience of implanters across the United States, providers should obtain specialty training prior to device implantation.

Other payer policies

1) **Wellmark BCBS 2021**: Considers Transperineal Implantation of Permanent Adjustable Balloon Continence Device (ProACT) to be experimental
2) **Aetna 2021:** Aetna considers transperineal implantation of a permanent adjustable balloon continence device (e.g., ACT, ProACT Therapy System, Uromedica, Inc.) for the treatment of urinary incontinence experimental and investigational because its effectiveness has not been established.
3) **Providence Health Plans 2021**: Transperineal periurethral balloon continence devices are listed as not covered

HERC staff summary:
Transperineal periurethral balloon continence devices are a new treatment with a limited evidence base (only non-comparative cohort studies). There is a high rate of reported complications and need for explantation. No private payer surveyed is currently covering these devices and the AUA notes that it "may be offered to patients with mild stress urinary incontinence after prostate treatment" but that there are concerns about complication rates and need for specialty training prior to implantation.

HERC staff recommendation

1) Place CPT **53453** (Periurethral transperineal adjustable balloon continence device; removal, each balloon) on line 424 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
2) Place the following CPT codes on line 662 and place entry in GN173 as shown below
    a. **53451**: Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance
    b. **53452**: Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance
    c. **53454**: Periurethral transperineal adjustable balloon continence device; percutaneous adjustment of balloon(s) fluid volume

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 662
The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
53451, 53452, 53454	Periurethral transperineal adjustable balloon continence device	Insufficient evidence of effectiveness	November 2021

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Neurourology Urodynamics ICS SUFU WILEY

REVIEW ARTICLE

Adjustable continence therapy (ProACT) for the treatment of male stress urinary incontinence: A systematic review and meta-analysis

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Funding information
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Abstract

Aims: First, to evaluate the efficacy of adjustable balloon devices or adjustable continence therapy (ProACT) in the treatment for male stress urinary incontinence (SUI). Second, to investigate the safety profile and rates of adverse events associated with the implantation of adjustable balloon devices.

Method: A review of the literature was performed by searching the PubMed database with the most applicable search terms. We narrowed included studies with adult male patients with SUI; outcomes included pads or pad weight per day and quality of life (QOL) questionnaires, as well as safety outcomes.

Results: In total, 19 studies were included with a total of 1264 patients and 4517 patient-years of follow-up data (mean follow-up time 3.6 years). ProACT implantation resulted in an incontinence QOL improvement of 30.8 points from baseline. At baseline, patients on average were using 4.0 pads per day (PPD) (95% confidence interval [CI]: 2.6-5.4), which was reduced to an average of 1.1 PPD (95% CI: 0.5-1.7) after ProACT implantation. The number of patients that were considered "dry" was 60.2% (95% CI: 54.2%-65.9%) and the number of patients who were found to be either "dry" or improved greater than 50% was 81.9% (95% CI: 74%-87.8%).

Conclusions: Implantation of adjustable balloon devices is efficacious and safe for the treatment of male SUI. Given the minimal invasiveness of the therapy, adjustable balloon devices may be a serious option as a first-line treatment in nonirradiated patients with SUI who are not ideal candidates for the artificial urinary sphincter.

KEYWORDS
minimally invasive therapy, postprostatectomy, stress urinary incontinence

1 | INTRODUCTION

Stress urinary incontinence (SUI) is a condition that is most frequently associated with prostate surgery. SUI accounts for nearly 10% of urinary leakage complaints expressed by males and contributes to 10% to 30% of mixed urinary incontinence cases.[1] It is proven that SUI poses harmful implications to patient health, yet, in addition, has a notable social and economic impact. With 3% to 11% of males impacted by some form of incontinence, the burden remains significant.[1] The variance in prevalence may be attributed to inconsistent definitions of incontinence, which inherently lead to variability in the diagnosis and management strategies of

Approved by the AUA Board of Directors October 2018

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

American Urological Association (AUA)/

Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU)

INCONTINENCE AFTER PROSTATE TREATMENT: AUA/SUFU GUIDELINE

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Purpose

Urinary incontinence after prostate treatment (IPT) is a clinically significant condition that causes a high degree of patient distress. It is one of the few urologic diseases that is iatrogenic, and, therefore, predictable and perhaps preventable. Although most clinicians are familiar with the more commonly known term "post-prostatectomy incontinence," this guideline uses the term IPT, which is more inclusive given that it covers the management of patients who have incontinence after undergoing radical prostatectomy (RP), radiation treatment (RT), and treatment of benign prostatic hyperplasia (BPH). Evaluation of the patient; risk factors for IPT, which should be discussed with all patients prior to treatment; assessment of the patient prior to intervention; and a stepwise approach to management are covered in this guideline. Possible maneuvers to decrease rates of IPT, with specific focus placed on patients with stress urinary incontinence (SUI) are also explored. The multiple treatments that exist for patients with IPT are discussed and evaluated, including physical therapy, medications, and surgery.

Methodologies

The systematic review utilized to inform this guideline was conducted by a methodology team at the Mayo Clinic Evidence-Based Practice Research Program. The scope of the topic and the discussion of the final systematic review used to develop guideline statements was conducted in conjunction with the Incontinence after Prostate Treatment expert panel. A research librarian conducted searches in Ovid MEDLINE (from 2000 to December 21st, 2017), Cochrane Central Register of Controlled Trials (from 2000 to December 21st, 2017) and Cochrane Databases of Systematic Reviews (from 2000 to December 21st, 2017). Searches of electronic databases were supplemented by reviewing reference lists of relevant articles. Panel members identified additional references through 12/31/2018.

Guideline Statements

Pre-Treatment

1. Clinicians should inform patients undergoing radical prostatectomy of all known factors that could affect continence. (Moderate Recommendation; Evidence Level: Grade B)

2. Clinicians should counsel patients regarding the risk of sexual arousal incontinence and climacturia following radical prostatectomy. (Strong Recommendation; Evidence Level: Grade B)

3. Clinicians should inform patients undergoing radical prostatectomy that incontinence is expected in the short-term and generally improves to near baseline by 12 months after surgery but may persist and require treatment. (Strong Recommendation; Evidence Level: Grade A)

4. Prior to radical prostatectomy, patients may be offered pelvic floor muscle exercises or pelvic floor muscle training. (Conditional Recommendation; Evidence Level: Grade C)

5. Patients undergoing transurethral resection of the prostate after radiation therapy or radical prostatectomy after radiation therapy should be informed of the high rate of urinary incontinence following these procedures. (Moderate Recommendation; Evidence Level: Grade C)

Post-Prostate Treatment

6. In patients who have undergone radical prostatectomy, clinicians should offer pelvic floor muscle exercises or pelvic floor muscle training in the immediate post-operative period. (Moderate Recommendation; Evidence Level: Grade B)

7. In patients with bothersome stress urinary incontinence after prostate treatment, surgery may be considered as early as six months if incontinence is not improving despite conservative therapy. (Conditional Recommendation; Evidence Level: Grade C)

8. In patients with bothersome stress urinary incontinence after prostate treatment, despite conservative therapy, surgical treatment should be offered at one year post-prostate treatment. (Strong Recommendation; Evidence Level: Grade B)

Evaluation of Incontinence after Prostate Treatment

9. Clinicians should evaluate patients with incontinence after prostate treatment with history, physical exam, *and appropriate diagnostic modalities* to categorize type and severity of incontinence and degree of bother. (Clinical Principle)

10. Patients with urgency urinary incontinence or urgency predominant mixed urinary incontinence should be offered treatment options per the American Urological Association Overactive Bladder guideline. (Clinical Principle)

11. Prior to surgical intervention for stress urinary incontinence, stress urinary incontinence should be confirmed by history, physical exam, or ancillary testing. (Clinical Principle)

12. Patients with incontinence after prostate treatment should be informed of management options for their incontinence, including surgical and non-surgical options. (Clinical Principle)

13. In patients with incontinence after prostate treatment, physicians should discuss risk, benefits, and expectations of different treatments using the shared decision-making model. (Clinical Principle)

14. Prior to surgical intervention for stress urinary incontinence, cystourethroscopy should be per formed to assess for urethral and bladder pathology that may affect outcomes of surgery. (Expert Opinion)

15. Clinicians may perform urodynamic testing in a patient prior to surgical intervention for stress urinary incontinence in cases where it may facilitate diagnosis or counseling. (Conditional Recommendation; Evidence Level: Grade C)

Treatment Options

16. In patients seeking treatment for incontinence after radical prostatectomy, pelvic floor muscle exercises or pelvic floor muscle training should be offered. (Moderate Recommendation; Evidence Level: Grade B)
17. Artificial urinary sphincter should be considered for patients with bothersome stress urinary incontinence after prostate treatment. (Strong Recommendation; Evidence Level: Grade B)
18. Prior to implantation of artificial urinary sphincter, clinicians should ensure that patients have adequate physical and cognitive abilities to operate the device. (Clinical Principle)
19. In the patient who selects artificial urinary sphincter, a single cuff perineal approach is preferred. (Moderate Recommendation; Evidence Level: Grade C)
20. Male slings should be considered as treatment options for mild to moderate stress urinary incontinence after prostate treatment. (Moderate Recommendation; Evidence Level: Grade B)
21. Male slings should not be routinely performed in patients with severe stress incontinence. (Moderate Recommendation; Evidence Level: Grade C)
22. Adjustable balloon devices may be offered to patients with mild stress urinary incontinence after prostate treatment. (Moderate Recommendation; Evidence Level: Grade B)
23. Surgical management of stress urinary incontinence after treatment of benign prostatic hyperplasia is the same as that for patients after radical prostatectomy. (Moderate Recommendation; Evidence Level: Grade C)
24. In men with stress urinary incontinence after primary, adjuvant, or salvage radiotherapy who are seeking surgical management, artificial urinary sphincter is preferred over male slings or adjustable balloons. (Moderate Recommendation; Evidence Level: Grade C)
25. Patients with incontinence after prostate treatment should be counseled that efficacy is low and cure is rare with urethral bulking agents. (Strong Recommendation; Evidence Level: Grade B)
26. Other potential treatments for incontinence after prostate treatment should be considered investigational, and patients should be counseled accordingly. (Expert Opinion)

Complications after Surgery

27. Patients should be counseled that artificial urinary sphincter will likely lose effectiveness over time, and reoperations are common. (Strong Recommendation; Evidence Level: Grade B)
28. In patients with persistent or recurrent urinary incontinence after artificial urinary sphincter or sling, clinicians should again perform history, physical examination, and/or other investigations to determine the cause of incontinence. (Clinical Principle)
29. In patients with persistent or recurrent stress urinary incontinence after sling, an artificial urinary sphincter is recommended. (Moderate Recommendation; Evidence Level: Grade C)
30. In patients with persistent or recurrent stress urinary incontinence after artificial urinary sphincter, revision should be considered. (Strong Recommendation; Evidence Level: Grade B)

Special Situations

31. In a patient presenting with infection or erosion of an artificial urinary sphincter or sling, explantation should be performed and reimplantation should be delayed. (Clinical Principle)
32. A urinary diversion can be considered in patients who are unable to obtain long-term quality of life after incontinence after prostate treatment and who are appropriately motivated and counseled. (Expert Opinion)
33. In a patient with bothersome climacturia, treatment may be offered. (Conditional Recommendation; Evidence Level: Grade C)
34. Patients with stress urinary incontinence following urethral reconstructive surgery may be offered artificial urinary sphincter and should be counseled that complications rates are higher. (Conditional Recommendation; Evidence Level: Grade C)
35. In patients with incontinence after prostate treatment and erectile dysfunction, a concomitant or staged procedure may be offered. (Conditional Recommendation; Evidence Level: Grade C)
36. Patients with symptomatic vesicourethral anastomotic stenosis or bladder neck contracture should be treated prior to surgery for incontinence after prostate treatment. (Clinical Principle)

Introduction

IPT causes emotional and financial distress to patients afflicted with this condition by delaying patients' re-entry into society, inhibiting relationships, and carrying an economic burden for families and stakeholders. It is a condition that has gained visibility not only due to the extensive use of surgery for prostate cancer but also given to the proliferation of men's continence products available to the lay public.

Since IPT is caused by treatment of the prostate, it is, by definition iatrogenic and perhaps preventable or predictable. Understanding the nature of IPT is crucial for patients and practitioners during recovery and extended survivorship. Practitioners benefit from being able to assess which patient will likely experience further symptom recovery versus those who will not. This allows clinicians to set clear and reasonable expectations regarding the short-, medium-, and long-term sequela of IPT.

Although most clinicians are familiar with the more commonly known term "post-prostatectomy incontinence," this guideline uses the term IPT, which is more inclusive given that it covers the management of patients who have incontinence after undergoing RP, RT, and treatment of BPH. Evaluation of the patient; risk factors for IPT, which should be discussed with all patients prior to treatment; assessment of the patient prior to intervention; and a stepwise approach to management are covered in this guideline. Possible maneuvers to decrease rates of IPT, with specific focus placed on patients with SUI, are also explored. The multiple treatments that exist for patients with IPT are discussed and evaluated, including physical therapy, medications, and surgery. Algorithms for patient evaluation, surgical management, and device failure are provided for practitioners.

Methodology

The systematic review utilized to inform this guideline was conducted by a methodology team at Mayo Clinic Evidence-Based Practice Research Program. Determination of the guideline scope and review of the final systematic review to inform guideline statements was conducted in conjunction with the Incontinence after Prostate Treatment expert panel.

Panel Formation

The IPT Panel was created in 2017 by the American Urological Association Education and Research, Inc. (AUAER). This guideline was developed in collaboration with the Society of Urodynamics, Female Pelvic

Medicine & Urogenital Reconstruction (SUFU). The Practice Guidelines Committee (PGC) of the American Urological Association (AUA) selected the Panel Chair, who in turn appointed additional panel members with specific expertise in this area, in conjunction with SUFU. Funding of the panel was provided by the AUA with contributions from SUFU; panel members received no remuneration for their work.

Searches and Article Selection

A comprehensive search of several databases from 2000 to December 21st, 2017 was completed. Databases included Ovid MEDLINE Epub Ahead of Print, Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced medical reference librarian with input from the guideline methodologist. Controlled vocabulary supplemented with keywords was used to search for studies on IPT. The search was restricted to studies published in English and available in full text in the peer reviewed literature.

Data Abstractions

Two reviewers independently selected studies and extracted data using standardized, pilot tested forms created in a systematic review software management system (Distiller SR, Evidence Partners, Ottawa, Canada). Disagreements were resolved by discussion between the two reviewers. Two main types of data were abstracted: baseline characteristics (study design, objective, inclusion and exclusion criteria, sample size, age, body mass index [BMI], intervention, period of follow up), and outcome data (number of patients who were incontinent and those with incontinence improvement, mean pads per day, quality of life [QoL], and complications).

Risk of Bias Assessment

The Newcastle Ottawa scale, which evaluates cohort selection, comparability and outcomes assessment, was used for non-randomized controlled trials (RCTs). The Cochrane risk of bias tool which evaluates random sequence generation, allocation concealment, blinding, and attrition was used for evaluation of RCTs.

Data Synthesis

When meta-analysis was appropriate, methodologists utilized the random-effects model *a priori* because of the anticipated heterogeneity across study populations and settings. Otherwise, outcomes were evaluated using narrative and descriptive approaches.

Determination of Evidence Strength

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes individual study quality in addition to consideration of study design; consistency of findings across studies; adequacy of sample sizes; and generalizability of samples, settings, and treatments for the purposes of the guideline. Investigators graded the strength of evidence for key comparisons and outcomes for each Key Question, using the approach described in the Agency for Healthcare Research and Quality Evidence-based Practice Center Methods Guide for Comparative Effectiveness and Effectiveness Reviews.[1] Strength of evidence assessments were based on the following domains:

- Study limitations, based on the overall risk of bias across studies (low, medium, or high)
- Consistency of results across studies
- Directness of the evidence linking the intervention and health outcomes
- Precision of the estimate of effect, based on the number and size of studies and confidence intervals for the estimates (precise or imprecise)
- Reporting bias, based on whether or not the studies defined and reported primary outcomes and whether or not we identified relevant unpublished studies (suspected or undetected)

The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable

RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (Table 1). ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/ burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/ burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but better evidence *is likely to change confidence*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances, and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, the Panel provides guidance in the form of ***Clinical Principles*** or ***Expert Opinions*** with consensus achieved using a modified Delphi technique if differences of opinion emerged.[2] A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence.

Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the treatment of IPT. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from

TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

	Evidence Strength A (High Certainty)	**Evidence Strength B (Moderate Certainty)**	**Evidence Strength C (Low Certainty)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/ Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/ Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/ Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/ Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/ Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/ Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members clinical training, experience, knowledge, and judgment for which there is no evidence		

AUA and SUFU as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from January 14-28, 2019 to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation to open the document further to the patient perspective. The draft guideline document was distributed to 49 external peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 33 reviewers (9 AUA PGC, SQC, and BOD reviewers; 22 external reviewers; and 2 public reviewers) provided comments. At the end of the peer review process, a total of 476 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC and BOD as well as the governing bodies of SUFU for final approval.

Guideline Statements

PRE-TREATMENT

1. Clinicians should inform patients undergoing radical prostatectomy of all known factors that could affect continence. (Moderate Recommendation; Evidence Level: Grade B)

Many patient and surgical based factors have been evaluated to determine their impact on recovery of continence after RP. Younger patient age, smaller prostate size, and longer membranous urethral length (measured by MRI) have been consistently associated with improved recovery of continence after RP. A meta-analysis of studies evaluating age as a risk factor of IPT found that increasing patient age at the time of RP increases risk of incontinence.[3-8] Similarly, increasing prostate size results in increased odds of IPT,[4-6, 9-17] while increasing membranous urethral length results in decreased risk.[4-6, 9, 12, 18-20] Although each of the above are risk factors, their relationship to IPT is complex and nonlinear. Predictive models should account for this nonlinearity and are best represented as nomograms.[9]

Surgical approaches do not seem to impact rates of IPT; in particular, open RP has similar rates of urinary incontinence as robot-assisted RP.[21, 22] There is no current evidence that any surgical maneuvers, beyond bilateral neurovascular bundle preservation, results in improved continence recovery.[23, 24,25, 26] Men receiving bilateral neurovascular bundle preservation were 26% more likely to be continent at six months compared to men who did not;[27-32] however, surgeons should base the degree of nerve sparing on the features of the cancer rather than pre-operative potency. Men with poor pre-operative potency still benefit from nerve sparing in terms of recovery of continence.[33, 34]

BMI may impact IPT in the short-term; however there is little evidence that it is a risk factor for incontinence after RP at one year.[4-6, 9, 11-17]

2. Clinicians should counsel patients regarding the risk of sexual arousal incontinence and climacturia following radical prostatectomy. (Strong Recommendation; Evidence Level: Grade B)

Urologists should inform patients of the risks of sexual arousal incontinence and climacturia. Sexual arousal incontinence is characterized by the inadvertent loss of urine during sexual arousal, foreplay, and/or masturbation. Climacturia (also known as orgasm-associated urinary incontinence) is the involuntary loss of urine at the time of orgasm. This can occur following RP, with or without adjuvant RT, and can even occur in those treated with RT alone. While precise prevalence has not been well-established, several studies report an incidence of sexual arousal incontinence and climacturia following prostate cancer surgery ranging from 20 -93%, with most reporting an overall rate close to 30%.[35]

Such leakage is reported as bothersome by up to half of those patients, and one-third report that they avoid sexual situations due to fear of leakage.[36]

The pathophysiology of climacturia is not completely understood. The mechanism is thought

to relate to removal of the internal sphincter during RP, which is exacerbated by prior transurethral resection of the prostate (TURP). Bladder contraction at the time of orgasms with some degree of external sphincter insufficiency is thought to result in leakage during orgasm.[37]

Although climacturia and SUI are not mutually exclusive, there is some overlap between the conditions. In patients with climacturia, 30% do not experience SUI; conversely, 30% of patients with SUI do not report climacturia.[38] While the risk factors for climacturia are not as well defined as those for SUI, the main risk factor is time since surgery (shorter time from surgery is associated with a higher rate of leakage). Additionally, there appears to be a faster recovery of continence during sexual activity following robotic RP compared to open or pure laparoscopic RP.[39] Improvement can be expected throughout the postoperative period, but it can take several years to resolve, and typically persists in one-third of patients.[35, 40]

Other risk factors include prior TURP, as well as shorter functional urethral and penile length following RP. It does not appear that age, pre-operative erectile function, or nerve sparing status significantly affect the risk of sexual arousal or orgasm-related incontinence.[38]

3. Clinicians should inform patients undergoing radical prostatectomy that incontinence is expected in the short-term and generally improves to near baseline by 12 months after surgery but may persist and require treatment.(Strong Recommendation; Evidence Level: Grade A)

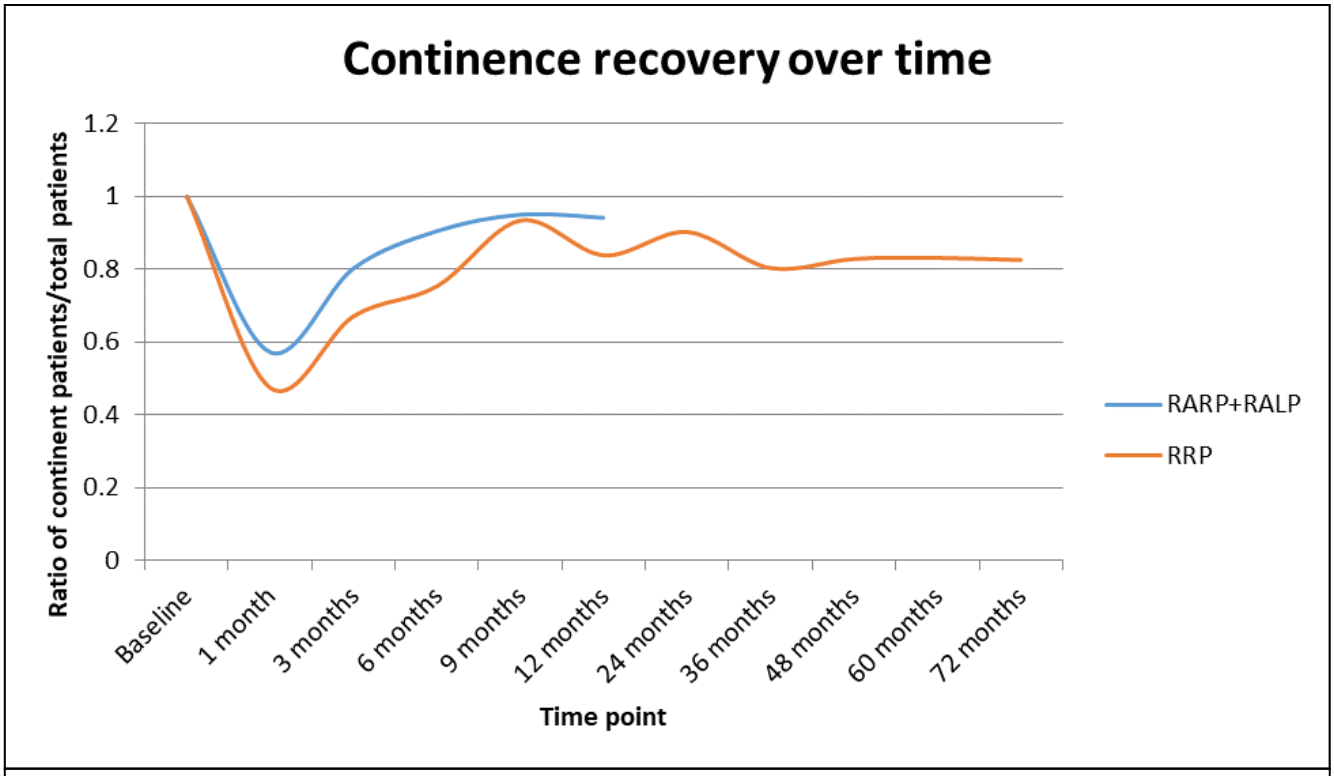
A commonly accepted definition of urinary continence is not requiring a pad or protective device to stay dry (pad-free).[41] Most men undergoing RP are not continent (pad-free) at the time of catheter removal and should be informed that continence is not immediate.[8] Continence after RP improves with time, and most men achieve continence within 12 months of surgery.[8] Men considering RP should be provided with reasonable expectations regarding recovery of continence. Because incontinence is expected in the early phase after surgery, conservative management with regular follow-up during the first year after surgery is recommended to assess patient progress. The spectrum of improvement over time based on procedure is shown in Figure 1.

4. Prior to radical prostatectomy, patients may be offered pelvic floor muscle exercises or pelvic floor muscle training. (Conditional Recommendation; Evidence Level: Grade C)

Voluntarily activating the pelvic floor muscles through an exercise program prior to RP is a common practice. Exercises for the pelvic floor muscle are easier to learn in the pre-operative period since mastery can be difficult postoperatively given muscle inhibition, sensory changes, urinary incontinence, and surgical pain.[42] Typical preliminary goals of a preoperative program include proper patient education regarding pelvic floor muscle anatomy, physiology, awareness, and motor control, which maximize the effectiveness of exercises.

Pelvic floor muscle exercises (PFME) is defined in this guideline as an exercise program specific to the pelvic floor muscle group that is self-guided as a home exercise program only. The patient may have learned the program through patient education literature or with a single basic instruction session from an appropriate practitioner. Pelvic floor muscle training (PFMT) is defined as a training program specific to the pelvic floor muscle group that is practitioner guided. Typically, PMFT will consist of individualized pelvic floor muscle awareness training using verbal, tactile, and/or visual feedback along with a home based PFME program to be progressed during follow-up visits with the practitioner.

Seven trials met inclusion criteria regarding the effectiveness of a pre-operative PFMT program improving post-prostatectomy continence. The robustness of the recommendation is limited by heterogeneous methods of evaluation and comparison among the different studies. The PFMT methods utilized to optimize pelvic floor



RARP: Robotic-assisted radical prostatectomy, RALP: Robot-assisted laparoscopic prostatectomy, RRP: Retropubic radical prostatectomy

muscle awareness included verbal cues,[43-45] tactile cues,[43, 45, 46] visualization of penile movement,[45] surface electromyography biofeedback,[44, 46, 47] pressure biofeedback,[48] and transabdominal ultrasound imaging.[43] Overall, these methods successfully assisted patients in isolating and contracting their pelvic floor muscles. However, it is not clear whether they are truly necessary or which methods are more beneficial.

To allow for neuromuscular adaptation, preoperative PFMT should be started three to four weeks prior to surgery.[43-46] However, the Panel can neither recommend the optimal time frame for initiation of pre-operative PFMT, nor the ideal intensity of the program due to reported variability in start times found in the literature.[47-49] The methods, dosage, and level of follow-up for PFMT and PFME in the post-operative period also varied among trials.

The benefit of starting pre-operative PMFT in not consistent in the outcome data. In one view, pre-operative PFMT has been shown to be effective in hastening continence recovery after surgery,[43, 45, 48, 49] while other efforts have failed to demonstrate a beneficial effect on continence.[44, 46] All trials varied with respect to assigned PFMT/ PFME regimens, definitions of continence, and length of follow-up. It is important to note that formal PFMT is not harmful, and the potential benefits clearly outweigh any potential risks and likely decrease regret.[46]

5. Patients undergoing transurethral resection of the prostate after radiation therapy or radical prostatectomy after radiation therapy should be informed of the high rate of urinary incontinence following these procedures. (Moderate Recommendation; Evidence Level: Grade C)

TURP. TURP following brachytherapy or external beam radiation has been associated with incontinence rates of up to 70%.[50, 51] The urethral fibrosis developing from radiation-related progressive endarteritis decreases the functional capabilities of the external sphincter. Even in the

absence of direct damage to the sphincter, adjacent surgical cautery or laser energy further compromises sphincter function. The need for subsequent resections, patient age, and pre-TURP urgency is correlated with higher rates of incontinence.[52]

There is little to no published evidence discussing post-TURP outcomes with patients who have undergone other forms of local therapy such as high-intensity focused ultrasound and cryotherapy. However, it is the opinion of this Panel that these patients have high risks of incontinence similar to post-TURP radiated patients.

Salvage Prostatectomy. Regardless of the initial form of non-operative therapy or the operative approach, salvage RP is associated with high rates of urinary incontinence rates (ranging from 20-70%) for both open and robotic techniques compared to standard RP.[53-59]

Patients undergoing TURP or salvage RP after primary non-surgical treatment for prostate cancer who seek long-term continence should be informed that they may require an artificial urinary sphincter (AUS).

POST-PROSTATE TREATMENT

6. In patients who have undergone radical prostatectomy, clinicians should offer pelvic floor muscle exercises or pelvic floor muscle training in the immediate post-operative period. (Moderate Recommendation; Evidence Level: Grade B)

Short-term PFMT may be offered to patients who are not able to perform self-directed PFME with appropriate quality and who request additional interventions to hasten the recovery of continence after RP. PFME after catheter removal has been shown to improve time-to-achieving continence compared to control groups in RCTs[60] and should be offered to all patients after RP upon removal of the urethral catheter. Those patients who are committed to a progressive PFMT or PFME program can expect an earlier return to continence than those who are not.[47] The timeframe for this early continence recovery after RP can be as early as three[47, 49, 61-63] to six months.[64] However, longer term assessment suggests that overall continence rates at one year remain similar between men who underwent PFME or PFMT and those who did not.[65]

Long-term assessment is skewed because of highly heterogeneous data and continence rates between men treated with PFME/PFMT are similar to those not treated (57% with urinary incontinence in intervention group versus 62% in control group, RR=0.85 at 12 months, 95% CI=0.60-1.22).[65] Overall these data suggest that if performed in the early post-operative period, PFME or PFMT improve time to continence (thus improving QoL) but not overall continence at 12 months.

7. In patients with bothersome stress urinary incontinence after prostate treatment, surgery may be considered as early as six months if incontinence is not improving despite conservative therapy. (Conditional Recommendation; Evidence Level: Grade C)

While almost all patients have reached their maximum improvement by 12 months, most patients with severe SUI will show no significant improvement after six months and may be candidates for early intervention. A review of the data indicates that 90% of patients will achieve continence at six months after robotic-assisted laparoscopic prostatectomy and only an additional 4% of patients will gain continence afterwards.[8, 66-71] Such data highlight that symptom improvement often plateaus earlier than one year. Patients who report a lack of symptom improvement or those experiencing more severe incontinence at six months may be offered early treatment in the form of surgical interventions with such a treatment decision made using a shared decision-making model.

8. In patients with bothersome stress urinary incontinence after prostate treatment, despite conservative therapy, surgical treatment should be offered at one year post-prostate treatment. (Strong Recommendation; Evidence Level: Grade: B)

Timing of treatment should be optimized to restore QoL as soon as possible without over-treatment. The natural history of incontinence after prostate surgery shows that the clear majority of patients will reach their maximum improvement by 12 months with minimal to no improvement afterwards. While cumulative data[8, 66-71] has shown that 94% of patients achieve continence by 12 months,[69, 72] patients followed for 24 months after robotic-assisted laparoscopic prostatectomy revealed that only an additional 1% of patients had continued improvement from 12-24 months. Withholding surgical treatment after 12 months is unlikely to result in improved patient symptoms and will delay restoration of continence. Patients who are eager to become dry and whose symptom improvement has reached a plateau may desire surgical treatment earlier than one year, and shared decision-making is key in initiating this intervention. Conversely, treatment should be offered with caution in patients who are displaying symptom improvement.

EVALUATION OF INCONTINENCE AFTER PROSTATE TREATMENT

9. Clinicians should evaluate patients with incontinence after prostate treatment with history, physical exam, *and appropriate diagnostic modalities* to categorize type and severity of incontinence and degree of bother. (Clinical Principle)

There is no formal evidence regarding the effects of history and physical exam on outcomes of IPT treatments; however, there is universal agreement that taking a history and performing a physical examination should be the first step in the assessment of anyone with urinary incontinence.[73] There is strong evidence that a history of pelvic RT[74, 75] is associated with the severity of incontinence, especially stress incontinence,[76, 77] after prostate surgery.

The Panel believes that before treating IPT, it is critical to categorize the type of incontinence (stress, urgency, mixed) and the severity and degree of bother of incontinence. The status of prostate cancer also should be known, particularly for men who are candidates for salvage RT, which may impact efficacy of continence treatment.

History is the first step in determining the type of incontinence, which is important because treatments for SUI (caused by sphincteric insufficiency) and urgency incontinence (caused by bladder dysfunction) are very different. In cases of mixed incontinence, it can be important to determine which component is more prevalent and bothersome, though many investigators feel that treatment outcomes for urgency incontinence may be difficult to determine in the face of significant sphincteric insufficiency.

History should focus on characterization of incontinence (stress or activity related versus urgency related), the severity of incontinence, the progression or resolution of incontinence over time, and degree of bother. Specifically, patients should be questioned on which activities causes incontinence. Increases in abdominal pressure such as that caused by straining, walking, cough, and exercise are suggestive of SUI, while the sudden compelling desire to void that is difficult to defer and results in leakage indicates urgency incontinence.[78] Presence of incontinence while asleep as well as nocturia are also important to note, because this may indicate urgency urinary incontinence or severe SUI. Confirmation of SUI can often be determined by history or physical exam alone; however there are times when a clinician may choose advanced testing such as urodynamic studies (UDS).

The severity of incontinence (i.e. volume lost over time) is important to know, especially in the case of sphincteric insufficiency as some treatments (e.g., male slings), clearly have inferior results in severe incontinence. Incontinence severity can be determined by history, or more objectively, by pad testing. It has been shown that careful questioning regarding pad number, size, and degree of wetness correlates well with pad weights and effect on QoL.[79] However, there may be times when a formal one-hour or 24-hour pad test may be helpful in determining incontinence severity.[79, 80] The Panel agrees that it is important to determine the degree of bother of incontinence and effect on QoL since this will

help to determine the type of initial treatment, or no treatment, and guide counselling through a shared decision-making model.

10. Patients with urgency urinary incontinence or urgency predominant mixed urinary incontinence should be offered treatment options per the American Urological Association Overactive Bladder guideline. (Clinical Principle)

The occurrence of urinary frequency, urgency, and urgency urinary incontinence is common after prostate treatment.[81-84] A review of urinary symptoms after RP reveals that 29% of patients will develop one or more symptoms, with 19% developing urinary urgency and 6% complaining of urgency incontinence.[81] Clinicians should be aware of the prevalence of overactive bladder (OAB), which has been described as high as 48% [85] and specifically assess for symptoms after prostate treatment. Evaluation and treatment can be initiated at any time post-prostate treatment and should follow the Overactive Bladder in Adults: AUA/SUFU Guideline.[86, 87] The presence of urgency urinary incontinence should not exclude a patient from surgical treatment of his bothersome SUI.

11. Prior to surgical intervention for stress urinary incontinence, stress urinary incontinence should be confirmed by history, physical exam, or ancillary testing. (Clinical Principle)

Prior to surgical intervention for SUI, clinicians should be certain that a patient truly has sphincteric insufficiency as a cause for his incontinence. History of SUI has a 95% positive predictive and 100% negative predictive value for the presence of SUI on UDS.[88] Evidence has not definitely shown whether or not the objective demonstration of SUI predicts surgical outcomes after prostate cancer treatment. The AUA/SUFU Guideline on the Surgical Management of Female Stress Urinary Incontinence states that the objective demonstration of SUI should be confirmed prior to surgical management (based on panel consensus).[89] Similarly, a recent International Continence Society consensus panel on AUS recommended that every effort should be made to objectively confirm the presence of SUI prior to AUS placement.[90] Clinicians should take all reasonable measures to demonstrate SUI on physical exam with or without provocative testing such as bending, shifting position, or rising from seated to standing position. Stress pad testing can also be performed. Finally, if there is any doubt as to whether the patient has SUI, UDS may be performed. Examples of this may be when the patient has significant mixed incontinence and stress incontinence is not demonstrated, in cases where impaired compliance is suspected and incontinence could be related to high storage pressures without urgency, or if overflow incontinence is suspected. In the case of the latter, a post-void residual (PVR) may be helpful to rule out significant retention of urine.

The presence of microscopic hematuria may warrant additional evaluation with upper tract imaging and cystoscopy. The assessment of PVR may alert the physician to the potential for incomplete bladder emptying; however, the reliability of a single elevated PVR value for predicting emptying dysfunction remains in question, just as a single low PVR value does not rule out the presence of incomplete emptying. Second, the threshold value of a significant PVR is similarly undefined. Finally, a persistently elevated PVR does not characterize the cause of impaired emptying, but rather indicates the need for further evaluation. Additionally, an elevated PVR in the presence of SUI may impact patient counseling regarding surgical interventions and patient expectations. Elevated PVR may be an indication of detrusor underactivity or obstruction (e.g., urethral stricture or bladder neck contracture [BNC]) and thus may prompt further diagnostic evaluation such as uroflowmetry, cystoscopy, or multichannel UDS.

12. Patients with incontinence after prostate treatment should be informed of management options for their incontinence, including surgical and non-surgical options. (Clinical Principle)

Prior to engaging in any active or invasive form of therapy, patients must be made aware of the conservative options for management of urinary incontinence, such as absorbent pads, penile compression devices (clamps), and catheters. These alternatives may be utilized while engaging in PFME/PFMT, considering future options, waiting an appropriate time before surgical intervention, or as an indefinite form of management. Those patients who are candidates for surgical intervention in the future require assistance in handling ongoing leakage in a comfortable, reliable, and cost-efficient manner.[91]

In IPT management, the conservative approach is first-line to control urinary leakage post catheter removal. Absorbent pads, which are available in an array of forms and sizes, are the primary tool of urinary containment. Penile compression devices can be used independently and as an adjunct to reduce daily absorbent product usage. Catheters (condom and urethral), may be necessary in patients with high volume pad usage suffering from skin excoriation, dermatitis, and cellulitis due to urinary leakage.

Absorbent Products – Liners, Guards, Briefs, Underwear. Most patients will start with absorbent pads and make adjustments in type based on the severity of leakage.[91] In general, milder incontinence is managed satisfactorily with shields or lower density guards, while severe incontinence requires briefs or underwear with or without inserts to prevent accidents. From a cost perspective, briefs and underwear systems have been demonstrated to be more effective than pads.[92] Thus, the patient should be advised along these lines if they wish to continue wearing pads as their primary mechanism for urinary containment.

In the individual patient, absorbent products alone may constitute a long-term management strategy. However, it has been demonstrated that the use of even one pad per day is a source of bother and decreased patient satisfaction.[93] Additionally, the use of pads may be associated with skin irritation and dermatitis, especially in the intertriginous areas. In those who need to use more than several pads or garments per day, financial considerations may influence the ability to change pads in a timely fashion. Therefore, it is important to ensure that the patient is utilizing the most effective product based on their degree of incontinence.

Occlusive Devices (Clamps). Occlusive devices may function as a stand-alone therapy for incontinence or as an adjunct to absorbent products. Combination therapy between the two types of devices, such as pads and clamps together, decreases the number of pads required during active periods with a resultant decrease in incontinence products expenditure. Patients must be instructed to release the clamp every two hours to allow for circulation regardless of the need to void. The clamp should not be left on the phallus overnight due to the risks of constant pressure. While successful in decreasing urine loss, compressive devices are associated with decreased penile Doppler flow.[94] Mechanical compression devices are not suitable for patients with memory deficits, poor manual dexterity, impaired sensation, or a significant component of OAB.

Catheters (Condom, Urethral, and Suprapubic). Patients with severe or total incontinence may resort to a catheter and drainage system as the best method to obtain complete control of urinary incontinence. This form of management is also advantageous when the number or frequency of absorbent product changes is disruptive and/or financially prohibitive. Condom type catheters or urinary sheaths are an effective method of urinary containment for men with severe incontinence. In comparison to compressive devices, condom catheter systems are acceptable for patients with any degree of urge incontinence. Theoretically, this approach would also be superior to urethral stricture, poor manual dexterity, or a large glans/ narrow phallus configuration.[95] In the appropriate patient, external catheters have been demonstrated to be superior to absorbent products in patient satisfaction. However, the success of a condom catheter is wholly dependent on proper sizing. The condom or sheath varies based on the material (latex or silicone), length of

adhesive surface, circumference, and overall length.[96] Urethral catheter drainage is a decision of last resort in a patient who is unsuitable for alternative management. Suprapubic catheter drainage is not a solution for the patient with severe intrinsic sphincter deficiency, as urethral leakage will persist.

13. In patients with incontinence after prostate treatment, physicians should discuss risk, benefits, and expectations of different treatments using the shared decision-making model. (Clinical Principle)

The treatment of IPT can be a complex process involving numerous risks and benefits for the patient. Given these inherent complexities, providers should engage patients in shared decision-making during evaluation, treatment, and follow-up. Shared decision-making is a process in which providers and patients work together to make decisions about tests, interventions, and care plans.[97] Shared decisions are made based on clinical evidence that takes into account the risks and benefits and is teamed with patient preferences and values. The approach is predicated on two principles: 1) Patients provide accurate information and can and will participate in the medical decision-making process by asking questions and expressing opinions about their treatment options. 2) Providers will honor patient preferences for goals and treatment and use them to guide recommendations. Evidence suggests that patient participation improves patient satisfaction. Shared decision-making produces better health outcomes by decreasing anxiety, promoting faster recovery, and improving compliance.[98-101]

14. Prior to surgical intervention for stress urinary incontinence, cystourethroscopy should be performed to assess for urethral and bladder pathology that may affect outcomes of surgery. (Expert Opinion)

The presence of urethral pathology (e.g., stricture, BNC, urethral lesions) may affect the outcome of surgery for SUI; therefore some assessment to rule out significant urethral pathology is recommended. The gold standard for this would be a visual assessment of the urethra, including the membranous urethra, prostatic urethra (if present), and bladder neck with cystourethroscopy. Cystourethroscopy has also been recommended prior to placement of transobturator slings to assess urethral function (patients should have visual voluntary contraction of the external sphincter), and luminal closure of the urethra should be demonstrated with bulbar compression and elevation (repositioning test).[102] However, success of the procedure has not been shown to be dependent on these findings in any controlled study. In addition to an evaluation of the urethra, sphincter and bladder neck, pre-operative cystourethroscopy can assess the bladder for any pathology that could affect the decision to perform surgery for stress incontinence. There is, however, no evidence that patients who undergo pre-operative cystourethroscopy have better outcomes for AUS or sling compared to those who do not. With this in mind, the International Continence Society consensus panel of AUS in 2015 stated that preoperative cystourethroscopy should be performed whenever feasible as unrecognized urethral and bladder neck pathology can significantly complicate AUS placement. Unrecognized significant pathology may result in aborting AUS placement in favor of a staged-approach. Having this information preoperatively is beneficial to the patient and the surgeon to clarify expectation and maximize patient satisfaction.[90]

In cases where pre-operative cystourethroscopy is not performed, it may be done at the start of the AUS or sling implantation before any incision is made. In such cases, patients should be made aware of the potential consequences and the possibility of aborting an AUS or sling insertion if significant urethral or bladder pathology is discovered.

15. Clinicians may perform urodynamic testing in a patient prior to surgical intervention for stress urinary incontinence in cases where it may facilitate diagnosis or counseling. (Conditional Recommendation; Evidence Level: Grade C)

UDS allows for a precise evaluation of lower urinary tract function with respect to storage and emptying. It can aid in determining if IPT is caused by sphincter dysfunction, bladder dysfunction, or a combination of both, and also assess bladder contractility and the presence of bladder outlet dysfunction. Thus, UDS can be helpful in situations where this information is not apparent from history, physical, or simple testing.

UDS are not required before surgical intervention for IPT unless the clinician is in doubt of the diagnosis or it is felt that patient counseling will be affected. Unlike for the surgical treatment of SUI in women, there are no controlled studies that assess the value of UDS versus no UDS in men with SUI prior to surgery. In women with uncomplicated SUI, studies show UDS added no value over simple office evaluation,[103] and there is no advantage to UDS-based treatment of abnormalities other than stress incontinence.[104] There are a number of retrospective cohort studies that have shown that the presence of UDS abnormalities of storage (e.g., detrusor overactivity, impaired compliance, small cystometric capacity) do not affect outcomes of AUS or sling surgery in men with SUI.[105-108] Similarly, detrusor overactivity found on UDS has not been shown to negatively impact sling outcomes in men with SUI after prostate treatment.[109] In addition, abdominal leak-point pressure has not been shown to affect outcomes of AUS.[106] Furthermore, abdominal leak-point pressure does not correlate well with the degree of urinary incontinence, as determined by the 24-hour pad test.[110]

Pre-operative UDS may have a role in patient counseling (e.g., which patients may need further treatment of OAB symptoms post implant); however, patient selection for this reason is not well characterized. Finally, if the clinician is unsure of how prevalent sphincteric versus bladder affecting incontinence, or if there is unexplained poor bladder emptying, then UDS may be helpful in providing that additional information.

It is also important that the catheter be removed and stress testing repeated in men with suspected SUI who do not demonstrate stress incontinence with a catheter in place. It has been shown that up to 35% of men with post-prostatectomy SUI will not demonstrate SUI with a catheter in place.[111] This may be due to some scarring at the site of the anastomosis. In such cases, even a small catheter can occlude the urethra and prevent stress leakage. Also, if obstruction is suspected based on UDS criteria, a uroflow should be repeated without the catheter in place due to the possible obstructive effects of the catheter.

The most concerning and potentially most dangerous UDS finding is poor bladder compliance. This finding, however, is rare in IPT, even in patients who have had RT.[112] UDS likely has the highest yield for poor compliance in patients with severe radiation cystitis or those who have advanced neurogenic lower urinary tract dysfunction. Patients with significantly elevated storage pressures can be treated primarily (if no stress incontinence) with anticholinergics or onabotulinumtoxin A to lower such pressures. UDS then can be repeated to document adequate reservoir function. For patients with poor compliance and SUI, the observation that untreated poor bladder compliance did not worsen the AUS continence outcomes must be viewed with caution. It is well known that increasing outlet resistance could potentially expose the upper tracts to even higher intravesical pressures as compliance worsens.[113] Such patients can be treated with anticholinergics or onabotulinumtoxin A and storage pressure can be rechecked prior to treating SUI.

Alternatively, periodic upper tract imaging and/or UDS can be done post- SUI surgery (sling or AUS) to follow "at risk" patients. While the risk damage to the upper tracts in pediatric patients with myelomeningocele is well documented,[114] it is not known if poor bladder compliance and an uncorrected storage pressure are absolute contraindications to SUI surgery in IPT patients. However, the Panel believes that when such patients are identified, they should be carefully followed to avoid upper tract decompensation.

TREATMENT OPTIONS

16. In patients seeking treatment for incontinence after radical prostatectomy, pelvic floor muscle exercises or pelvic floor muscle training should be offered. (Moderate Recommendation; Evidence Level: Grade B)

IPT is caused by damage to the voluntary urethral sphincter. Both injury to striated muscle and nerve fibers of the rhabdo-sphincter can lead to IPT. PFMT is thought to support muscle strength and enhance blood flow to the sphincter to promote healing.[64] PFMT is a safe treatment with minimal side-effects that is readily accepted by patients and provides them with an opportunity to participate in, and have some control over, their health outcomes. Relative downsides to PFMT include time and effort needed by the patient and health care team, and cost of repeated visits, depending on the intensity of the program.[115, 116]

There are numerous RCTs that suggest benefit of undertaking PFMT[47, 49, 61, 115, 117-119] while other studies did not show benefits.[115, 116] Trials differ on the regimen of PFMT employed, with some including biofeedback or electrical stimulation, the amount of caregiver contact,[62, 64] and whether or not the therapy was before or after surgery.[47, 120-122] Further, trials lack a common urinary incontinence definition, making comparison more challenging.

Although PFMT and PFME may both be beneficial in restoring pelvic floor muscle function to assist with continence recovery, there is some evidence that PFMT may be preferred over self-directed PFME potentially due to the practitioner guided support and follow-up instruction offered with PFMT.[62, 64, 118]

17. Artificial urinary sphincter should be considered for patients with bothersome stress urinary incontinence after prostate treatment. (Strong Recommendation; Evidence Level: Grade B)

Multiple studies have demonstrated that AUS produces long-term continence and high patient satisfaction in men with any level of bothersome SUI.[30, 123-132] AUS should be discussed as a treatment option when surgical treatments are being considered.[130] Patients should be informed regarding inherent risks of AUS placement including persistent leakage, mechanical failure, erosion, and infection.[126, 127, 130]

In one study of AUS outcomes with two-year follow-up, complete continence was achieved in 20%, 55% had leakage of a few drops daily, and 22% had leakage of less than a teaspoon.[126] The patients were highly satisfied, with 92% reporting they would do the surgery again, and 96% willing to recommend the surgery to a friend.[126] In another study with follow-up of 2-11 years, a significant pad reduction was seen after AUS placement (4.0 to 0.6 pads per day).[127]

18. Prior to implantation of artificial urinary sphincter, clinicians should ensure that patients have adequate physical and cognitive abilities to operate the device. (Clinical Principle)

While AUS is the most predictable and reliable treatment for SUI after prostate treatment, it is important to remember that it is a mechanical device and that current versions of AUS require manual dexterity and cognitive ability in order for the patient to use it properly. Patients must demonstrate the cognitive ability to know when, where, and how to use the device. Furthermore, there should be some assurance that patients can physically pump a device that is in a normal position in the scrotum. There are no uniform ways to demonstrate such dexterity, but a simple demonstration of strength in the fingers and the ability to squeeze the pump between the index finger and thumb should be minimal requirements.

19. In the patient who selects artificial urinary sphincter, a single cuff perineal approach is preferred. (Moderate Recommendation; Evidence Level: Grade C)

The traditional placement of AUS has been a single cuff via perineal incision.[133] The introduction of new techniques such as the transverse scrotal incision and tandem cuff placement have been evaluated to be inferior

in non-randomized studies and should not be the standard of care for the customary AUS patient.[92, 134-137]

While AUS placement is feasible via a transverse scrotal incision,[92] comparative studies indicate inferior outcomes. A review of complication rates between perineal and scrotal incisions revealed an increase complication rate requiring short-term explantation in 9% versus 19% when comparing the perineal versus transverse scrotal incisions, respectively.[134] In a multi-center cohort study, the transverse scrotal approach demonstrated decreased completely dry rates, increased need for revision surgery due to continued incontinence, and a decrease in number of socially continent patients ($\leq$1 pad/day).[135] Taken together, these studies indicate that the transverse scrotal approach has a decrease in efficacy, likely due to a more distal cuff placement, along with an increase in complications and need for revision surgery.

In regard to placement of a tandem cuff compared to a single cuff placement, a review of the data indicates equivalent continence outcomes but with an increased risk of complications in the tandem cuff group.[136, 137] In a cohort of 124 tandem cuff and 57 single cuff patients, outcomes indicated equal pad weight and total number of daily pads between the two groups, but the tandem cuff group had a 17% risk of explant at 48 months compared to 4% for the single cuff group.[136] In another cohort, overall dry rate and daily pad use between the two groups was similar, but the tandem cuff group had 12 additional surgeries related to complications versus seven in the single cuff group.[137]

These comparative studies continue to support the traditional surgical approach of a single cuff via perineal approach as the standard technique that should be used. Furthermore, it is important to note that meticulous sterile technique needs to employed during this approach, preoperative antibiotics should be always given to cover skin flora as per the AUA Antimicrobial Prophylaxis Best Practice Statement,[138] and surgeons must be able to select the appropriate cuff based on intraoperative measurements, fill the components of the AUS with fluid, connect the tubing to make a watertight system, and test the AUS. If an intraoperative urethral injury is identified during implantation of an AUS, the procedure should be abandoned and subsequent implantation should be delayed.

20. Male slings should be considered as treatment options for mild to moderate stress urinary incontinence after prostate treatment. (Moderate Recommendation; Evidence Level: Grade B)

The literature is replete with both prospective and retrospective cohort studies of male sling placement for IPT. However, insufficient follow-up, different definitions of incontinence prior to treatment, variable definitions of "cure" and "improvement" following treatment, and use of a plethora of validated and non-validated outcome measures limits the ability to accurately compare the various male sling options currently available to patients.

Nine prospective[102, 139-147] and five retrospective cohort studies[148-152] met criteria for inclusion in analysis for this guideline in determining the cure rate for male sling surgery IPT. The 14 studies included 758 patients, 470 of whom were considered cured by the respective investigator. Definition of "cure" varied from zero pads or one pad daily used for protection to a negative one-hour pad weight test. Overall, 62% of patient achieved cure (range 34-91%); 95% CI=0.51-0.72.

Ten studies, eight of which were prospective,[139, 140, 142, 144-147, 153, 154] and two of which were retrospective,[148,151] met criteria for assessment of "improvement" after sling implantation. In general, improvement was defined as at least a 50% improvement in pad weight or pad use and does not include patients who were less incontinent but did not meet the 50% threshold. In the overall group, 518 patients were included, 176 of whom were improved. Overall, 34% of patients achieved at least 50% improvement in leakage, with a range of 4-100%; 95% CI=0.18-0.51. Two trials[153,154] did not separate cured and

improved patients, categorizing all such patients as "improved." When these two studies were omitted, the improvement rate was 28%.

The cohort studies did not include patients with radiation, and some excluded those with severe incontinence, generally considered >500 g urine per day leakage, or >5 pads per day. For those studies that included patients with severe leakage, sling failure was generally highest in that sub-group. Complications are not consistently reported, but in general, complication rates are low, with urinary retention typically resolving within one week, and pelvic and perineal pain and paresthesia resolving within 12 weeks. Erosion of the male sling is exceedingly rare.[155] If this happens, however, removal of the sling is necessary. Prior male sling does not typically interfere with subsequent sling revision or placement of an artificial sphincter in the setting of an unsatisfactory continence outcome.[156]

21. Male slings should not be routinely performed in patients with severe stress incontinence. (Moderate Recommendation; Evidence Level: Grade C)

Men suffering with severe SUI electing treatment should not have a male sling and should consider an AUS. Male slings have been shown to have poor efficacy in comparison to an AUS in this subset of patients.[157, 158] Clinicians might consider a sling in patients who have not undergone radiation, who have minimal incontinence at night, or who would be unable to use the AUS given poor hand function or cognitive abilities. If a sling procedure is done, it would be imperative to counsel the patient regarding appropriate expectations.

22. Adjustable balloon devices may be offered to patients with mild stress urinary incontinence after prostate treatment. (Moderate Recommendation; Evidence Level: Grade B)

In 2017, adjustable balloon devices became available in the United States for treatment of male intrinsic sphincter deficiency after prostatectomy or TURP. At the time of this publication, clinical experience in the United States with this device remains limited.

Patients with mild incontinence and no history of prior RT tend to have better outcomes.[159] Pre-market studies have shown a 60-81% "cure" rate defined as 0-1 pads/day after implantation of the adjustable balloon.[106, 159-163] The success of the device should be weighed against the complication rate. Intraoperative complications and need for explant tend to be higher than other anti-incontinence procedures. Explantation of the device due to complications or failure of treatment was common across all series and ranged from 4-30% during the first two years.[106, 159-162, 164]

In a group of men with severe incontinence (5 pads per day; n=50), implantation of the adjustable balloon led to a significant improvement 12 months after surgery (1.8 pads per day, $p<0.0001$).[162] In a larger series from the same group, 80/101 (79.2%) patients were considered as dry, with a pad test of 0-1g (70 patients, 0g; 10 patients, 1g) at 2.2 years follow-up. Significant improvements in QoL were also reported.[150]

While the adjustable balloon devices have been shown to improve incontinence, providers should be aware of an increased incidence of intraoperative complications and need for explanation within the first two years compared to the male sling and AUS. Given the limited clinical experience of implanters across the United States, providers should obtain specialty training prior to device implantation.

23. Surgical management of stress urinary incontinence after treatment of benign prostatic hyperplasia is the same as that for patients after radical prostatectomy. (Moderate Recommendation; Evidence Level: Grade C)

BPH is one of the main causes of lower urinary tract symptoms in men. Around 30% of men over age 65 are diagnosed with BPH.[165] Transurethral removal of prostate tissue (e.g., TURP, laser TURP, holmium laser enucleation of the prostate) or open simple prostatectomies are offered to

men in whom behavioral and drug therapy fail to relieve symptoms. The rate of persistent SUI in patients undergoing open laparoscopic or endoscopic surgical management of BPH ranges between 0-8.4%.[165, 166] Evaluation of patients with SUI after surgical therapy for BPH should be similar to those who have undergone RP; however care must be taken to rule out a primary bladder pathology such as OAB. Management of SUI after surgical management of BPH should follow the algorithm as that of a patient who underwent RP for prostate cancer. Patients who fail conservative measures should be offered surgical management. However, it should be noted that literature on surgical outcomes in this patient population is limited. Most studies evaluating results of AUS or male sling either combine BPH patients with RP patients or exclude them. There are a few studies that have demonstrated that AUS or male sling are safe and efficacious. A Cochrane review only identified one RCT evaluating surgical management of SUI after BPH surgery.[165] This study compared the efficacy of AUS implantation versus injectable therapy. Men undergoing AUS placement were more likely to be dry with an odds ratio of 5.67. Another study in which 56 patients were undergoing AUS placement after TURP found that continence was significantly improved in 90% of patients with a satisfaction rate of 87%,[167] and 14 patients required surgical revisions of their AUS. A study looking at 18 men undergoing transobturator male sling after TURP[168] found that 47% of men were cured and 60% were cured or improved using a cure definition of 0-5 g in the 24-hour pad test. In another study evaluating the use of the quadripolar male sling, four of eight patients were continent and two were improved at one year follow-up.[169]

24. In men with stress urinary incontinence after primary, adjuvant, or salvage radiotherapy who are seeking surgical management, artificial urinary sphincter is preferred over male slings or adjustable balloons. (Moderate Recommendation; Evidence Level: Grade C)

Over the last decade there has been an increase in the use of multimodal therapy for prostate cancer including adjuvant RT.[170] Radiation causes small vessel obliteration and endarteritis, resulting in ischemic tissue changes such as fibrosis and necrosis that can ultimately affect continence and outcomes following AUS or sling placement.[171, 172] Patients with IPT following adjuvant or salvage RT should be offered the same conservative management as a patient with post-prostatectomy SUI. Patients who fail conservative measures should be offered surgical management, preferably placement of AUS. Radiated patients undergoing AUS placement should be counseled on potentially compromised functional outcomes and an increased risk of complications. Overall 66% of radiated patients will demonstrate significant improvement in their continence after AUS placement. However, when compared to the non-radiated patients, continence in the radiated patient after AUS placement may be compromised. Previous studies evaluating AUS placement in radiated versus non-radiated patients have shown mixed results, with some demonstrating equivalent and some worse outcomes in the radiated group. [105, 124 173, 174] However, a more contemporary cohort study comparing continence outcomes in radiated versus non-radiated patients showed that 89% of non-radiated patients were continent compared to 56% in the radiated group.[128]

Radiated patients may also be at increased risk of complications after AUS placement. Recent meta-analysis demonstrated AUS revision was higher in radiated compared to non-radiated patients with a random effects risk ratio of 1.56 and a risk difference of 16%.[175] The majority of the revisions in the radiated group were secondary to erosion, whereas in the non-radiated group was secondary to urethral atrophy. A recent study evaluated whether temporal improvements in RT technique had an impact on AUS outcomes.[176] Patients undergoing RT prior after 2007 had equivalent outcomes to those undergoing RT prior to 2006. As a result, the Panel recommends that patients with RT for prostate cancer, whether as monotherapy or in combination with surgery be counseled in an equivalent manner regarding the

outcomes, risks, and complications associated with anti-incontinence surgery.

Male slings are not recommended for patients who have undergone adjuvant or salvage RT due to a lack of compelling evidence regarding their effectiveness in this subgroup. The literature suggests that slings are not as successful in patients who have undergone adjuvant or salvage RT compared to those patients who have not. Also, when reviewing the literature, it appears that there is a decline in efficacy over time, which will likely continue to worsen.[74, 75]

Publications looking at RT patients have relatively low numbers and do not look at the efficacy in mild, moderate, or severely incontinent patients. Therefore, it is difficult to determine if male slings work in any level of severity of incontinence. There may be improved efficacy in patients with milder SUI; however there is minimal data in this group. As such, it is still generally recommended that male slings should not be considered even in this group of patients.

25. Patients with incontinence after prostate treatment should be counseled that efficacy is low and cure is rare with urethral bulking agents. (Strong Recommendation; Evidence Level: Grade B)

There are currently no FDA-approved available agents for the treatment of male incontinence, and while the use of bulking agents to treat SUI is considered off-label, they remain the most commonly used procedure.[177] This is likely because urethral bulking agents are the least invasive technique available; however they are also the least effective surgical technique in the treatment of male SUI. The utilization of materials to improve urethral coaptation evolved from initial application in females for intrinsic sphincter deficiency.[178]

Injectable therapy is a consideration in patients who are unable to tolerate or refuse more invasive surgical therapy. In male patients, the best success rates have been described in patients with a high Valsalva leak point pressure, unscarred vesicourethral anastomosis, and no RT history.[15, 179, 180] Data on the efficacy of injectable agents, including collagen, carbon coated zirconium beads, and silicone implants, in male patients are generally limited by the number of reports, patient cohort size, and length of follow-up.

In the largest published study of the utilization of collagen for male SUI, improvement was reported in approximately 50% of patients with a mean duration of 6 months whereas complete continence was achieved in 17% with a mean duration of 9 months. Of note, 1.5% of patients reported an increase in incontinence following collagen injections.[181]

Success with the injection of carbon coated beads in male patients is characterized by transient partial improvement and risk of retention. Efficacy of carbon beads has been studied in the treatment of mild to moderate IPT. In a study of eight patients who had SUI after RP, only three patients reported subjective transient improvement and five patients opted for a more invasive surgical option after injection of pyrolytic carbon microspheres.[182] One patient reported worsening of his incontinence and another had acute urinary retention requiring an indwelling catheter for four days.

Injectable polydimethylsiloxane is a large molecule with a mean diameter of 140 μm that becomes encapsulated in fibrin and collagen, thereby minimizing the risk of migration. However, due to its size and associated viscosity, special equipment is required for particle delivery.[15] Reported efficacy in post prostatectomy patients ranges widely from 10 – 80%. The associated complications rates are variable: urinary retention (6-18%), urinary frequency (0-72%), dysuria (0-100%), and rarely urinary tract infection (0-6%).[183, 184]

26. Other potential treatments for incontinence after prostate treatment should be considered investigational, and patients should be counseled accordingly. (Expert Opinion)

Outside of PFMT, AUS and perineal sling, no other

IPT interventions have vigorous data to support sustained efficacy. There have been some promising results reported in small case series for interventions such as extracorporeal magnetic intervention[185] and penile vibratory stimulation.[186] More data in larger cohorts are needed to better understand these treatment's durability in treating IPT; as such patients should be counseled accordingly regarding the lack of outcome data. Stem and regenerative cell injections also offer a potential new form of intervention for treating IPT. However, there are data currently supporting this intervention and patients should be counseled that this is considered investigational. Patients wishing to pursue this modality should be referred to clinical research trials where safety and outcomes are monitored.

COMPLICATIONS AFTER SURGERY

27. Patients should be counseled that the artificial urinary sphincter will likely lose effectiveness over time, and reoperations are common. (Strong Recommendation; Evidence Level: Grade B)

AUS is an implant used for the treatment of stress -predominant IPT. The current version consists of a hydraulic system composed of three separate parts: a urethral cuff of varying sizes, a pressure regulating balloon reservoir with three available pressure profiles, and a control pump. The device will fail if any of the three parts, the tubing, or connections suffer a micro-perforation with loss of fluid. The rate of device failure increases with time, with failure rates of approximately 24% at 5 years[187] and 50% at 10 years.[132]

A malfunctioning AUS does not necessarily need to be replaced, but if the patient is healthy and requests a replacement, the AUS can be explanted and a new one replaced at the same operative setting. The durability and efficacy of a secondary re-implant in this setting is the same as that of a primary AUS.[187]

Device infection and cuff erosion are also causes of reoperation and should be discussed in detail with the patient prior to implantation of the AUS. Device infection is quite uncommon, with rates in long-term series ranging from less than 1% up to 5%.[132, 188] It is a dramatic presentation with pain at the site of the AUS; fever; scrotal warmth or erythema; or skin changes and necessitates an urgent explantation of the device. An AUS should not be replaced in the setting of infection for at least three months to allow the infection to clear and inflammation to subside. Cuff erosion can be due to unrecognized urethral injury at the time of initial surgery or more likely due to subsequent instrumentation of the urethra including catheterization. Rate of erosion is difficult to obtain due to varying patient populations and techniques but typically range from 1% to 10% on long-term follow-up.[132, 188] A cuff erosion can present insidiously but generally presents with hematuria, dysuria, or difficulty emptying the bladder and is diagnosed with a cystoscopic demonstration of the AUS cuff within the urethra.[189, 190] Management of cuff erosion is via AUS explant with the urethral catheter left in place for a few weeks to allow the urethral defect to heal. Similar to an infection, the AUS should not be reimplanted until at least three months and preferably at a different location along the urethra. In this setting, a transcorporal approach may be used.

Finally, an AUS might need to be replaced over time due to persistent or recurrent incontinence generally due to urethral atrophy, improper cuff sizing, or partial fluid loss. As previously stated, secondary AUS placements generally have similar outcomes to primary AUS placements;[187, 188, 191] however, patient satisfaction is driven by the degree of continence after AUS and not by the number of reoperations.[130, 192]

28. In patients with persistent or recurrent urinary incontinence after artificial urinary sphincter or sling, clinicians should again perform history, physical examination, and/ or other investigations to determine the cause of incontinence. (Clinical Principle)

In the patient with persistent urinary incontinence after AUS placement, a history and physical examination is necessary. In the case of the patient inadvertently deactivating the device or

inadequately cycling the device, re-education must be performed to ensure that the device is being utilized properly. In the event that an acute fluid loss is suspected, the volume in the pressure regulating balloon can be assessed using computerized tomography or ultrasound.[193] Cuff coaptation may be evaluated by cycling the device during cystoscopic visualization. Although rare, poor coaptation in the absence of fluid loss in the early post-operative phase is related to improper cuff sizing or incomplete engagement of the cuff tab. Either situation can only be addressed by operative revision.

Recurrent incontinence after years of normal function suggests either development of a new leak due to wear or urethral atrophy (with or without erosion). A leak can be confirmed by decreased volume in the pressure regulating balloon, which can be assessed by using ultrasound or computerized tomography.[193] The mainstay for evaluation of atrophy and erosion is cystoscopy.

In a patient with a normally functioning AUS, as determined by physical examination and imaging, leakage due to elevated storage pressures or detrusor over-activity should be suspected. UDS may be performed to evaluate filling pressures, capacity, presence of uninhibited detrusor contractions, and effective voiding. As a technical point, the cuff needs to be temporarily deflated and deactivated to allow for safe and atraumatic urodynamic sensor placement. If there are concerns regarding cuff damage, cystoscopy must be performed immediately to evaluate. In all cases of detrusor dysfunction, the underlying abnormalities must be addressed rather than performing any adjustments to the AUS with the exception of deflating and deactivating in the patient experiencing retention.

29. In patients with persistent or recurrent stress urinary incontinence after sling, an artificial urinary sphincter is recommended. (Moderate Recommendation; Evidence Level: Grade C)

Failure of a male sling can be due to infection or erosion, or more likely, due to patient dissatisfaction with continence recovery. Rates of infection or erosion after male slings are thought to be very low with almost no long-term series of outcomes reporting these events. However, if a male sling is thought to be infected or documented to be eroded on cystoscopy, the management is similar to management of an infected or eroded AUS. Specifically, in this setting as much of the sling should be explanted as soon as possible with a catheter left in place in the setting of an erosion.

In patients who are not satisfied with the results of a sling due to inadequate continence recovery, a subsequent AUS is the most efficacious option. While a secondary sling can be performed with cure rate of about 45% and satisfaction rates of approximately 70% in highly experienced centers,[147, 194, 195] most authors recommend an AUS in this setting. A retrospective cohort study of 61 men looked at continence outcomes between salvage AUS and secondary transobrurator slings.[195] Twenty-nine men underwent a repeat sling and 32 underwent an AUS following sling. Repeat sling patients had a failure rate of 55% compared to 6% after AUS. Multiple authors have shown that AUS after sling[196, 197] have similar outcomes to primary AUS, and the Panel recommends and AUS following sling failure.

30. In patients with persistent or recurrent stress urinary incontinence after artificial urinary sphincter, revision should be considered. (Strong Recommendation; Evidence Level: Grade B)

Patients with persistent or recurrent incontinence or those dissatisfied with their continence recovery after AUS placement should undergo evaluation. Inadequate recovery of continence after AUS placement can be due to a host of factors, including suboptimal cuff sizing at the time of original operation or inadequate pressure regulating balloon gradient.

The original operative report should be evaluated to note surgical approach, size of urethral cuff, and location of pressure regulating balloon. In patients with a possible distally located cuff, or

those with a larger cuff, proximal relocation or downsizing of the cuff are both reasonable options and will likely lead to better continence.

Tandem cuff placement is the addition of a cuff to the original cuff and has also been shown to be effective as a salvage procedure for patients with persistent incontinence. Specific additional risks of tandem cuff placement should be discussed with the patient prior to proceeding. Such risks include injury to the urethra during dissection, which would lead to aborting the case and the higher risk of subsequent erosion.

Some authorities have advocated moving the pressure regulating balloon to a different location or replacing it with a higher-pressure balloon.[198, 199] Others have used a transcorporal approach to improve urethral coaptation in patients with small urethral caliber, especially in the setting of prior RT and/or erosion;[200] however there is limited evidence to support either of these approaches.

Any of the above maneuvers can be combined with replacement of an AUS at the time of device failure. It is important to note that, in general efficacy and durability after secondary AUS placement appear to be similar to those after primary AUS placement, except in the setting of erosion.[187, 188, 191]

SPECIAL SITUATIONS

31. In a patient presenting with infection or erosion of an artificial urinary sphincter or sling, explantation should be performed and reimplantation should be delayed. (Clinical Principle)

Similar to other synthetic devices, explantation is indicated in cases of AUS or male sling device infection. Timing of removal is usually influenced by severity of the infection and acuity of the clinical situation as indicated by the associated signs and symptoms (e.g., purulent drainage, erythema, tenderness, fever, chills). In general, explantation should be performed as soon as possible. In the case of the AUS, the most conservative course of action is removal of all components, regardless of whether the infection and any associated reaction are limited to a single component. Even in the absence of purulent fluid and erythema, a wash-out procedure combined with immediate device replacement has not been consistently proven to be reliable or effective.[201] As discussed previously, an infected male sling should be removed as completely as feasible without damaging any adjacent structures.

Often times an infection is secondary to a pre-existing erosion. For AUS isolated cuff infections are rare without an associated erosion. Like infection, erosion requires device explantation. The urethral defect will usually heal by leaving a urethral catheter in place for three weeks. Some authors, however, recommend a urethral repair in cases of larger urethral defects due to decreased rates of stricture.[202]

For patients seeking a replacement device (AUS or male sling) after infection and/or erosion, a waiting period of three to six months is recommended. In the AUS patient, it may be necessary to proceed with transcorporal placement of the cuff.[203, 204] This approach would be recommended in the radiated patient with the prior erosion with thinned spongiosal tissue who has insufficient tissue to obtain a satisfactory fitting cuff. Xenograft tissue buttressed to supplement the urethra (theoretically decreasing risk of erosion) has been associated with significant complications and thus has not been advantageous.[205, 206]

32. A urinary diversion can be considered in patients who are unable to obtain long-term quality of life after incontinence after prostate treatment and who are appropriately motivated and counseled. (Expert Opinion)

In patients who are unable to obtain a satisfactory QoL long-term with an AUS due to multiple device failures, intractable BNC, or severe detrusor instability, urinary diversion with or without cystectomy may be an option. If bladder preservation is feasible, conversion to a Mitrofanoff (e.g. Appendix, Monti), incontinent ileovesicostomy, or suprapubic tube with bladder neck closure may confer an improved QoL. In the event of the "hostile" bladder, cystectomy in

combination with either an ileal conduit or continent catheterizable pouch would best manage incontinence while protecting the upper tracts.

33. In a patient with bothersome climacturia, treatment may be offered. (Conditional Recommendation; Evidence Level: Grade C)

As with post-prostatectomy SUI, for those with sexual arousal incontinence or climacturia, conservative management should be the initial treatment. The complaint may resolve in two-thirds of patients over time.[40] For those with persistent leakage, behavioral management includes emptying the bladder prior to sex, use of condoms to catch the urine, and PFME, which has demonstrated improvement in one small randomized trial.[46]

Anecdotal success has been reported with the tricyclic antidepressant imipramine, but this medication is generally contraindicated in men over the age of 65 years due to the risk of somnolence, falling down, and changes in cognition.[207]

The use of a penile variable tension loop (a soft silicone tube placed around the penis and adjusted to provide pressure on the urethra to physically prevent leaking during sex) has been used with success, decreasing the degree of orgasm-associated leakage in those with mild, moderate, and even severe self-reported leakage. Decreasing distress has been reported in both patients and partners, from 14% to 2% and 61% to 11%, respectively.[208]

Surgical treatment has been reported as very successful, but all trials included patients who were operated on for other indications. For example, implantation of an inflatable penile prosthesis for erectile dysfunction (ED) with a small polypropylene mesh anchored to the medial aspects of the bilateral corporotomies was successful in most of patients, with 93% noting improvement in climacturia postoperatively.[209] The mechanism of action is one where the mesh compresses the bulbar urethra as the inflatable penile prosthesis cylinders expand with inflation. Similarly, both the AUS and the transobturator male sling, when implanted for daytime SUI, are associated with high rates of improvement in climacturia, similar to the rates of improvement in SUI.[153, 210]

34. Patients with stress urinary incontinence following urethral reconstructive surgery may be offered artificial urinary sphincter and should be counseled that complications rates are higher. (Conditional Recommendation; Evidence Level: Grade C)

Urethral strictures of the anterior urethra and urethral stenosis of the posterior urethra can arise after RP, RT, or treatment for IPT.[211] Anterior urethral strictures may be synchronous with prostate-related conditions and persist after treatment, occur *de novo* after therapy for prostate-related conditions or arise after an AUS erosion. Posterior urethral stenosis typically arises after treatment for prostate-related conditions. Urethral reconstructive surgery is often used to treat narrowing in the urethra. Often IPT exists prior to urethroplasty or is caused by urethral reconstruction in rare cases. AUS is the preferred surgical treatment for IPT after urethral reconstruction. Depending on the technique employed (urethra transecting or not) the blood supply to the urethra may be diminished and potentially decrease the life span of an AUS.

Transcorporal placement of the AUS might be beneficial in some cases due to concerns about alterations in urethral blood supply. AUS can be successfully replaced after erosion-related urethral strictures and subsequent reconstruction.[212] Given post-surgical changes related to most types of urethral reconstruction in the posterior and anterior urethra, male slings will not be effective.

35. In patients with incontinence after prostate treatment and erectile dysfunction, a concomitant or staged procedure may be offered. (Conditional Recommendation; Evidence Level: Grade C)

In patients with both IPT and post-prostatectomy

ED, concomitant surgery to treat both conditions should be considered. Though initial investigations showed concern for infection during concomitant surgery, various studies have demonstrated that concomitant surgery is safe and may actually provide significant benefits.[213, 214] In a report of 55 patients undergoing combined penile prosthesis and AUS surgical procedures, combined procedures had a significantly longer operative time;[215] however, the rate of device infection, erosion or malfunction was not increased in combined compared to staged procedures. Another study described similar continence, sexual function, and overall satisfaction in patients undergoing staged versus combined procedures.[216] Despite these positive results of concomitant surgery most recent study using the SPARCS (New York State Department of Health Statewide Planning and Research Cooperative) database found that men undergoing combination of penile prosthesis and AUS placement had a higher rate of reoperation compared to men undergoing penile prosthesis alone.[217] Even though combination surgery is feasible, men considering surgical management of both ED and SUI should be counseled of the possible increase risk of complications.

36. Patients with symptomatic vesicourethral anastomotic stenosis or bladder neck contracture should be treated prior to surgery for incontinence after prostate treatment. (Clinical Principle)

Patients who are diagnosed with a symptomatic vesicourethral anastomotic stenosis (VUAS) or BNC should have treatment of their obstruction prior to surgical correction of their incontinence. Following treatment of VUAS, an interval cystoscopy should be performed at least four to six weeks later to document improvement and stabilization, after which IPT treatment can be considered. Although a VUAS or BNC will not necessarily cause SUI, treatment of them may worsen SUI. This is important because a patient may be considered for a sling procedure if he had "mild" incontinence, but he would likely need an AUS if it worsens after treatment. It is also generally felt that patients with a VUAS or BNC have decreased success rates when undergoing male slings; therefore an AUS would generally be considered a better option in this group.[157]

Treatment of a VUAS or BNC after a sling or AUS could be difficult or might place the patient at a higher risk of complications such as worsening of urinary incontinence, erosion of the AUS cuff, or possible infection. Endoscopic treatment of VUAS/ BNC after AUS has been described using a semi-rigid ureteroscope and holmium laser although this is still not the optimal approach.[218]

FUTURE DIRECTIONS

In the future significant changes are expected in the management of IPT, including enhancements in diagnostics and treatment options that will continue to improve patient continence and decrease the incidence of IPT. Since most papers are single center experiences, the Panel expects and hopes to have increased multicenter research collaboration. Patient reported outcome measures, which are very important in the treatment of QoL surgery have also become more prevalent; as such the Panel expects these to also improve in use and quality, allowing clinicians to fully address patient concerns.

Newer treatments will encompass not only improvements in surgical products such as the AUS and male slings, but also will include continued research into muscle injections, stem cells, and newer treatments for urgency and urge incontinence.

Developments regarding surgical products will likely include improvements to the current AUS, possibly improving the patient's ability to use the pump. It may also include a more automated system controlled from an external device. With newer technologies the Panel hopes to see automatic adjustments in cuff pressures or fluid volumes that would allow increased pressures improving continence with any increase in abdominal pressure.

Male slings have continued to evolve from bone anchored slings to the current products on the

market. As clinicians learn more about etiology, continued development and improvements will increase efficacy of newer products.

Some advances in the treatment of male SUI are expected to parallel those for female SUI. Regenerative medicine will continue to shape future treatments attempting to restore normal function with either autologous muscle-derived cells or multipotent mesenchymal stem cells injected into the sphincter. These cell-based therapies will continue to improve and provide clinicians with increased success rates. Ethical and legal issues associated with these regenerative treatments still need to be clarified.

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ABBREVIATIONS

AUA	American Urological Association
AUAER	American Urological Association Education and Research, Inc.
AUS	Artificial urinary sphincter
BMI	Body mass index
BNC	Bladder neck contracture
BOD	Board of directors
BPH	Benign prostatic hyperplasia
ED	Erectile dysfunction
FDA	Food and Drug Administration
IPT	Incontinence after prostate treatment
MRI	]Magnetic resonance imaging
OAB	Overactive bladder
PFME	Pelvic floor muscle exercise
PFMT	Pelvic floor muscle training
PGC	Practice guidelines committee
PVR	Post-void residual
QoL	Quality of life
RCT	Randomized controlled trial
RP	Radical prostatectomy
RT	Radiation treatment
SQC	Science and Quality Council
SUFU	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction
SUI	Stress urinary incontinence
TURP	Transurethral resection of the prostate
UDS	Urodynamic testing
VUAS	Vesicourethral anastomotic stenosis

INCONTINENCE AFTER PROSTATE TREATMENT PANEL, CONSULTANTS, AND STAFF

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CONFLICT OF INTEREST DISCLOSURES

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DISCLAIMER

This document was written by the Incontinence After Prostate Treatment Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2017. The PGC of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology with specific expertise on this disorder. The mission of the Panel was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the treatment of stress urinary incontinence.

Funding of the Panel was provided by the AUA and SUFU. Panel members received no remuneration for their work. Each member of the Panel provides an ongoing conflict of interest disclosure to the AUA.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

2022 CPT Code Review

Laser Interstitial Thermal Therapy (LITT)

Codes**:**
61736: Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; single trajectory for 1 simple lesion
61737: Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; multiple trajectories for multiple or complex lesion(s)

Description: Laser interstitial thermal therapy (LITT) is a minimally invasive treatment using a focused beam of electromagnetic radiation emitted from a laser that is stereotactically placed into a targeted location. The laser then induces hyperthermia to ablate the target minimizing injury to the surrounding tissues while magnetic resonance imaging (MRI) thermography is used to monitor tissue temperatures. The use of laser interstitial thermal therapy (LITT) is currently being researched to include but not limited to the following indications, brain tumors and breast tumors, prostate cancer, osteoid osteoma (bone tumor), lung cancer, liver cancer, radiation necrosis and epilepsy. The best studied use of LITT is in treatment of epilepsy and brain tumors.

Evidence

1) **CADTH 2019:** evidence review on laser interstitial therapy for epilepsy and/or brain tumors https://cadth.ca/sites/default/files/pdf/htis/2019/RC1140%20LITT%20Final.pdf
    a. N=5 publications
        i. 2 systematic reviews
            1. N=404 with intractable temporal lobe epilepsy
                a. 239 LITT vs 165 stereotactic radiosurgery
                b. Authors of one systematic review reported that across 18 retrospective chart reviews, case studies and case reports and one RCT that followed patients for 12 to 36 months, there was no statistically significant difference in the mean incidence of seizure freedom in patients with drug-resistant, medically-intractable TLE treated with MR-guided LITT compared with those treated with SRS
                    i. Mean incidence of seizure freedom: 50% (CI, 44% to 56%; range, 35% to 71%) vs. 42% (CI, 27% to 59%; range, 0% to 73%); *P* = 0.39; indicating that the difference between the groups was not statistically significant
                c. Complications: Mean incidence of complications: 20% (CI, 14% to 26%) vs. 32% (20% to 46%); *P* = 0.06; indicating no statistically significant difference between the groups with a trend in favor of LITT
                    i. LITT complications: gait abnormalities (n = 9), cranial nerve deficits (n = 8), cerebral hemorrhage (n = 4), headache and nausea (n = NR)
                    ii. SRS complications: cerebral edema (n = 11), psychotic and cognitive symptoms (n = 7), and nerve deficits (n = 2)

Laser Interstitial Thermal Therapy (LITT)

d. Conclusions*:* On the basis of current literature, we found that whereas seizure outcome rates … may be similar between the 2 procedures, [MR-guided] LITT may be associated with lower complication rates. However, more largescale comparative studies are required to validate our findings.

2. N=589 patients with high grade tumors in or near areas of eloquence
    a. 67 LITT vs 522 with open craniotomy
    b. Examined only adverse events
    c. Mean major neurocognitive complication rates (lasting >3 months): 5.7% (CI, 1.8% to 11.6%; I2 = 0%) vs. 13.9% (CI, 10.3% to 17.9%; I2 = 65%)
        i. Absolute risk difference: -0.10 (CI, -0.15 to -0.05; *P* < 0.0001); in favor of LITT
    d. Conclusions: LITT … may reduce major neurocognitive complications compared to open craniotomy in patients with high-grade gliomas.

ii. 2 prospective cohort studies
1. N=100 patients with brain tumors, epilepsy or unspecified indications
    a. Conclusion: Analysis of the first 100 patients from the registry suggests that SLA is a safe, minimally invasive procedure for the treatment of intracranial pathologies. The morbidity and hospitalization time profiles compare favorably to those previously reported for conventional craniotomies.
2. N=20 patients with recurrent tumors following stereotactic radiosurgery for brain metastases
    a. The overall survival rate was 71% at three months of follow-up among 13 patients and 64.5% at six and a half months of follow-up in an undisclosed number of patients
    b. Conclusions: In summary, this prospective study confirmed that LITT is a low-risk surgical procedure that can control radiographic lesion growth after SRS in patients with brain metastases and should be considered in those who are surgically eligible. Further studies with a control group for better characterization of possible benefits are warranted.

iii. 1 cost-effectiveness study
1. Conclusion: The use of brain LITT under magnetic resonance imaging guidance in complex craniotomies where high-grade gliomas reside in or near areas of eloquence (or where these types of tumors are deep seated) appears to be cost effective"

b. In summary, the outcomes of interest were seizure freedom, disease progression and overall survival, quality of life, hospitalization, and adverse events. Evidence of limited quality and quantity suggested that LITT proffers no advantage over stereotactic radiosurgery in inducing seizure freedom in patients with drug-resistant, medically intractable temporal lobe epilepsy. Relative to patients who were treated with stereotactic radiosurgery and craniotomy, patients treated with LITT appeared to experience fewer adverse events and complications. No comparative evidence on disease progression, overall survival, hospitalization, or quality of life was found. None

of the studies reported on the incidence of epileptic episodes, post-operative pain, use of medication, or hospital readmissions.

c. Considerable caution must be taken in interpreting the evidence presented in this report due to the paucity of comparative data and other limitations. While the systematic reviews on clinical effectiveness and safety had some noteworthy strengths, there were serious limitations related to the quality of the included primary studies, potential for patient selection, measurement, and reporting biases.

2) **Kim 2020,** LAANTERN study
   a. Prospective cohort registry study, N=223 patients
      i. Of the ablated tumors, 131 were primary and 92 were metastatic. Most patients with primary tumors had high-grade gliomas (80.9%). Nearly all metastatic lesions (92.4%) were previously treated, and the LITT procedure was indicated for tumor recurrence (50.6%), radiation necrosis (40%), or unknown (9.4%)
      ii. Median follow up 223 days
   b. The 1-yr estimated survival rate was 73%, and this was not impacted by disease etiology. Overall survival in the total cohort of patients was consistent with prior publications in similar patient populations.
   c. Patient-reported QoL as assessed by the Functional Assessment of Cancer Therapy-Brain was stabilized postprocedure. KPS declined by an average of 5.7 to 10.5 points postprocedure; however, 50.5% had stabilized/improved KPS at 6mo.
   d. **CONCLUSION:** Results from the ongoing LAANTERN registry demonstrate that LITT stabilizes and improves QoL from baseline levels in a malignant brain tumor patient population with high rates of comorbidities. Overall survival was better than anticipated for a real world registry and comparative to published literature.

Expert guidelines

1) **NCCN 2.2021**, Central Nervous System Cancers
   a. Principles of brain tumor surgery
      i. MRI-guided laser interstitial thermal therapy (LITT) (category 2B) may be considered for patients who are not surgical candidates (craniotomy or resection). Potential indications include relapsed brain metastases and radiation necrosis
   b. Included articles from CADTH
      i. Ahluwalia 2018 (cohort study of 20 patients with brain tumors)

Other payer policies

1) **Cigna 2021**
   a. Laser Interstitial Thermal Therapy (LITT) is considered experimental, investigational or unproven for all indications.
2) **Aetna 2021**
   a. Aetna considers magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) (e.g. the NeuroBlate and the Visualase Thermal Therapy System) medically necessary as an alternative to standard surgery where criteria in section I on epilepsy surgery are met.
3) **Wellmark BCBS 2020**:
   a. The treatment of medically refractory epilepsy using MRI-guided laser interstitial thermal therapy (MRIgLITT) is considered medically necessary when ALL of the following criteria are met:

Laser Interstitial Thermal Therapy (LITT)

i. Documented disabling seizures despite the use of two or more tolerated antiepileptic drug regiments; and
ii. Documented (i.e. imaging or EEG) presence of well-defined epileptogenic foci accessible by laser interstitial thermal therapy (LITT).

b. MRI-guided laser interstitial thermal therapy (MRIgLITT) when the above criteria is not met and for all other indications, including but not limited to the following is considered investigational because the evidence is insufficient to determine the effects of the technology on health outcomes:
   i. Epilepsy except as indicated above
   ii. Brain tumors (primary and metastatic)
   iii. Breast cancer (benign or malignant)
   iv. Liver cancer (primary and metastatic)
   v. Lung cancer (primary and metastatic)
   vi. Osteoid osteoma
   vii. Prostate cancer
   viii. Radiation necrosis

Expert input:
Dr. Ahmed Raslan, OHSU neurosurgery

I don't believe these are experimental for epilepsy or brain tumors.

I will follow up with a list of publications that demonstrates the efficacy of the therapy and the relative safety and often big advantage when compared to open approaches in specific situations (hypothalamic hamartomas for example).

There hasn't been a RCT to compare against open surgery for obvious logistical reasons but there is a myriad of studies to show the beneficial effect. Will be happy to participate in any in-depth review.

Laser Interstitial Thermal Therapy (LITT)

HERC staff summary:

Laser interstitial thermal therapy (LITT) is a new technology that is best studied for treatment of refractory epilepsy and brain tumors. A trusted source systematic review (CADTH 2019) found limited quality and quantity of evidence that LITT had equivalent outcomes to stereotactic radiosurgery for refractory epilepsy. No comparative evidence was found on LITT for treatment of brain tumors on disease progression, overall survival or quality of life. NCCN gives LITT a category 2 B recommendation for patients who are not surgical candidates for treatment of brain metastases or radiation necrosis. Private payer coverage of LITT is mixed, and mainly is for refractory epilepsy.

HERC staff recommendation:

1) Place the following CPT codes on line 662 and place entry in GN173 as shown below
    a. **61736:** Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; single trajectory for 1 simple lesion
    b. **61737:** Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; multiple trajectories for multiple or complex lesion(s)

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
61736, 61737	Laser interstitial thermal therapy (LITT) of lesion, intracranial	Insufficient evidence of effectiveness	November 2021

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Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN): 12-Month Outcomes and Quality of Life After Brain Tumor Ablation

BACKGROUND: Laser Ablation of Abnormal Neurological Tissue using Robotic NeuroBlate System (LAANTERN) is an ongoing multicenter prospective NeuroBlate (Monteris Medical) LITT (laser interstitial thermal therapy) registry collecting real-world outcomes and quality-of-life (QoL) data.

OBJECTIVE: To compare 12-mo outcomes from all subjects undergoing LITT for intracranial tumors/neoplasms.

METHODS: Demographics, intraprocedural data, adverse events, QoL, hospitalizations, health economics, and survival data are collected; standard data management and monitoring occur.

RESULTS: A total of 14 centers enrolled 223 subjects; the median follow-up was 223 d. There were 119 (53.4%) females and 104 (46.6%) males. The median age was 54.3 yr (range 3-86) and 72.6% had at least 1 baseline comorbidity. The median baseline Karnofsky Performance Score (KPS) was 90. Of the ablated tumors, 131 were primary and 92 were metastatic. Most patients with primary tumors had high-grade gliomas (80.9%). Patients with metastatic cancer had recurrence (50.6%) or radiation necrosis (40%). The median postprocedure hospital stay was 33.4 h (12.7-733.4). The 1-yr estimated survival rate was 73%, and this was not impacted by disease etiology. Patient-reported QoL as assessed by the Functional Assessment of Cancer Therapy-Brain was stabilized postprocedure. KPS declined by an average of 5.7 to 10.5 points postprocedure; however, 50.5% had stabilized/improved KPS at 6 mo. There were no significant differences in KPS or QoL between patients with metastatic vs primary tumors.

CONCLUSION: Results from the ongoing LAANTERN registry demonstrate that LITT stabilizes and improves QoL from baseline levels in a malignant brain tumor patient population with high rates of comorbidities. Overall survival was better than anticipated for a real-world registry and comparative to published literature.

KEY WORDS: LITT, Laser ablation, Survival, Quality of life, Brain tumor

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Laser interstitial thermal therapy (LITT) with magnetic resonance imaging (MRI) guidance has been used for more than 10 yr to treat patients with glioblastoma (GBM), brain metastases, gliomas, radiation necrosis, and epilepsy.[1] Since 2015, over 700 patient

ABBREVIATIONS: ADL, activities of daily living; **CI,** confidence interval; **EQ-5D,** EuroQol 5-dimensional; **FACT-Br,** Functional Assessment of Cancer Therapy-Brain; **GBM,** glioblastoma; **IADL,** instrumental ADL; **IRB,** institutional review board; **KPS,** Karnofsky Performance Score; **LAANTERN,** Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System; **LITT,** laser interstitial thermal therapy; **MRI,** magnetic resonance imaging; **QoL,** quality of life; **STROBE,** Strengthening the Reporting of Observational Studies in Epidemiology; **VAS,** visual analog scale; **WHO,** World Health Organization

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2022 CPT Code Review

Hypoglossal Nerve Neurostimulator

Codes**:**
64582: Open implantation of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array
64583: Revision or replacement of hypoglossal nerve neurostimulator array and distal respiratory sensor electrode or electrode array, including connection to existing pulse generator
64584: Removal of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array

Similar code:
Previously coded with CPT 64568 (Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator) which is on lines 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS and 441 TRIGEMINAL AND OTHER NERVE DISORDERS

Description: Hypoglossal nerve stimulation is a treatment for obstructive sleep apnea. The hypoglossal nerve is the twelfth cranial nerve and innervates all the extrinsic and intrinsic muscles of the tongue. The hypoglossal nerve stimulator is an implanted device that stimulates this nerve to stimulate the tongue to improve tongue obstruction in sleep apnea. Alternative treatments for OSA include CPAP, tonsillectomy, adenoidectomy, and mandibular advancement devices.

Current Prioritized List status

GUIDELINE NOTE 27, TREATMENT OF SLEEP APNEA
Line 202
For adults over the age of 18 years:

A) CPAP is covered initially when all of the following conditions are met:
   1) 12 week 'trial' period to determine benefit. This period is covered if apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) is greater than or equal to 15 events per hour; or if between 5 and 14 events with additional symptoms including one or more of the following:
   2) excessive daytime sleepiness defined as either an Epworth Sleepiness Scale score>10 or daytime sleepiness interfering with ADLs that is not attributable to another modifiable sedating condition (e.g. narcotic dependence), or
   3) documented hypertension, or
   4) ischemic heart disease, or
   5) history of stroke
   6) Additionally:
      a) Providers must provide education to patients and caregivers prior to use of CPAP machine to ensure proper use; and
      b) Positive diagnosis through polysomnogram (PSG) or Home Sleep Test (HST).

B) CPAP coverage subsequent to the initial 12 weeks is based on documented patient tolerance, compliance, and clinical benefit. Compliance (adherence to therapy) is defined as use of CPAP for at least four hours per night on 70% of the nights during a consecutive 30-day period.

C) Mandibular advancement devices (oral appliances) are covered for those for whom CPAP fails or is contraindicated.
D) Surgery for sleep apnea in adults is not included on this line (due to lack of evidence of efficacy). Surgical codes are included on this line only for children who meet criteria below
E) Hypoglossal nerve stimulation for treatment of obstructive sleep apnea is not included on this line due to insufficient evidence of effectiveness and evidence of harm.

For children age of 18 years or younger:

A) Adenotonsillectomy is an appropriate first line treatment for children with OSA. Adenoidectomy without tonsillectomy is only covered when a child with OSA has previously had a tonsillectomy, when tonsillectomy is contraindicated, or when tonsillar hypertrophy is not present. More complex surgical treatments are only included on this line for children with craniofacial anomalies.
B) Intranasal corticosteroids are an option for children with mild OSA in whom adenotonsillectomy is contraindicated or for mild postoperative OSA.
C) CPAP is covered for a 3 month trial for children through age 18 who have
   1) undergone surgery or are not candidates for surgery, AND
   2) have documented residual sleep apnea symptoms (sleep disruption and/or significant desaturations) with residual
      daytime symptoms (daytime sleepiness or behavior problems)
D) CPAP will be covered for children through age 18 on an ongoing basis if:
   1) There is documentation of improvement in sleep disruption and daytime sleepiness and behavior problems with CPAP
      use, AND
   2) Annual re-evaluation for CPAP demonstrates ongoing clinical benefit and compliance with use, defined as use of CPAP
      for at least four hours per night on 70% of the nights in a consecutive 30 day period

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

Evidence

1) **NICE 2017**, review of hypoglossal nerve stimulation for moderate to severe obstructive sleep apnea https://www.nice.org.uk/guidance/ipg598/documents/overview-2;
   a. Overall recommendation: Current evidence on the safety and efficacy of hypoglossal nerve stimulation for moderate to severe obstructive sleep apnea is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research
   b. N=7 studies (1 systematic review, 4 prospective case series, 1 RCT, and 1 retrospective case series
      i. N=326 patients
   c. Effectiveness
      i. In a systematic review and meta-analysis of 200 patients
         1. there was a statistically significant decrease in the AHI (a normal AHI is less than 5 events per hour). At 3-, 6-, and 12-month follow-up the mean differences from baseline were −23.94 (95% confidence interval

[CI] −31.45 to −16.43, 34 patients), −25.60 (95% CI −31.18 to −20.01, 60 patients) and −17.51 (95% CI −20.69 to −14.34, 170 patients) respectively (p<0.001 for all time points).

2. there was a statistically significant decrease in the ODI (defined as the number of times per hour of sleep that the blood oxygen level drops by 4 or more percentage points from baseline). At 3-, 6-, and 12-month follow-up the mean differences from baseline were −10.04 (CI −16.31 to −3.78, 34 patients), −11.68 (95% CI −17.16 to −6.19, 60 patients) and −13.73 (95% CI −16.87 to −10.58, 170 patients) respectively (p<0.01 at 3 months and p<0.001 at 6 and 12 months)
3. there was a statistically significant decrease in the ESS (scores range from 0 to 24 with higher scores indicating more daytime sleepiness). At 3-, 6-, and 12-month follow-up the mean differences from baseline were -4.17 (CI −6.45 to −1.90, 34 IP 1470 [IPG598] IP overview: hypoglossal nerve stimulation for moderate to severe obstructive sleep apnea patients), −3.82 (95% CI −5.37 to −2.27, 60 patients) and −4.42 (95% CI −5.39 to −3.44, 170 patients) respectively (p

ii. In a prospective case series of 126 patients, there was a statistically significant decrease in the mean AHI ± standard deviation (SD) from 32.0±11.8 at baseline to 15.3±16.1 at 1 year (p<0.001). There was a statistically significant decrease in the mean ODI ± SD from 28.9±12.0 at baseline to 13.9±15.7 at 1 year (p<0.001). there was a statistically significant decrease in the mean ESS score ± SD from 11.6±5.0 at baseline to 7.0±4.2 at 1 year (p<0.001).

iii. In a prospective case series of 60 patients, there was a statistically significant decrease in the mean AHI ± SD from 31.2±13.2 at baseline to 13.8±14.8 at 12-month follow-up (p<0.05) The proportion of responders s (AHI<20 with at least 50% reduction) was 68% (41/60) after 12 months. there was a statistically significant decrease in the mean ODI ± SD from 27.6±16.4 at baseline to 13.7±14.9 at 12- month follow-up (p<0.05). there was a statistically significant decrease in the mean ESS score ± SD from 12.8±5.3 at baseline to 6.5±4.5 at 12-month follow-up (p<0.05).

iv. In a prospective case series of 46 patients, there was a statistically significant decrease in the mean AHI ± SD from 34.9±22.5 at baseline to 25.4±23.1 at 6-month follow-up (p=0.004). The proportion of responders (AHI<20 with at least 50% reduction) was 35% (15/43) after 6 months. There was a statistically significant decrease in the mean ODI ± SD from 32.4±22.3 at baseline to 23.6±22.3 at 6- month follow-up (p=0.006). The proportion of ODI responders (ODI with at least 50% reduction) was 40% (17/43) after 6 months. There was a statistically significant decrease in the mean ESS score ± SD from 12.0±4.8 at baseline to 8.3±4.4 at 6- month follow-up (p<0.001)

v. In a prospective case series of 31 patients, there was a statistically significant decrease in the mean AHI± SD from 32.9±11.2 at baseline to 7.1±5.9 at 1-year follow-up (p<0.001). In the prospective case series of 31 patients, there was a statistically significant decrease in the mean ODI ± SD from 30.7±14.0 at baseline to 9.9±8.0 at 1-year follow-up (p=0.004). There was a statistically significant decrease in the mean ESS score ± SD from 12.6± 5.6 at baseline to 5.9±5.2 at 1- year follow-up (p=0.006)

d. Adverse events

Hypoglossal Nerve Neurostimulator

i. Transient ipsilateral hemi-tongue paresis was reported in 15% (2/13) of patients in a prospective case series of 13 patients from a systematic review and metaanalysis of 200 patients. Temporary tongue weakness was reported in 18% (23/126) of patients in a prospective case series of 126 patients within 1 year of the procedure. Paresis was reported in 11% (5/46) of patients within 30 days of implantation in a prospective case series of 46 patients; all cases resolved spontaneously
ii. Paraesthesia was reported in 13% (6/46) of patients (within 30 days of implantation in 5 patients, and more than 30 days after implantation in 1 patient) in the prospective case series of 46 patients.
iii. Mechanical pain associated with the presence of the device was reported in 10% (12/126) of patients in the prospective case series of 126 patients within 3 years of the procedure. Discomfort due to electrical stimulation was reported in 58% (73/126) of patients in the prospective case series of 126 patients within 4 years of the procedure. In the same study, discomfort related to incisions was reported in 29% (37/126) of patients and discomfort not related to incisions was reported in 27% (34/126) of patients within 4 years of the procedure. Pain was reported in 41% (19/46) patients in the prospective case series of 46 patients (7 patients reported non-serious pain within 30 days of implantation, 12 reported it more than 30 days after implantation); 3 patients reported serious pain (1 case within 30 days and 2 cases more than 30 days after implantation).
iv. Device migration more than 30 days after implantation was reported in 1 patient in the prospective case series of 46 patients
v. Temporary internal device usability or functionality complaint was reported in 16% (20/126) of patients within 4 years of the procedure in the prospective case series of 126 patients. In the same study, temporary external device usability or functionality complaint was reported in 24% (30/126) of patients within 4 years of the procedure
vi. Leads breaking was reported in 15% (2/13) of patients in the prospective case series of 13 patients from the systematic review and meta-analysis of 200 patients

Other payer policies

1) **Aetna 2021:**
    a. Aetna considers Food and Drug Administration (FDA)-approved hypoglossal nerve neurostimulation (e.g., Inspire II System, Inspire 3028 system for Upper Airway Stimulation (UAS) Therapy) medically necessary for the treatment of moderate to severe obstructive sleep apnea when *all* of the following criteria are met:
        i. Member is 18 years of age or older; *and*
        ii. Body mass index (BMI) is less than 32 kg/m^2; *and*
        iii. A polysomnography (PSG) is performed within 24 months of first consultation for Inspire implant; *and*
        iv. Member has predominantly obstructive events (defined as central and mixed apneas less than 25% of the total AHI); *and*
        v. Apnea hypopnea index (AHI) is 15 to 65 events per hour; *and*

vi. Member has a minimum of one month of CPAP monitoring documentation that demonstrates CPAP failure (defined as AHI greater than 15 despite CPAP usage) or CPAP intolerance (defined as less than 4 hours per night, 5 nights per week); *and*
vii. Absence of complete concentric collapse at the soft palate level as seen on a drug-induced sleep endoscopy (DISE) procedure; *and*
viii. No other anatomical findings that would compromise performance of device (e.g., tonsil size 3 or 4 per tonsillar hypertrophy grading scale. See Appendix).

b. Aetna considers hypoglossal nerve neurostimulation experimental and investigational for all other indications.

2) CMS LCD 2020

a. FDA-approved hypoglossal nerve neurostimulation is considered medically reasonable and necessary for the treatment of moderate to severe obstructive sleep apnea when all of the following criteria are met:
i. Beneficiary is 22 years of age or older; **and**
ii. Body mass index (BMI) is less than 35 kg/m^2; **and**
iii. A polysomnography (PSG) is performed within 24 months of first consultation for HGNS implant; **and**
iv. Beneficiary has predominantly obstructive events (defined as central and mixed apneas less than 25% of the total AHI); **and**
v. AHI is 15 to 65 events per hour; **and**
vi. Beneficiary has documentation that demonstrates CPAP failure (defined as AHI greater than 15 despite CPAP usage) or CPAP intolerance (defined as less than 4 hours per night, 5 nights per week or the CPAP has been returned) including shared decision making that the patient was intolerant of CPAP despite consultation with a sleep expert; **and**
vii. Absence of complete concentric collapse at the soft palate level as seen on a drug-induced sleep endoscopy (DISE) procedure; **and**
viii. No other anatomical findings that would compromise performance of device (e.g., tonsil size 3 or 4 per standardized tonsillar hypertrophy grading scale).

2022 CPT Code Review

Hypoglossal Nerve Neurostimulator

HERC staff summary:

Hypoglossal nerve stimulation was previously reviewed as part of a coverage guidance on treatments for sleep apnea and recommended for non-coverage. One of our highly trusted sources (NICE) found limited evidence of effectiveness and high rates of harms and recommended use only as part of research. Medicare published LCDs covering this procedure in 2020; subsequently, most payers appear to be covering in certain situations.

Note: if a decision to add coverage is made, then the topic "2022 CPT Code Review Drug Induced Sleep Endoscopy" needs to be readdressed as that test is required prior to hypoglossal nerve stimulator placement.

HERC staff recommendation:

1) Place CPT **64584** (Removal of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array) on line 424 COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT
2) Place the following CPT codes on line 662 and place entry in GN173 as shown below
    a. **64582:** Open implantation of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array
    b. **64583:** Revision or replacement of hypoglossal nerve neurostimulator array and distal respiratory sensor electrode or electrode array, including connection to existing pulse generator

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
64581, 64583	Implantation, revision or replacement of hypoglossal nerve neurostimulator array	Insufficient evidence of effectiveness	November 2021

NICE guidance

Hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea

Interventional procedures guidance
Published: 22 November 2017
www.nice.org.uk/guidance/ipg598

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

1 Recommendations

1.1 Current evidence on the safety and efficacy of hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

1.2 Clinicians wishing to do hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea should:

- Inform the clinical governance leads in their NHS trusts.
- Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information to support shared decision-making. In addition, the use of NICE's information for the public is recommended.
- Audit and review clinical outcomes of all patients having hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea using NICE's interventional procedure outcomes audit tool.

1.3 Patient selection and the procedure should be done by clinicians with special expertise in the management of obstructive sleep apnoea.

1.4 Further research including the use of observational data from registries should provide information on patient selection, safety outcomes, quality of life, long-term outcomes and the position of the procedure in the treatment pathway. NICE may update the guidance on publication of further evidence.

2 Indications and current treatments

2.1 Obstructive sleep apnoea (OSA) is characterised by repeated episodes of apnoea and hypopnoea during sleep, loud snoring and excessive daytime sleepiness. The main cause is collapse of the upper airway during sleep. OSA has a big impact on quality of life and increases the risk of having a stroke and developing conditions such as hypertension and atrial fibrillation.

2.2 OSA may be improved by lifestyle changes such as weight loss, avoiding alcohol or sedative medication, and change of sleeping position. The most common

treatment for severe OSA is continuous positive airway pressure, applied through a face mask during sleep. Surgical interventions include tonsillectomy, adenoidectomy, uvulopalatopharyngoplasty and, rarely, tracheostomy and bariatric surgery.

3 The procedure

3.1 Hypoglossal nerve stimulation aims to treat obstructive sleep apnoea by preventing the tongue prolapsing backwards and causing upper airway obstruction during sleep. It works by delivering an electrical current to the hypoglossal nerve. This contracts the genioglossus muscle, the major muscle responsible for tongue protrusion, and all other intrinsic muscles of the tongue. Using general anaesthesia, a neurostimulator is implanted in an infraclavicular subcutaneous pocket and a stimulating lead is placed on the main trunk of the hypoglossal nerve. The neurostimulator delivers electrical pulses to the hypoglossal nerve. With some devices, stimulation can be synchronised with respiration using sensing leads that measure changes in breathing. The respiratory-sensing leads are positioned between the external and internal intercostal muscle. The stimulator is programmed and controlled wirelessly to adapt to specific patient needs.

4 Efficacy

This section describes efficacy outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see NICE's interventional procedure overview.

In a systematic review and meta-analysis of 200 patients, there was a statistically significant decrease in the apnoea–hypopnoea index (AHI; a normal AHI is less than 5 events per hour). At 3-, 6-, and 12-month follow-up the mean differences from baseline were -23.94 (95% confidence interval [CI] -31.45 to -16.43, 34 patients), -25.60 (95% CI -31.18 to -20.01, 60 patients) and -17.51 (95% CI -20.69 to -14.34, 170 patients) respectively ($p<0.001$ for all time points).

4.1 In a randomised controlled therapy-withdrawal trial of 46 'responders' from a prospective case series of 126 patients (23 therapy-maintenance responders compared with 23 therapy-withdrawal responders), there was a statistically significant increase in the mean AHI from 7.6 at 1-year follow-up (before

randomisation into the trial) to 25.8 at 1 week after randomisation, in the group in which the device was turned off for 1 week ($p<0.001$). There was no statistical difference in mean AHI within the therapy-maintenance group, who continued to use the device (7.2 compared with 8.9). At 18-month follow-up, the mean AHI scores were 9.6 in the therapy-maintenance group and 10.7 in the group who had the device turned off for 1 week ($p<0.05$ for the differences compared with baseline within groups). There was a statistically significant difference between the therapy-withdrawal group and the therapy-maintenance group for change in mean AHI, from assessment at 1 year to assessment at the end of the therapy-withdrawal study ($p<0.001$).

4.2 In the systematic review and meta-analysis of 200 patients, there was a statistically significant decrease in the oxygen desaturation index (defined as the number of times per hour of sleep that the blood oxygen level drops by 4 or more percentage points from baseline). At 3-, 6-, and 12-month follow-up the mean differences from baseline were -10.04 (CI -16.31 to -3.78, 34 patients), -11.68 (95% CI -17.16 to -6.19, 60 patients) and -13.73 (95% CI -16.87 to -10.58, 170 patients) respectively ($p<0.01$ at 3 months and $p<0.001$ at 6 and 12 months).

4.3 In the systematic review and meta-analysis of 200 patients, there was a statistically significant decrease in the Epworth sleepiness scale (scores range from 0 to 24 with higher scores indicating more daytime sleepiness). At 3-, 6-, and 12-month follow-up the mean differences from baseline were -4.17 (CI -6.45 to -1.90, 34 patients), -3.82 (95% CI -5.37 to -2.27, 60 patients) and -4.42 (95% CI -5.39 to -3.44, 170 patients) respectively ($p<0.001$ for all time points).

4.4 In a follow-up study of 95 patients from the prospective case series of 126 patients, there was a statistically significant increase in the mean functional outcomes of sleep questionnaire score (FOSQ, ranging from 5 to 20 with higher scores indicating better subjective sleep quality) from 14.6±3.0 at baseline to 17.5±2.9 at 4-year follow-up ($p<0.05$).

4.5 In the follow-up study of 95 patients from the prospective case series of 126 patients, the rates of bed-partner reported 'no snoring' or 'soft snoring' were 17% (18/108) at baseline and 85% at 4-year follow-up.

4.6 In a prospective case series of 46 patients, there was a statistically significant

improvement in the mean sleep apnoea quality of life index from 4.3±1.0 at baseline to 4.7±1.2 at 6-month follow-up (p=0.019).

4.7 The specialist advisers listed the key efficacy outcomes as: reduction in severity of obstructive sleep apnoea, improved sleep and reduced daytime sleepiness.

5 Safety

This section describes safety outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see NICE's interventional procedure overview.

5.1 Transient ipsilateral hemi-tongue paresis was reported in 15% (2/13) of patients in a prospective case series of 13 patients from a systematic review and meta-analysis of 200 patients.

5.2 Tongue abrasion was reported in 26% (33/126) of patients in a follow-up study of 95 patients from a prospective case series of 126 patients within 4 years of the procedure.

5.3 Bleeding was reported in 1 patient within 30 days of implantation in a prospective case series of 46 patients. This was caused by a hypertensive crisis and surgical intervention was needed; hypertension was treated with medication. In the same study, haematoma was reported in 7% (3/46) of patients. One of the 2 cases classified as non-serious occurred within 30 days of implantation and the other occurred more than 30 days after implantation. The third case was classified as a serious event and occurred within 30 days of implantation.

5.4 Rupture of a vein was reported in 6% (2/31) of patients during cervical tunnelling in a prospective case series of 31 patients; 1 of the patients needed 1 further cervical incision.

5.5 Seroma at an incision site was reported in 10% (2/20) of patients after the procedure in a retrospective case series of 20 patients. One seroma occurred at the sensing-lead incision 1 week after surgery and the other occurred at the implantable pulse-generator incision 4 weeks after surgery. Both resolved uneventfully with percutaneous needle drainage.

5.6 Headache was reported in 6% (8/126) of patients in the prospective case series of 126 patients within 1 year of the procedure.

5.7 Infection was reported in 1 patient in a prospective case series of 22 patients from the systematic review and meta-analysis of 200 patients; the device was removed.

5.8 Dry mouth was reported in 13% (16/126) of patients in the prospective case series of 126 patients within 3 years of the procedure.

5.9 Discomfort due to electrical stimulation was reported in 58% (73/126) of patients in the prospective case series of 126 patients within 4 years of the procedure. In the same study, discomfort related to incisions was reported in 29% (37/126) of patients and discomfort not related to incisions was reported in 27% (34/126) of patients within 4 years of the procedure.

5.10 Paraesthesia was reported in 13% (6/46) of patients (within 30 days of implantation in 5 patients, and more than 30 days after implantation in 1 patient) in the prospective case series of 46 patients.

5.11 Device migration more than 30 days after implantation was reported in 1 patient in the prospective case series of 46 patients. Cuff dislodgement was reported in 2 patients in a prospective case series of 31 patients, and in 1 patient in a prospective case series of 21 patients, from the systematic review and meta-analysis of 200 patients; all 3 patients needed a new procedure to replace it.

5.12 Device removal was reported in 4 patients in the prospective case series of 31 patients, and in 2 patients in the prospective case series of 21 patients, from the systematic review and meta-analysis of 200 patients. Device removal was also reported in 3 patients, 1 to 4 years after the procedure, in the prospective case series of 126 patients. The reasons for removal were insomnia, septic sternoclavicular joint adjacent to the device and non-response to therapy. Device removal for cosmetic reasons was reported in 1 patient in a case series of 60 patients.

5.13 Leads breaking was reported in 15% (2/13) of patients in the prospective case series of 13 patients from the systematic review and meta-analysis of

200 patients.

5.14 Defective implanted pulse-generator connector was reported in 1 patient in the prospective case series of 13 patients from the systematic review and meta-analysis of 200 patients.

5.15 Other complications reported in the systematic review and meta-analysis of 200 patients included postoperative pain and stiffness, sore throat, stitch abscess, local swelling, fever and lack of tongue response to stimulation.

5.16 In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never done so). For this procedure, the specialist advisers did not list any anecdotal adverse events. They considered that the following were theoretical adverse events: fatigue of the upper airway dilator muscles leading to worsening sleep apnoea, and hypoglossal nerve damage.

6 Committee comments

6.1 There is more than 1 device available for this procedure.

6.2 Drug-induced sedated endoscopy was used for patient screening in the studies, but this assessment technique is not commonly used in the UK.

6.3 A transcutaneous approach can be used for hypoglossal nerve stimulation but this is not covered by this guidance.

6.4 In the studies reviewed, the procedure was used in patients who could not tolerate continuous positive airway pressure.

7 Further information

7.1 For related NICE guidance, see the NICE website.

7.2 No patient commentary was sought because the procedure is not currently done in the UK. The Sleep Apnoea Trust Association provided feedback on this

procedure.

7.3 This guidance requires that clinicians doing the procedure make special arrangements for audit. NICE has identified relevant audit criteria and has developed NICE's interventional procedure outcomes audit tool (which is for use at local discretion).

Information for patients

NICE has produced information on this procedure for patients and carers. It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind.

ISBN: 978-1-4731-2733-3

Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

Accreditation

2022 CPT Code Review
Thermal Destruction of Intraosseous Basivertebral Nerve

Codes:

1) **64628**: Thermal destruction of intraosseous basivertebral nerve, including all imaging guidance; first 2 vertebral bodies, lumbar or sacral
2) **64629**: Thermal destruction of intraosseous basivertebral nerve, including all imaging guidance; each additional vertebral body, lumbar or sacral

Similar codes: none

Description: The sensory nerves within the center of the vertebral body converge to form the basivertebral nerve (BVN). The BVN exits the vertebral body posteriorly via the basivertebral foramen. In patients with vertebrogenic back pain, utilizing therapeutic radiofrequency (RF) ablation of the BVN has been proposed as a method of treating low back pain.

Evidence

1) **Khalil 2019**, the INTRACEPT trial
    a. RCT of patients with low back pain
        i. N= 51 treated with BVN ablation, N=53 treated with standard care
        ii. Followed for 3 months
    b. Comparing the RF ablation arm to the standard care arm, the mean changes in Oswestry Disability Index (ODI) at 3 months were -25.3 points versus -4.4 points, respectively, resulting in an adjusted difference of 20.9 points (p<.001). Mean changes in VAS were -3.46 versus -1.02, respectively, an adjusted difference of 2.44 cm (p<.001). In the RF ablation arm, 74.5% of patients achieved a ≥10-point improvement in ODI, compared with 32.7% in the standard care arm (p<0.001).
2) **Fischgrund 2018**, SMART trial
    a. RCT of radiofrequency ablation (RA) of the basivertebral nerve vs sham
        i. N=147 patients in the RA group, N=78 patients in the sham group
        ii. 12 month follow up
    b. At 3 months, the average Oswestry Disability Index (ODI) in the treatment arm decreased 20.5 points, as compared to a 15.2 point decrease in the sham arm (p = 0.019, per-protocol population). A responder analysis based on ODI decrease ≥ 10 points showed that 75.6% of patients in the treatment arm as compared to 55.3% in the sham control arm exhibited a clinically meaningful improvement at 3 months.
        i. No ODI scores reported after 3 months
    c. The least mean squares (LSM) improvement in VAS in the treatment arm was 2.97, 3.04, and 2.84 cm at 3, 6, and 12 months, respectively. The LSM improvement in VAS in the sham arm was 2.36, 2.08, and 2.08 cm at 3, 6, and 12 months, respectively
    d. Eight procedure-related events were reported in six patients following the 225 index procedures, for a complication rate of 2.7%. Two of these six patients were in the sham arm. The events included nerve root injury (n = 1), lumbar radiculopathy (n = 2), retroperitoneal hemorrhage (n = 1), and transient motor or sensory deficits (n = 4).

Expert guideline:

1) **Lorio 2019**, ISASS guideline on intraosseous ablation of the basivertebral nerve for relief of chronic back pain
    a. Noted only two trials to date (INTRACEPT and SMART reviewed above)

b. Intraosseous ablation of the BVN is a relatively new minimally invasive treatment for the relief of CLBP that is diagnosed using well-established clinical and MRI findings. The procedure is supported by level 1 evidence including 2 RCTs demonstrating a statistically significant decrease in pain and an improvement in function with outcomes sustained to at least 24 months in a limited number of studies. BVN ablation may provide a treatment option to fill the gap in the treatment paradigm for patients that fail nonsurgical treatment.
c. Noted all studies are industry funded, short term and may be biased

Other payer policies

- Aetna 2021: Intracept System (intra-osseous basivertebral nerve ablation) for the treatment of low back pain is investigational
- Cigna 2021: intraosseous radiofrequency nerve ablation of basivertebral nerve (e.g., INTRACEPT® Intraosseous Nerve Ablation System) (CPT codes 64999, C9752, C9753) is investigational
- Anthem BCBS 2021: Intraosseous basivertebral nerve ablation is investigational

HERC staff summary

Basivertebral nerve ablation is a new treatment for chronic low back pain, with an evidence base consisting of two RCTs (N=320 patients) which reported only short term outcomes. All private payers surveyed consider it experimental.

HERC staff recommendation

1) Add the following CPT codes to line 662 and add an entry to GN173 as shown below
    a. **64628**: Thermal destruction of intraosseous basivertebral nerve, including all imaging guidance; first 2 vertebral bodies, lumbar or sacral
    b. **64629**: Thermal destruction of intraosseous basivertebral nerve, including all imaging guidance; each additional vertebral body, lumbar or sacral

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
64628-64629	Thermal destruction of intraosseous basivertebral nerve	Insufficient evidence of effectiveness	November 2021

The Spine Journal 19 (2019) 1620–1632

Clinical Study

A prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain

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Abstract

BACKGROUND CONTEXT: Current literature suggests that degenerated or damaged vertebral endplates are a significant cause of chronic low back pain (LBP) that is not adequately addressed by standard care. Prior 2-year data from the treatment arm of a sham-controlled randomized controlled trial (RCT) showed maintenance of clinical improvements at 2 years following radiofrequency (RF) ablation of the basivertebral nerve (BVN).

Research Oversight & Ethics: This research was conducted under the oversight of the Western Institutional Review Board, Advarra IRB and the investigational site's local IRB. Informed consent was obtained for participants in this study. This research was conducted in accordance with the Helsinki Declaration.

FDA device/drug status: Approved (Intracept).

Author disclosures: ***JK:*** Grant: Relievant INTRACEPT Trial (F); Consulting: Stryker (D), Camber Spine (B), Johnson & Johnson (B), Innovasis (B); Speaking and/or Teaching Arrangements: Stryker (C); Research Support (Investigator Salary, Staff/Materials): K2M, Johnson & Johnson, Centinel Spine, Medtronic, Mainstay, Limiflex, Fziomed. ***MS:*** Grant: Relievant Medsystems INTRACEPT Trial (F); Private Investments: Vivametrica ($15); Consulting: State Farm (F);.Trips/Travel: Spine Intervention Society (B); Board of Directors: Spine Intervention Society (0); Scientific Advisory Board/Other Office: NuSpine ($1), BlueJay Mobile Health ($1); Grants: ReWalk (E). ***TK:*** Fees for participation in review activities such as monitoring boards, statistical analysis, end point committees and the like: St. Lukes (F); CSRS (C). ***JK:*** Other: Emory University (F). ***DB:*** Research Support (Investigator Salary, Staff/Materials): Clinical; Investigations LLC (F). ***BG:*** Grant: Relievant Medsystems INTRACEPT Study (E); Royalties: Elsevier, Atlas book (F); Consulting: Discgenics/Consultant; Scientific Advisory Board/Other Office: Discgenics. ***PK:*** Grant: Milton S Hershey Medical Center (F); . ***DN:*** Grant: Oklahoma Spine Hospital (B); Trips/Travel: American Spine Society of Radiology (A); Research Support (Investigator Salary, Staff/Materials): Oklahoma Spine Hospital (B). ***SG:*** Consulting Training: Relievant Medsystems (B).

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https://doi.org/10.1007/s00586-018-5496-1

ORIGINAL ARTICLE

Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: a prospective randomized double-blind sham-controlled multi-center study

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Abstract

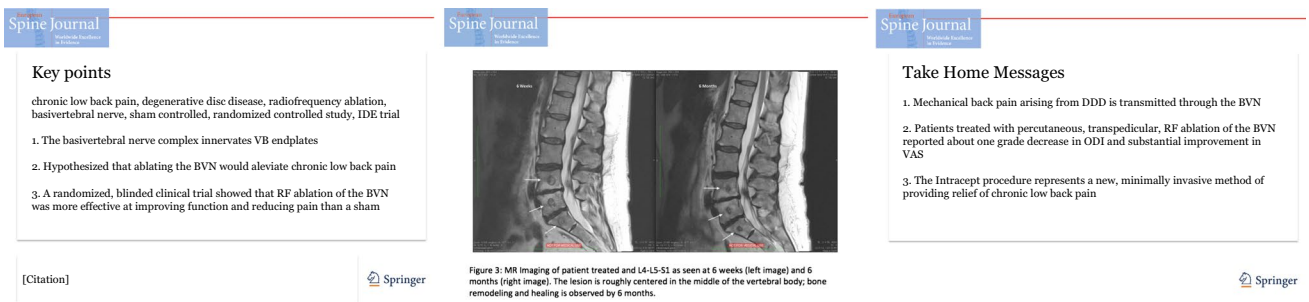
Purpose To evaluate the safety and efficacy of radiofrequency (RF) ablation of the basivertebral nerve (BVN) for the treatment of chronic low back pain (CLBP) in a Food and Drug Administration approved Investigational Device Exemption trial. The BVN has been shown to innervate endplate nociceptors which are thought to be a source of CLBP.

Methods A total of 225 patients diagnosed with CLBP were randomized to either a sham (78 patients) or treatment (147 patients) intervention. The mean age within the study was 47 years (range 25–69) and the mean baseline ODI was 42. All patients had Type I or Type II Modic changes of the treated vertebral bodies. Patients were evaluated preoperatively, and at 2 weeks, 6 weeks and 3, 6 and 12 months postoperatively. The primary endpoint was the comparative change in ODI from baseline to 3 months.

Results At 3 months, the average ODI in the treatment arm decreased 20.5 points, as compared to a 15.2 point decrease in the sham arm ($p = 0.019$, per-protocol population). A responder analysis based on ODI decrease $\geq$ 10 points showed that 75.6% of patients in the treatment arm as compared to 55.3% in the sham control arm exhibited a clinically meaningful improvement at 3 months.

Conclusion Patients treated with RF ablation of the BVN for CLBP exhibited significantly greater improvement in ODI at 3 months and a higher responder rate than sham treated controls. BVN ablation represents a potential minimally invasive treatment for the relief of chronic low back pain.

Graphical abstract These slides can be retrieved under Electronic Supplementary Material.



Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-018-5496-1) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

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International Society for the Advancement of Spine Surgery Guideline—Intraosseous Ablation of the Basivertebral Nerve for the Relief of Chronic Low Back Pain

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RATIONALE

This International Society for the Advancement of Spine Surgery guideline is generated to respond to growing requests for background, supporting literature and evidence, and proper coding for intraosseous ablation of the basivertebral nerve for chronic low back pain.

Testing & Regulatory Affairs

Keywords: intraosseous ablation, basivertebral nerve, chronic low back pain, vertebrogenic pain

INTRODUCTION

Prevalence and Clinical Presentation

Low back pain (LBP) is the most expensive occupational disorder in the United States and the leading cause of disability worldwide.[1–3] Thirty percent of Americans have LBP at any given time, leading to approximately 50 million physician visits in the US annually. Although many of these patients improve with little to no treatment, an estimated 30 million adults in the US currently suffer from chronic LBP (CLBP), defined as pain lasting for greater than 12 weeks.[4–10] These CLBP patients have direct yearly costs of over $90 billion/year.[11] As is the case with many medical conditions, a minority of CLBP patients consume the majority of health care resources. Analyses of commercial payer and Medicare claims databases reveals that 15% of CLBP patients account for 75% of health care costs, with average claims of $24 700 over a 3-year period in the high health care use group (MarketScan, Truven Health Analytics from October 2011 to September 2016).

Disc degeneration (DD) is a strong risk factor for CLBP,[12–14] and the disc has been the target of many treatments. Recent scientific research has reexamined CLBP sources, and there is evidence suggesting that the disc and adjacent endplates act as 1 functional unit and that the vertebral endplate is a source of pathologic innervation that occurs with DD.

Indeed, the endplates must balance conflicting requirements of being strong to prevent vertebral fracture and being porous to facilitate transport between disc cells and vertebral capillaries. Consequently, endplates are particularly susceptible to damage leading to inflammation and nerve proliferation.

The sensory nerves within the center of the vertebral body converge to form the basivertebral nerve (BVN).[15,16] The BVN exits the vertebral body posteriorly via the basivertebral foramen before communicating with the sinuvertebral nerve then the ventral rami of the spinal nerves or by nerves derived from the gray rami communicantes[16] When the density of pain fibers between normal endplates and degenerated endplates is compared, the BVN density is considerably higher in patients with degenerated endplates, further suggesting the role of pain transmission via the BVN in patients with CLBP.[16] The pain transmission of the endplates toward the BVN has been named of "vertebrogenic" origin.[14,15] Patients with vertebrogenic pain are thought to present with LBP, with or without referral into the buttocks or thighs (somatic referred pain).

Traditional Treatments for CLBP

CLBP may lead to a compromised quality of life, strained societal and familial relationships, and increased absenteeism or work-related disability

Table 1. Nonsurgical management often used for chronic low back pain.

1. Avoidance of activities that aggravate pain
2 .Trial of chiropractic manipulation
3. Trial of physical therapy
4. Cognitive support and recovery reassurance
5. Spine biomechanics education
6. Specific lumbar exercise program
7. Home use of heat/cold modalities
8. Low-impact aerobic exercise as tolerated
9. Pharmacotherapy (eg, nonnarcotic analgesics, nonsteroidal anti-inflammatory drugs)

claims. A lack of current validated diagnostic reference standards leads 85% of individuals to be diagnosed with *nonspecific LBP*. This nonspecific diagnosis leads to nonspecific care that follows care pathways that are not scientifically validated (Table 1). Individuals are advised to stay active, engage in core strengthening, lose weight, and avoid bed rest. They are put through nonsequential, palliative injection treatments in the hope that these treatments will help the patient's function and that the pain will then regress. For refractory cases, surgical intervention may be recommended.

Radiologic Imaging

The magnetic resonance imaging (MRI) correlation between vertebral endplate pathology and CLBP was made by Modic et al[17] in 1988, who described intraosseous MRI changes adjacent to damaged vertebral endplates in individuals with CLBP.

This correlation is based on the T1- and T2-weighted signal of the endplates. Three types of signal change have been described: Modic change 1 (MC1), Modic change 2 (MC2), and Modic change 3 (MC3). MC1 corresponds to bone marrow edema and inflammation (hypointense T1-weighted signal and hyperintense T2-weighted signal; Figures 1A and 1B). MC2 is characterized by hyperintense T1-weighted signal and hyperintense T2-weighted signal (Figures 1C and 1D) and is the conversion of normal red hemopoietic bone marrow into yellow fatty marrow. MC3 is described as bone sclerosis and is characterized by hypointense T1-weighted signal and hypointense T2-weighted signal. MC1 is considered unstable, and some studies have suggested this to be painful.[18,19] MC2 has been suggested to be less correlated to pain.[20] Patients with MC3 change are rarely symptomatic. Some speculate that the MC1 change is caused by an inflammatory response due to fissuring and disruption between the disc and the bone that develops along with endplate microfractures,[18–22] while others think that some of these changes could be due to a chronic infection.[23]

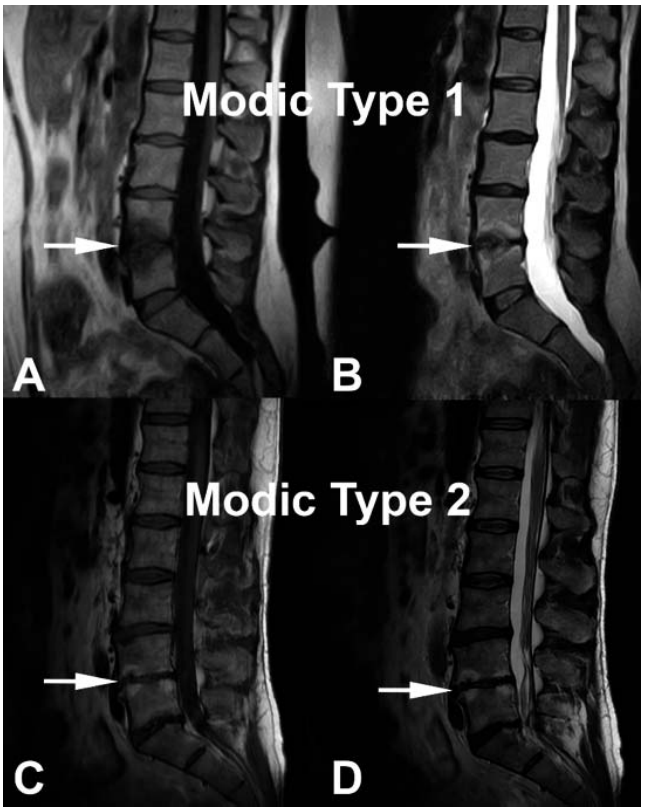

Figure 1. Modic change 1 (MC1) and Modic change 2 (MC2) illustrated. (A) and (B) demonstrate decreased signal intensity on T1-wighted images and increased signal intensity on T2-weighted images, respectively (white arrows) corresponding to MC1. (C) and (D) correspond to MC2 with increased signal intensity on T1-weighted images and on T2-weighted images, respectively (white arrows).

The afferent pain pathway travels from the disc and endplate to converge as the BVN before being transmitted through the dorsal root ganglion to the central nervous system and perceived as LBP. The initial neural convergence at the BVN in the midportion of the vertebral body provides a potential target for treatment. Having an MRI done prior to the patient's consultation with CLBP is essential to adequately determine the pain generator and viable treatment alternatives. Painful Modic changes most frequently affect the L4–L5 and L5–S1 levels; in fact, Kuisma et al[24] found a 2.28 odds ratio for the presence of Modic changes at L5–S1 in individuals with CLBP.

Procedure

A unilateral transpedicular approach is used to advance a straight introducer under fluoroscopic guidance to the juncture of the pedicle and the vertebral body. A curved cannula assembly is used to penetrate the vertebral body and navigate toward the BVN, which is located in the posterior half of

the vertebral body. A straight channeling stylet is then used to extend the channel to the midline location of the BVN. A bipolar probe is inserted into the posterior half of the vertebral body, connected to the radiofrequency (RF) generator, and energy is applied for 15 minutes to destroy the BVN. Once ablated, these nerves no longer transmit pain signals.

Data from the 2 level 1 randomized controlled trials (RCTs) would suggest that, in approximately 80% of patients, 2 vertebral bodies are treated, which constitute 1 vertebral motion segment. In the remaining patients, 1 or 2 additional vertebral bodies are treated for a total of 2–3 vertebral motion segments.

Animal studies performed as a part of a Food and Drug Administration (FDA) submission also showed that the intraosseous BVN does not regenerate and that the vertebrae return to pretreatment strength after a period of normal healing (written communication, Professor Jeffrey C. Lotz, PhD [David S. Bradford, MD Endowed Chair in Orthopaedic Surgery at UCSF] and corroborated by published bovine research by Hoopes et al[25]).

PUBLISHED LITERATURE

Becker et al[26] Pilot Study

Single-arm, open-label, first-in-human pilot study to determine the early efficacy and safety of intraosseous BVN ablation for the treatment of CLBP. Seventeen patients with 6 or more months of CLBP and MC1 or MC2 changes were enrolled. Sixteen patients were successfully treated using RF energy to ablate the BVN within the vertebral bodies adjacent to the diagnosed level (based on positive discography).

The mean age of enrolled patients was 48 years. Baseline measurements of mean Oswestry Disability Index (ODI) and visual analog scale (VAS) were 52 ± 13 (severe disability on the 0- to 100-point disability impact scale) and 61 (on the 0- to 100-point LBP scale). Statistically significant improvements were noted in all outcome measures at 3 months. ODI decreased an average of 29 points to a mean of 23 ± 21 at 3 months of follow up ($P < .001$). This statistically significant improvement in ODI was maintained through the 12 month follow up.

Truumees et al[27] Case Series

This study was a prospective, single-arm, multicenter, open-label study to evaluate the effectiveness of intraosseous RF ablation of the BVN for the treatment of presumed vertebrogenic-related CLBP in typical spine practice settings with more permissive inclusion of typical CLBP patients (such as patients who have had prior discectomy and users of extended-release narcotics). Consecutive patients with CLBP of at least 6 months duration and with MC1 or MC2 vertebral endplate changes between L3 to S1, were treated with RF ablation of the BVN in up to 4 vertebral bodies. The primary endpoint was patient-reported change in ODI from the baseline to 3 months postprocedure. Secondary outcome measures included change in LBP pain VAS, Short Form 36 (SF-36), EQ-5D-5L, and responder rates.

The median age of patients was 45 years within the 28 patients enrolled. The baseline ODI was 48.5 and VAS was 6.36 cm (on a 0 to 10 cm scale). Seventy-five percent of the study patients reported LBP symptoms for $\geq$5 years with 25% actively using opioids and 61% previously treated with injections. Clinically meaningful and statistically significant improvements were demonstrated in all outcome measures at the 3 month primary endpoint. Mean reduction in ODI from the baseline at 3 months posttreatment was $-30.07 + 14.52$ points ($P < .0001$). The mean reduction in VAS pain score from the baseline was $-3.50 + 2.33$ ($P < .0001$). Using a minimal clinically important difference (MCID) of $\geq$10-point improvement in ODI, 93% of patients were responders; using MCID of a $\geq$20-point improvement in ODI, 75% were responders. Likewise, VAS MCID of a $\geq$2.0 cm reduction was achieved in 75% of patients. Importantly, in this population of working-aged individuals, 83% reported improvement in work function. This nonrandomized consecutive series study demonstrated that minimally invasive RF ablation of the BVN resulted in a significant improvement in pain and function at 3 months in this population of real-world patients with chronic suspected vertebrogenic related LBP.

INTRACEPT Study[28]

This prospective, parallel, open-label, randomized control trial conducted at 20 US sites compared the effectiveness of intraosseous RF ablation of the BVN with standard care for the treatment of CLBP in patients suspected to have vertebrogenic-related pain symptomatology. A total of 140 patients with CLBP of at least 6 months duration, with MC1 or

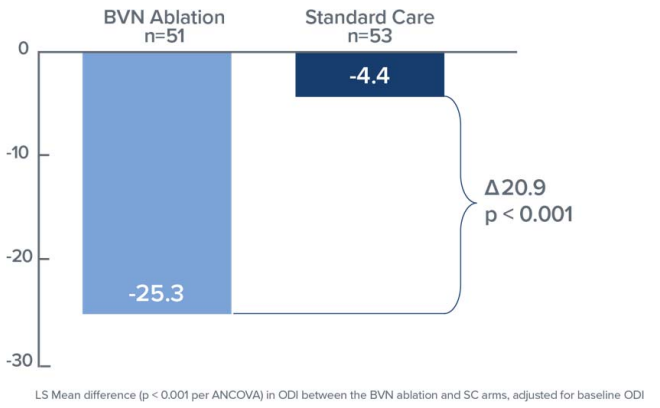

Figure 2. Bar graph demonstrating mean Oswestry Disability Index changes at 3 months both for the basivertebral nerve (BVN) ablation and the standard care groups. Statistically significant improvement of the patients' function is noted in the BVN group ($P < .001$).

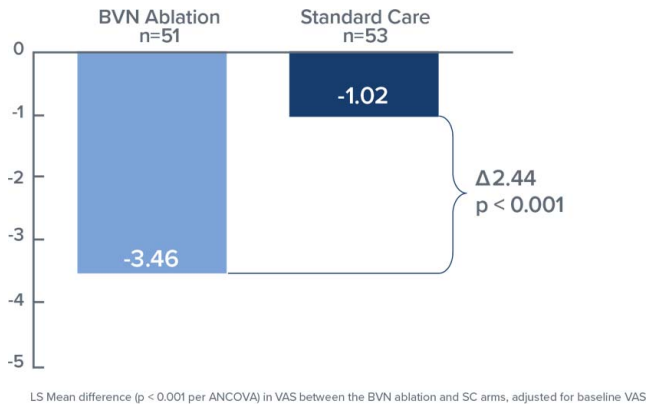

Figure 3. Bar graph demonstrating the mean difference in the visual analog scale at 3 months both for the basivertebral nerve (BVN) ablation and standard care groups. Statistically significant improvement in patients treated with BVN is noted ($P < .001$).

MC2 vertebral endplate changes between L3 to S1, were randomized 1:1 to undergo either RF ablation of the BVN or continue standard care. The primary endpoint was a between-arms comparison of the mean change in ODI from the baseline to 3 months posttreatment. Secondary outcome measures included LBP pain scores via VAS, ODI, VAS responder rates, SF-36, and EQ-5D-5L at 3, 6, 9, and 12 months postprocedure. An interim analysis to assess for superiority was prespecified and overseen by an independent data management committee (DMC) when a minimum of 60% of patients had completed their 3 month primary endpoint visit.

The interim analysis showed clear statistical superiority ($P < .001$) for all primary and secondary patient-reported outcome measures in the RF ablation arm compared with ongoing standard care arm. This resulted in a DMC recommendation to halt enrollment in the study and offer early crossover to the control arm. As a result, the study reported the outcomes of the 104 patients included in the intent-to-treat analysis of the 3 month primary endpoint, which included 51 patients in the RF ablation arm and 53 patients in the standard care arm. At the baseline, the mean age was 50 years, mean ODI was 46.1 (severe pain disability), and mean VAS was 6.67 cm (on a 0 to 10 cm scale). More than 67% of patients reported experiencing LBP for greater than 5 years, and more than 70% had received prior injections at the baseline.

Comparing the RF ablation arm with the standard care arm (Figure 2), the mean changes in ODI at 3 months were –25.3 points versus –4.4 points, respectively, resulting in an adjusted difference of 20.9 points ($P < .001$); and mean changes in VAS were –3.46 versus –1.02, respectively, an adjusted difference of 2.44 cm ($P < .001$; Figure 3). In the RF ablation arm, 74.5% of patients achieved the MCID of ≥10-point improvement in ODI, compared with 32.7% in the standard care arm ($P < .001$). With a MCID of 2.0 cm improvement in VAS, 72.5% of patients in the RF ablation arm reached clinical success compared with 34.0% of patients in the standard care arm. No RF ablation patients received a spinal injection prior to the 3 month endpoint, while in the standard care arm, 6 standard of care patients (11%) received injections across 5 study sites. The study concluded that minimally invasive RF ablation of the BVN leads to significant improvement of pain and function at 3 months in patients with suspected chronic vertebrogenic related LBP.

SMART Trial[29]

The SMART trial was a prospective randomized, sham-controlled, double-blinded, FDA-Investigational Device Exemption trial conducted to evaluate the safety and efficacy of RF ablation of the BVN for the treatment of CLBP. A total of 225 CLBP patients with MC1 or MC2 noted in vertebral bodies L3 to S1 were randomized to either a sham-control (78 patients) or BVN ablation treatment (147 patients). All study participants were treated with the same operating protocol and pedicle access. The sham-control arm received simulated RF ablation therapy. Treatment success was adjudicated in a blinded review of the 6-week MRI. Study participants were followed at 2 and 6 weeks and 3, 6, 9, and 12 months postrandomized intervention. The primary efficacy endpoint was change in ODI from

the baseline to 3 months postprocedure. The primary safety endpoint was a comparison of musculoskeletal and neurologic adverse events at 12 months.

Participants in this study were of working age (mean of 47 years), reported severe disability impact from their LBP (mean ODI of 42), and more than 68% had been experiencing CLBP for greater than 5 years. At 3 months, the mean ODI in the treatment arm decreased 20.5 points, as compared with a 15.2 point decrease in the sham arm ($P = .019$, per-protocol population). The reduction in ODI experienced by the treatment arm was twice the MCID of $\geq$10 points and responder rates were 75.6% in the treatment arm compared with 55.3% in the sham-control arm. There were no serious device- or procedure-related adverse events reported in patients randomized to the RF ablation treatment arm through 12 months.

This level 1 trial demonstrated significant functional improvement in patients treated with RF ablation of the BVN for CLBP compared with patients treated with a sham procedure. Safety of the procedure was also demonstrated. The results supported BVN ablation as a minimally invasive treatment for the relief of CLBP.

SMART 24 Month Outcomes[30]

This prospective, single-arm study is an extension of follow up for the RF ablation treatment arm of the SMART trial. Per the original SMART RCT protocol, at completion of the 12 month primary safety endpoint, patients in the sham-control arm could cross to BVN ablation treatment; 73% elected to cross. Due to this high rate of crossover, the 147 RF ablation treatment arm participants acted as their own control in comparing 24 month outcomes with the baseline.

Clinical improvements in the ODI, VAS, and the SF-36 physical component summary (PCS) were statistically significant compared with the baseline at all follow-up timepoints through 2 years (3, 6, 9, 12, 18, and 24 months). The mean percent improvements at 2 years in ODI (Figure 4) and VAS compared with the baseline were 53.7% and 52.9%, respectively. Responder rates for ODI and VAS were also maintained through 2 years for both a 10-point ODI MCID threshold (76.4% of patients) and an ODI 20-point improvement threshold (57.5% of patients); the MCID threshold for VAS of 1.5 cm improvement was reported in 70.2% of patients at 24 months (Figure 5). In summary, patients treated with RF ablation of the BVN for CLBP exhibited sustained clinical benefits in ODI and VAS and maintained high responder rates through 2 years following treatment.

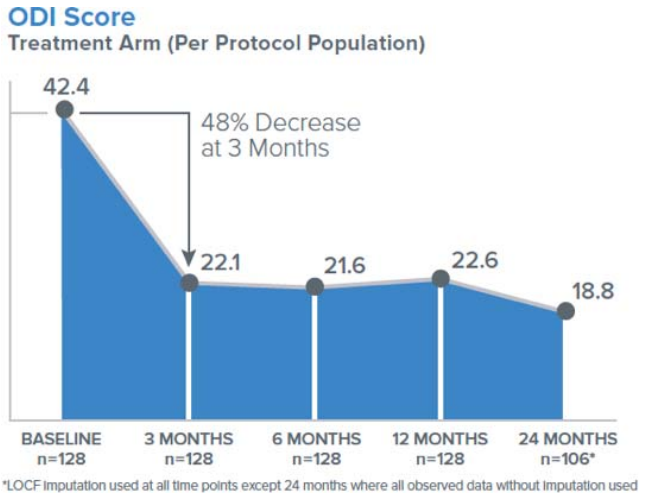

Figure 4. Mean Oswestry Disability Index score in per-protocol treatment arm followed up to 24 months.

Evidence and Literature Conclusion

Intraosseous ablation of the BVN is supported by a basic and clinical evidence foundation, including a level 1, sham-controlled RCT and a second level 1 RCT against standard conservative management. Data through 24 months suggest durability of the treatment effect. Collectively, these studies demonstrate that BVN ablation provides clinically meaningful improvements in pain and function to 2 years with an excellent safety profile. This evidence supports BVN as a treatment option for a well-defined subpopulation of CLBP patients.

INDICATIONS FOR SURGERY

Intraosseous ablation of the BVN from the L3 through S1 vertebrae may be considered medically

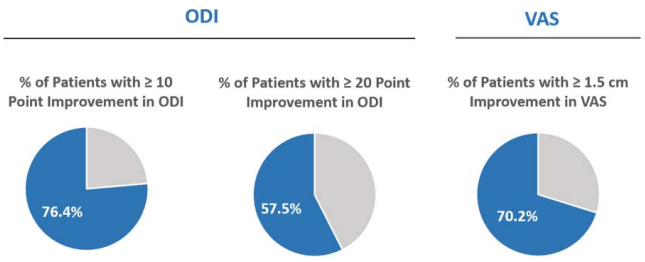

Figure 5. Shows the 24 month Oswestry Disability Index and visual analog scale responder rate per-protocol arm at 24 months (N = 106).

indicated for individuals with CLBP when all the following criteria are met:

- CLBP of at least 6 months duration,
- Failure to respond to at least 6 months of nonsurgical management, and
- MRI-demonstrated MC1 or MC2 in at least 1 vertebral endplate at 1 or more levels from L3 to S1.

CODING AND COVERAGE HISTORY

Intraosseous ablation of the BVN is a new procedure not previously performed. As such, this procedure currently should be reported with Current Procedural Terminology 22899 (unlisted procedure, spine).

Typical International Classification of Diseases, 10th Revision diagnosis codes that indicate medical necessity are as follows:

- M47.816: Spondylosis without myelopathy or radiculopathy, lumbar region,
- M47.817: Spondylosis without myelopathy or radiculopathy, lumbosacral region,
- M51.36: Other intervertebral DD, lumbar,
- M51.37: Other intervertebral DD, lumbosacral,
- M54.5: LBP.

Corresponding Healthcare Common Procedure Coding System codes, effective January 1, 2019, are as follows:

- C9752: Destruction of intraosseous BVN, first 2 vertebral bodies, including imaging guidance (eg, fluoroscopy), lumbar/sacrum,
- C9753: Destruction of intraosseous BVN, each additional vertebral body, including imaging guidance (eg, fluoroscopy), lumbar/sacrum (list separately in addition to code for primary procedure.

CONCLUSIONS

Intraosseous ablation of the BVN is a relatively new minimally invasive treatment for the relief of CLBP that is diagnosed using well-established clinical and MRI findings. The procedure is supported by level 1 evidence including 2 RCTs demonstrating a statistically significant decrease in pain and an improvement in function with outcomes sustained to at least 24 months in a limited number of studies. These results were seen in a patient population that is one of the most expensive and difficult to provide care for, and in this era of rising health care costs and increasing need for therapies to reduce the use of opioids, BVN ablation may provide a treatment option to fill the gap in the treatment paradigm for patients that fail nonsurgical treatment.

LIMITATIONS

(1) Industry funding is a potential source of study bias for the available data reviewed.
(2) Limited number of studies.
(3) Short-term follow up for the majority of studied patients.
(4) Unknown effect on the primary degenerative process.

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OC: None.

DB:

- Medtronic—Advisory Board, Consultant, Research Funding
- Spineology—Consultant, Stock Owner
- Merit Medical—Consultant
- Lilly—Consultant
- Johnson & Johnson—Consultant
- SpinTech—Consultant, Board Member, Research Funding
- Nocimed—Board Member
- Artio—Stockholder
- Flow Forward—Stockholder
- Imaging3—Adviser, Consultant, Stockholder
- IZI—Consultant
- Medlantis—Consultant
- Techlamed—Consultant
- Sway Inc—Stockholder
- Boston Scientific—Consultant, Speaker, Research Funding
- Peterson Enterprises—Consultant
- Nanofuse—Consultant, Advisory Board
- Medical Metrics—Consultant, Research Funding
- Radius Pharmaceuticals—Consultant, Speaker, Stockholder
- Avanos—Consultant, Speaker, Research Funding
- Relievant—Research Funding
- Stryker—Speaker, Research Funding
- Sollis Pharmaceuticals—Research Funding, Consultant
- Simplify Medical—Consultant, Research Funding
- Eleven Biotherapeutics—Stockholder
- Sophiris Bio—Stockholder
- Lenoss Medical—Consultant, Research Funding, Stockholder
- Spine BioPharma—Consultant, Research Funding, Stockholder
- Piramal—Consultant, Speaker
- ReGelTec—Consultant, Advisory Board

TJ:

- Medtronic—Consulting

- Stryker Spine—Consulting
- Stryker Navigation—Consulting
- Camber Spine/IMSE—Consulting
- Aurora Spine—Consulting, Stock options
- Ulrich—Consulting, Surgeon's Advisory Board
- RTI Surgical—Consulting, Surgeon's Advisory board
- Spinal Elements—Consulting
- Bio Ventus Surgical—Consulting
- CoreLink—Consulting
- NovaBone—Consulting

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2022 CPT Code Review
Drug-Eluting Lacrimal Canaliculus Stents

Code: **68841** Insertion of drug-eluting implant, including punctal dilation when performed, into lacrimal canaliculus, each

Similar codes: Previously coded with CPT level III code 0356T

Description: This code is for use for Ocular Therapeutix's Dextenza, with is an FDA approved device for the treatment of ocular inflammation and pain following ophthalmic surgery, such as cataract or glaucoma surgery. DEXTENZA is a corticosteroid intracanalicular insert placed in the punctum, a natural opening in the inner portion of the lower eyelid, and into the canaliculus and is designed to deliver dexamethasone to the ocular surface for up to 30 days without preservatives. DEXTENZA resorbs and exits the nasolacrimal system without the need for removal.

Similar devices are being investigated for delivery of other drugs to the ocular system, such as OTX-TP, which delivers travoprost, a corticosteroid.

Evidence:

1) **Ittoop 2019**, review of novel glaucoma devices
    a. OTX-TP (Ocular Therapeutix, Bedford, MA, USA) is a rod-shaped, punctal plug made from a polyethylene glycol hydrogel, which is embedded with microspheres that contain an encapsulated formula of travoprost. The device is placed vertically into the superior or inferior canaliculus. As the tear film fills the canaliculus, the medication is slowly released by hydrolysis of the microspheres
        i. Two studies: 17 patient feasibility study and 73 patient phase II study.
        ii. OcularTherapeutix appears to be actively enrolling patients in a phase III clinical trial
2) **Tyson 2019,** phase 3 study of sustained-release intracanalicular dexamethasone insert for treatment of ocular inflammation and pain after cataract surgery
    a. N=438 patients (216 drug eluting insert, 222 placebo insert)
    b. Study sponsored by Ocular Therapeutix
    c. At Day 14, significantly more patients had an absence of anterior chamber cells in the dexamethasone insert arm compared with the placebo arm (52.3% versus 31.1%; P< .0001). At Day 8, significantly more patients had an absence of ocular pain in the dexamethasone insert arm compared with placebo (79.6% versus 61.3%; P < .0001). The dexamethasone insert arm showed no increase compared with placebo in incidence of all adverse events or ocular adverse events. Twice as many placebo patients required rescue therapy, compared with treated patients at Day 14.
    d. The most common ocular adverse events reported in the study eye were eye inflammation, increase in IOP, and anterior chamber inflammation in the dexamethasone insert arm. In the placebo arm, the most common ocular adverse events reported were eye inflammation, increase in IOP, anterior chamber inflammation, worsened corrected distance visual acuity, and cystoid macular edema
    e. In conclusion, the efficacy and safety data presented in this study demonstrate that the sustained-release dexamethasone intracanalicular insert provides a statistically significant sustained reduction in inflammation after cataract surgery and statistically significant sustained reduction in ocular pain starting in the first few days after cataract

surgery and continuing for a month after surgery, while maintaining a favorable safety profile.

Other payer policies:

1) Cigna 2021: EACH of the following devices is considered experimental, investigational or unproven for any indication:
    a. drug-eluting ocular devices (CPT Codes® 0356T, 0444T, 0445T)
2) Aetna 2021: Aetna considers insertion of a drug-eluting implant, including punctal dilation and implant removal when performed, into the lacrimal canaliculus experimental and investigational for the treatment of glaucoma or ocular hypertension because its effectiveness has not been established.

HERC staff summary

Drug eluting stents for the lacrimal canaliculus are being actively studied as a method to delivery medications after cataract and other eye surgery. The evidence to date is very limited and no private payer surveyed is covering this procedure.

HERC staff recommendation:

1) Place CPT 68841 on line 662/GN 173

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
68841	Insertion of drug-eluting implant, including punctal dilation when performed, into lacrimal canaliculus, each	Insufficient evidence of effectiveness	November 2021

Current opinion in ophthalmology: novel glaucoma devices in the pipeline

Sabita M. Ittoop[a], *Leonard K. Seibold*[b], *and Malik Y. Kahook*[b]

Purpose of review
Adherence to chronic use of topical intraocular pressure (IOP) lowering medications is a fundamental barrier to successful, long-term control in patients suffering from glaucoma. This has fueled innovation to create new vehicles for drug administration, new drug formulations with enhanced bioavailability, and minimally invasive glaucoma surgeries (MIGS) with improved risk–benefit profiles to enhance sustained IOP control. The present article is an overview of novel devices in the pipeline.

Recent findings
Several new devices that promise to deliver sustained drug therapy and reduce dependence on daily patient adherence are currently being vetted through clinical trials. In addition, the pipeline for new MIGS devices that target sustained IOP control continues to grow.

Summary
Alternative drug delivery approaches and novel MIGS devices broaden the treatment options for patients with glaucoma. This will allow the clinician to customize treatment by selecting specific approaches based on each patient's individual needs and coexisting ocular pathologies. Additional comprehensive, large-scale, clinical studies will help define the role that these options hold in a constantly evolving treatment paradigm.

Keywords
bimatoprost SR, hydrus microshunt, iStent Inject, minimally invasive glaucoma surgeries, punctal plugs, sustained-release drug delivery

INTRODUCTION

Glaucomatous optic neuropathy is a chronic, progressive disease that causes permanent vision loss. It is a leading cause of preventable, worldwide blindness and the focal point of treatment is to reduce intraocular pressure (IOP), which is the only known modifiable risk factor [1]. The principle treatment for this disease is chronic use of topical medications, however medication side effects and obstacles to adherence are significant and can lead to disease progression [2–4].

There is an unmet need to reduce the burden of daily adherence to topical glaucoma medications. This has fueled innovation to create new vehicles for drug administration, new drug formulations with enhanced bioavailability, and minimally invasive glaucoma surgeries (MIGS) with improved risk–benefit profiles to improve sustained IOP control. The present article is an overview of novel devices that are currently in clinical trials.

NOVEL DEVICES FOR SUSTAINED RELEASE MEDICATION DELIVERY

Bimatoprost SR

Bimatoprost SR (Allergan, Dublin, Ireland) is a reconstituted formula of the prostaglandin analog (PGA) bimatoprost using a biodegradable NOVADUR platform, which consists of a polylactic-co-glycolic acid copolymer matrix that contains the drug (Fig. 1). The implant is injected intracamerally and allows for a slow, extended-release of the medication [5].

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ARTICLE

Multicenter randomized phase 3 study of a sustained-release intracanalicular dexamethasone insert for treatment of ocular inflammation and pain after cataract surgery

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Purpose: To assess the efficacy and safety of a sustained-release intracanalicular dexamethasone insert for the treatment of postoperative ocular inflammation and pain in patients having cataract surgery.

Setting: Twenty-one United States sites.

Design: Prospective multicenter randomized parallel-arm double-masked vehicle-controlled phase 3 study.

Methods: Patients with planned clear corneal cataract surgery were randomized (1:1) to receive dexamethasone insert or placebo, and the treatment was placed in the canaliculus of the eye immediately after surgery (Day 1). The primary efficacy endpoints were complete absence of anterior chamber cells at Day 14 and complete absence of pain at Day 8.

Results: The study comprised 438 adult patients (216 in the treatment arm and 222 in the placebo arm). At Day 14, significantly more patients had an absence of anterior chamber cells in the dexamethasone insert arm compared with placebo (52.3% versus 31.1%; $P < .0001$). At Day 8, significantly more patients had an absence of ocular pain in the dexamethasone insert arm compared with placebo (79.6% versus 61.3%; $P < .0001$). The dexamethasone insert arm showed no increase compared with placebo in incidence of all adverse events or ocular adverse events. Twice as many placebo patients required rescue therapy, compared with treated patients at Day 14.

Conclusions: Both primary endpoints were successfully met. In addition, patients receiving the dexamethasone insert experienced a decrease in inflammation after surgery as early as Day 4 through Day 45, and a decrease in pain as early as one day after surgery (Day 2) through Day 45. The dexamethasone insert was well-tolerated, and the adverse events profile was similar to placebo.

J Cataract Refract Surg 2019; 45:204–212

Corticosteroids are routinely prescribed for the postoperative management of inflammation and pain related to cataract surgery as part of a prophylactic perioperative regimen in conjunction with a nonsteroidal antiinflammatory drop. Persistent ocular inflammation can increase the risk for secondary ocular complications,

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From the Eye Associates of Vineland (Tyson), Vineland, New Jersey, Cleveland Eye Clinic (Bafna), Brecksville, Ohio, Ophthalmology Consultants (Gira), St. Louis, Missouri, Wolstan & Goldberg Eye Associates (Goldberg), Torrance, California, Jones Eye Clinic (J. Jones), Sioux City, Iowa, Quantum Vision Centers (M. Jones), Belleville, Illinois, Hull Eye Center (Kim), Lancaster, California, Martel Eye Medical Group (Martel), Rancho Cordova, California, Cincinnati Eye Institute (Nordlund), Cincinnati, Ohio, Centro Oftalmico Metropolitano (Piovanetti-Perez), San Juan, Puerto Rico, Eye Centers of Racine & Kenosha (Singh), Racine, Wisconsin, and Ocular Therapeutix, Inc. (Metzinger, Mulani, Sane, Talamo, Goldstein), Bedford, Massachusetts, USA.

Presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Baltimore, Maryland, May 2017 and the ASCRS Symposium on Cataract, IOL and Refractive Surgery, Los Angeles, California, May 2017.

The members of the Dextenza Study Group are Louis Alpern, MD, Y. Ralph Chu, MD, Neel Desai, MD, Alice Epitropoulos, MD, John F. Kozlovsky, MD, Mark Lesher, MD, Ranjan P. Malhotra, MD, Newton T. Peters, MD, Francis W. Price, Jr., MD, Tariq Qamar, MD, Steven M. Silverstein, MD, Navin H. Tekwani, MD, David T. Vroman, MD.

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2022 Biennial Review
Trabecular bone score

Codes:

1) **77089**: Trabecular bone score (TBS), structural condition of the bone microarchitecture; using dual X-ray absorptiometry (DXA) or other imaging data on gray-scale variogram, calculation, with interpretation and report on fracture-risk
2) **77090:** Trabecular bone score (TBS), structural condition of the bone microarchitecture; technical preparation and transmission of data for analysis to be performed elsewhere
3) **77091**: Trabecular bone score (TBS), structural condition of the bone microarchitecture; technical calculation only
4) **77092**: Trabecular bone score (TBS), structural condition of the bone microarchitecture; interpretation and report on fracture-risk only by other qualified health care professional

Similar codes: DEXA scans (CPT 77080-77081) are the standard test for bone density and are on the DIAGNOSTIC PROCEDURES file

Description: Bone strength is determined by bone mineral density (BMD) and non-BMD skeletal properties, such as bone geometry, mineralization, microdamage, remodeling, and microarchitecture. Trabecular bone score is a textural index that evaluates pixel gray level variations in the lumbar spine (LS) image by dual-energy X-ray absorptiometry (DXA). It provides an indirect assessment of trabecular microarchitecture that is an independent predictor of fracture risk. TBS is included as a risk factor with the fracture risk tool, FRAX, and may influence treatment decisions by altering the estimated 10-yr fracture probability. TBS has been cleared by the US Food and Drug Administration for use as a complement to DXA analysis and clinical examination for assessment of fracture risk and monitoring the effects of therapy

Evidence:

1) **Rajan 2020:** review of trabecular bone score
    a. TBS is associated with incident vertebral, hip and major osteoporotic fractures in postmenopausal women and in men greater than 50 years of age. TBS may be used to adjust FRAX probabilities of fracture, though data available till date doesn't support any additional benefit.

   b. Though TBS predicts fracture risk independently in both genders, with the currently available data, it cannot be recommended as a standalone tool for decision regarding treatment of osteoporosis. TBS can be used as a tool to complement BMD in assessment of bone health. Additional studies are needed to assess its utility in clinical practice.

2) **Viswanathan 2018**: Screening to Prevent Osteoporotic Fractures: An Evidence Review for the U.S. Preventive Services Task Force
   a. Accuracy of Bone Measurement Tests Used to Predict Fracture:
      i. The AUCs of machine-based tests, including centrally measured DXA (areal bone mineral density and trabecular bone score) and calcaneal quantitative ultrasound, for predicting fractures ranged from 0.59 to 0.86 (21 studies).
      ii. Regarding type of bone test, AUC estimates for fracture prediction based on centrally measured DXA BMD, trabecular bone score, or a combination of both were as follows: any osteoporotic fracture (0.63 to 0.74), vertebral or spine fracture (0.61 to 0.75), and hip (0.64 to 0.85). The AUC estimate of hip fracture based on DXL was 0.61.
   b. Other Measures of Test Performance:
      i. One study evaluated reclassification arising from adding trabecular bone score to spine BMD in a sample of 665 Japanese women age 50 years or older who completed the baseline study and at least one followup survey over 10 years. The study reported no significant differences in AUC, but reported an NRI of 0.235 (95% CI, 0.15 to 0.54); no risk categories were specified for the NRI. This finding can potentially be explained by chance (given the small sample size) or miscalibration.

<u>Expert guidelines</u>:

1) **USPSTF 2016** screening for osteoporosis
   a. Among different bone measurement tests performed at various anatomical sites, bone density measured at the femoral neck by dualenergy x-ray absorptiometry (DXA) is the best predictor of hip fracture and is comparable to forearm measurements for predicting fractures at other sites. Other technologies for measuring peripheral sites include quantitative ultrasonography (QUS), radiographic absorptiometry, single energy x-ray absorptiometry, peripheral dual-energy x-ray absorptiometry, and peripheral quantitative computed tomography
   b. Trabecular bone score is not mentioned

2) Krohn 2019, International Society of Clinical Densitometry official position on trabecular bone score
   a. TBS should not be used alone to determine treatment recommendations in clinical practice.
   b. TBS can be used in association with FRAX and BMD to adjust FRAX-probability of fracture in postmenopausal women and older men.
   c. TBS is not useful for monitoring bisphosphonate treatment in postmenopausal women with osteoporosis.
   d. TBS is potentially useful for monitoring anabolic therapy.
   a. TBS is associated with major osteoporotic fracture risk in postmenopausal women with type II diabetes

2022 Biennial Review
Trabecular bone score

Other payer policies:

1) **Aetna 2021**
    a. Aetna considers tomosynthesis-based trabecular bone analysis for determination of bone strength in person with diabetes mellitus experimental and investigational because the effectiveness of this approach has not been established.
2) **Cigna 2021**
    a. Trabecular bone score not listed as a covered test of osteoporosis screening

Expert input

Dr. Eric Orwoll, osteoporosis expert at OHSU

I think you should give serious consideration to covering it, at least in certain situations.

From the Kennel article: "Although derived from standard DXA images, the information procured from TBS is independent from and is complementary to the information provided by both BMD assessment and the World Health Organization (WHO) Fracture Risk Assessment (FRAX) algorithm. Further, the incorporation of TBS into the FRAX algorithm generates TBS-adjusted fracture risks that have been shown to be more accurate than use of the standard FRAX tool alone. This is of significant clinical value in high risk populations in whom there has been shown to be discrepancy between the estimated risk of fracture as assessed by FRAX/BMD and the observed fracture incidence, such as occurs in patients with type 2 diabetes mellitus or chronic kidney disease."

Of course the USPSTF won't be easily ready to endorse it since they are extremely conservative and usually quite behind clinical practice

2022 Biennial Review
Trabecular bone score

HERC staff summary

Trabecular bone score has been used to screen for osteoporosis, but its use in clinical care has not yet been determined. Private payers with identified policies do not appear to be covering this test.

HERC staff recommendation:

1) Add the following CPT codes to line 662 and add an entry to GN173 as shown below
    a. **77089**: Trabecular bone score (TBS), structural condition of the bone microarchitecture; using dual X-ray absorptiometry (DXA) or other imaging data on gray-scale variogram, calculation, with interpretation and report on fracture-risk
    b. **77090:** Trabecular bone score (TBS), structural condition of the bone microarchitecture; technical preparation and transmission of data for analysis to be performed elsewhere
    c. **77091**: Trabecular bone score (TBS), structural condition of the bone microarchitecture; technical calculation only
    d. **77092**: Trabecular bone score (TBS), structural condition of the bone microarchitecture; interpretation and report on fracture-risk only by other qualified health care professional

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
77089-77092	Trabecular bone score	Insufficient evidence of effectiveness	November 2021

Review Article

Trabecular Bone Score—An Emerging Tool in the Management of Osteoporosis

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Abstract

Areal bone mineral density (aBMD) is currently the gold standard for the diagnosis of osteoporosis, however, it has its own pitfalls. Trabecular bone score (TBS), a novel tool in the evaluation of osteoporosis is an indirect indicator of bone microarchitecture. It is a textural index that evaluates pixel gray-level variations in the lumbar spine DXA (dual energy X-ray absorptiometry) image. Both cross-sectional and longitudinal studies have demonstrated that TBS may independently predict fragility fractures. TBS can also be used to adjust FRAX probabilities of fracture, though data available till date doesn't support any additional benefit. TBS also shows an improving trend with anti-osteoporotic treatment; however, the least significant change (LSC) is high that it takes more than 2 years for the change to manifest. TBS is also used in the evaluation of bone strength in cases of secondary osteoporosis. Though TBS predicts fracture risk independently in both genders, with the currently available data, it cannot be recommended as a standalone tool for decision regarding treatment of osteoporosis. TBS can be used as a tool to complement BMD in assessment of bone health. Additional studies are needed to assess its utility in clinical practice.

Keywords: Bone microarchitecture, fragility fracture, osteoporosis, trabecular bone score

Introduction

Osteoporosis, which is reported to occur in about 25–60% of Indian postmenopausal women, is a common, yet under recognized public health problem.[1,2] The lifetime risk of osteoporotic fracture is around 40–50% in women and the mortality rate following fragility fractures is as high as 25% in the first year.[3]

Osteoporosis is a disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk.[4] Thus the definition itself brings forth the concept that not only bone mass, but also microarchitectural quality is an important determinant of bone strength. However, areal bone mineral density (aBMD) assessment by DXA (dual energy X-ray absorptiometry) being the gold standard for non-invasive diagnosis of osteoporosis doesn't provide information on bone microarchitecture. Also, around 50% individuals with fragility fractures can have aBMD value in the osteopenic/normal range, which suggests that in addition to bone mass, there are other factors that determine bone strength.[5]

Microarchitecture of the bone can be measured by histomorphometric analysis of the transiliac crest bone biopsy, quantitative computed tomography (QCT), high-resolution peripheral QCT (HRpQCT), high-resolution magnetic resonance imaging (HRMRI), microcomputed tomography (mCT), and trabecular bone score (TBS). Among these, TBS appears to be a non-invasive, readily available technology that permits efficient and accurate clinical evaluation of skeletal microarchitecture.[6,7] Moreover, it has minimal radiation exposure and can be retrieved retrospectively through previously available lumbar spine aBMD images.[8]

A study on cadaveric vertebrae to determine the level of correlation between mCT and TBS showed a good correlation ($0.77 \leq r^2 \leq 0.96$).[9] In the study by Silva *et al*. TBS positively correlated with LS trabecular volumetric

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Screening for Osteoporosis in Postmenopausal Women

Recommendations and Rationale

U.S. Preventive Services Task Force

This statement summarizes the current U.S. Preventive Services Task Force (USPSTF) recommendations on screening for osteoporosis and the supporting scientific evidence, and it updates the 1996 recommendations contained in the *Guide to Clinical Preventive Services*, second edition.[1] Explanations of the ratings and of the strength of overall evidence are given in Appendix A and Appendix B, respectively. The complete information on which this statement is based, including evidence tables and references, is available in the article Screening for Osteoporosis: A Summary of the Evidence for the U.S. Preventive Services Task Force[2] (which follows this recommendation) and in the Systematic Evidence Review[3] on this topic. These documents can be obtained through the USPSTF Web site (www.preventiveservices.ahrq.gov), and through the National Guideline Clearinghouse (www.guideline.gov). The summary of the evidence and the recommendation statement are also available in print through the AHRQ Publications Clearinghouse (call 1-800-358-9295 or e-mail ahrqpubs@ahrq.gov).

This was first released on the AHRQ Web site on Septemeber 17, 2002, and an abridged version of this recommendation also appeared in *Ann Intern Med.* 2002;137(6):526-528.

Summary of Recommendations

- The U.S. Preventive Services Task Force (USPSTF) recommends that women aged 65 and older be screened routinely for osteoporosis. The USPSTF recommends that routine screening begin at age 60 for women at increased risk for osteoporotic fractures (*see* "*Clinical Considerations" for discussion of women at increased risk*). **B recommendation.**

The USPSTF found good evidence that the risk for osteoporosis and fracture increases with age and other factors, that bone density measurements accurately predict the risk for fractures in the short term, and that treating asymptomatic women with osteoporosis reduces their risk for fracture. The USPSTF concludes that the benefits of screening and treatment are of at least moderate magnitude for women at increased risk by virtue of age or presence of other risk factors.

- The USPSTF makes no recommendation for or against routine osteoporosis screening in postmenopausal women who are younger than 60 or in women aged 60-64 who are not at increased risk for osteoporotic fractures. **C recommendation.**

The USPSTF found fair evidence that screening women at lower risk for osteoporosis or fracture can identify additional women who may be eligible for treatment for osteoporosis, but it would prevent a small number of fractures. The USPSTF concludes that the balance of benefits and harms of screening and treatment is too close to make a general recommendation for this age group.

Clinical Considerations

- Modeling analysis suggests that the absolute benefits of screening for osteoporosis among women aged 60-64 who are at increased risk for osteoporosis and fracture are comparable to those

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of routine screening in older women. The exact risk factors that should trigger screening in this age group are difficult to specify based on evidence. Lower body weight (weight < 70 kg) is the single best predictor of low bone mineral density.[4,5] Low weight and no current use of estrogen therapy are incorporated with age into the 3-item Osteoporosis Risk Assessment Instrument (ORAI).[4,5] There is less evidence to support the use of other individual risk factors (for example, smoking, weight loss, family history, decreased physical activity, alcohol or caffeine use, or low calcium and vitamin D intake) as a basis for identifying high-risk women younger than 65. At any given age, African American women on average have higher bone mineral density (BMD) than white women and are thus less likely to benefit from screening. Additional characteristics of screening tools are discussed in the "Accuracy and Reliability of Screening Tests" section below.

- Among different bone measurement tests performed at various anatomical sites, bone density measured at the femoral neck by dual-energy x-ray absorptiometry (DXA) is the best predictor of hip fracture and is comparable to forearm measurements for predicting fractures at other sites. Other technologies for measuring peripheral sites include quantitative ultrasonography (QUS), radiographic absorptiometry, single energy x-ray absorptiometry, peripheral dual-energy x-ray absorptiometry, and peripheral quantitative computed tomography. Recent data suggest that peripheral bone density testing in the primary care setting can also identify postmenopausal women who have a higher risk for fracture over the short term (1 year). Further research is needed to determine the accuracy of peripheral bone density testing in comparison with dual-energy x-ray absorptiometry (DXA). The likelihood of being diagnosed with osteoporosis varies greatly depending on the site and type of bone measurement test, the number of sites tested, the brand of densitometer used, and the relevance of the reference range.
- Estimates of the benefits of detecting and treating osteoporosis are based largely on studies of bisphosphonates. Some women, however, may prefer other treatment options (for example, hormone replacement therapy, selective estrogen receptor modulators, or calcitonin) based on personal preferences or risk factors. Clinicians should review with patients the relative benefits and harms of available treatment options, and uncertainties about their efficacy and safety, to facilitate an informed choice.
- No studies have evaluated the optimal intervals for repeated screening. Because of limitations in the precision of testing, a minimum of 2 years may be needed to reliably measure a change in bone mineral density; however, longer intervals may be adequate for repeated screening to identify new cases of osteoporosis. Yield of repeated screening will be higher in older women, those with lower BMD at baseline, and those with other risk factors for fracture.
- There are no data to determine the appropriate age to stop screening and few data on osteoporosis treatment in women older than 85. Patients who receive a diagnosis of osteoporosis fall outside the context of screening but may require additional testing for diagnostic purposes or to monitor response to treatment.

Scientific Evidence

Epidemiology and Clinical Consequences

One-half of all postmenopausal women will have an osteoporosis-related fracture during their lives, including 25% who will develop a vertebral deformity[6] and 15% who will suffer a hip fracture.[7] Risk for fracture increases steadily as bone density declines, with no threshold. The commonly used definition of osteoporosis, derived from the World Health Organization (WHO) recommendations for epidemiologic studies, defines a BMD more than 2.5 standard deviations (SD) below the mean for a young healthy adult woman as osteoporosis, and a BMD between 1 and 2.5 SD below the mean as

osteopenia. Based on the WHO criteria and DXA measurements at the femoral neck, population-based studies estimate that 41% of white women older than 50 have osteopenia.[8] When bone density is measured at the hip, spine, and wrist, 15% of white women aged 50-59 and 70% of white women older than 80 have osteoporosis by WHO criteria at at least one site.[9]

The prevalence of osteoporosis in Mexican American women is similar to the prevalence in white women. While rates of osteoporosis in African American women are approximately one-half those of the other groups, they are still substantial (8% among women older than 50). Including all races, an estimated 14 million women older than 50 have osteopenia, and over 5 million have osteoporosis.[10] The actuarial risk of a 65-year-old white woman sustaining a fracture by age 90 is 16% for the hip, 9% for distal forearm, and 5% for proximal humerus.[9] Sixteen percent of postmenopausal women have osteoporosis of the lumbar spine.[11]

Accuracy and Reliability of Screening Tests

The USPSTF examined 2 components of screening: the accuracy of risk factors or risk assessment instruments for identifying women at risk for osteoporosis or fracture; and the accuracy of different bone density measurement techniques for identifying women at risk for fracture who can benefit from osteoporosis treatment.

Predicting Risk for Osteoporosis or Fracture

The USPSTF evaluated both individual risk factors and prescreening assessment tools that incorporate two or more of the risk factors. Risk for osteoporosis increases steadily and substantially with age. Relative to women aged 50-54, the odds of having osteoporosis were 5.9-fold higher in women aged 65-69 and 14.3-fold higher in women aged 75-79, in a study of over 200,000 postmenopausal women.[12] Low body weight or body-mass index (BMI) and not using estrogen replacement were also consistently associated with osteoporosis but to a lesser degree than age. Other risk factors for fracture or low bone density found in some, but not all, studies include white or Asian ethnicity, history of fracture, family history of osteoporotic fracture, history of falls, low levels of physical activity, smoking, excessive alcohol or caffeine use, low calcium or vitamin D intake, and the use of various medications.

Specific instruments to assess risk for low bone density or fractures generally have moderate-to-high sensitivity and low specificity. The best validated instruments include the 3-item ORAI and the 6-item Simple Calculated Osteoporosis Risk Estimation tool (SCORE). The ORAI uses age, weight, and current use of hormone replacement therapy to identify women at risk for osteoporosis and has a sensitivity of 94% and specificity of 41%.[4] The SCORE has a sensitivity of 91% and specificity of 40% in one validation population (n = 259), but it has much lower specificity in an older population.[11]

Among 8 studies of prediction instruments for fracture risk, most had only modest sensitivity and specificity. The best performing model for hip fracture outcomes included age, gender, height, use of a walking aid, current smoking, and weight and had a sensitivity of 70% with specificity of 84%.[13]

Measurements of Bone Density

To date, bone density measured at the femoral neck by DXA is the best predictor of hip fracture and is comparable to forearm measurements for predicting fractures at other sites. Recent prospective studies have evaluated QUS measurements at the heel.[14, 15] While QUS measurements are not highly correlated with DXA measurements, a result in the osteoporotic range on either test is associated with an increased short-term probability of hip fracture. Several other radiologic methods that measure bone density at peripheral sites[2] (including sites in the hand, heel, wrist, and forearm) include single photon absorptiometry, quantitative computed tomography, single-energy x-ray absorptiometry, and peripheral quantitative computed tomography. In a study of over 200,000 women in a primary care setting, women diagnosed with osteoporosis by peripheral bone density measurements were 4 times more likely to have

fractures than women with normal bone density over the subsequent year. The likelihood of being diagnosed with osteoporosis varies greatly depending on the site and type of bone measurement test, the number of sites tested, the brand of densitometer, and the relevance of the reference range.

Effectiveness of Early Treatment

No controlled studies have evaluated the effect of screening on fractures or fracture-related morbidity. The Task Force reviewed the evidence to determine whether treatment for osteoporosis or low bone density in asymptomatic patients reduced fractures.

Available trials that reported fracture outcomes have examined the efficacy of bisphosphonates (alendronate and risendronate), estrogen, and selective estrogen receptor modulators (raloxifene) and calcitonin. A meta-analysis[16] of 11 randomized trials[17-27] involving a total of 12,855 women, found that alendronate significantly reduced vertebral fractures (RR, 0.52; 95% CI, 0.43-0.65), forearm fractures (RR, 0.48; 0.29-0.78), hip fractures (RR, 0.63; 0.43-0.92), and other nonvertebral fractures (RR, 0.51; 0.38-0.69). There were non-significant trends toward reduction in hip fractures. No randomized trial of treatment for osteoporosis has demonstrated an impact on mortality. One trial in women aged 70-79 with very low bone density (T-score less than -3) reported that risendronate reduced the risk for hip fracture (RR, 0.60; 95% CI, 0.40-0.90).[28]

There are no direct comparisons of alendronate and estrogen or raloxifene that report fracture outcomes. Estrogen, either alone or with progestin, consistently improves bone density in randomized trials. The effects of estrogen and the selective estrogen receptor modulators on fractures are reviewed in more detail in a separate report.[13] Only a few small randomized clinical trials of estrogen indicate mixed results for fracture outcomes, but these studies are methodologically limited. Observational studies report a 25% to 30% reduction in the risk for hip fracture with estrogen use. A good-quality study of raloxifene reported a reduced risk for vertebral fractures (RR, 0.59; 95% CI, 0.50-0.70).[29]

The benefits of treating osteoporosis are larger in women at higher risk for fracture than in women at lower risk. The Fracture Intervention Trial (FIT) was conducted with 2 different groups of participants: 2,027 high-risk women who had T-scores of -1.6 or lower and pre-existing vertebral fractures, and 4,432 women with comparable T-scores but no pre-existing vertebral fracture. Over 3 years of treatment in high-risk women, alendronate reduced the risk for hip fracture (1.1% vs. 2.2 % in the placebo group; relative hazard [RH], 0.49 [0.23-.099]) and the risk for any clinical fracture (18.2% vs. 13.6%; RH 0.72 [0.58-0.90]). Among women with no pre-existing fracture, only the subgroup of patients who had a T-score less than -2.5 had a significant reduction in all clinical fractures from treatment, from 19.6% to 13.1% (RR, 0.64; 0.50-0.82). Alendronate had no effect on fractures among lower risk women who had T-scores between -1.6 and -2.5. These results suggest that treatment will produce larger benefits in women with more risk factors for fracture, such as those who are older, have very low bone density, or have pre-existing vertebral fractures. FIT, as well as other therapy trials, enrolled highly selected patients thus limiting the generalizability of their results to asymptomatic women detected in a typical primary care setting.

There is little evidence regarding which patients are likely to benefit from screening and treatment. It is not known whether women who have a similar overall risk for fracture, but different bone densities, will benefit similarly from treatment. This uncertainty is clinically important because the lack of accepted criteria for initiating treatment remains a problem.

To estimate the benefits of routine screening for women in different age groups, the USPSTF used estimates from recent studies to project the number of fractures that would be prevented over 5 years from screening and treatment of a hypothetical cohort of 10,000 postmenopausal women.[2] For women aged 55-59, more than 4,000 would need to be screened to prevent 1 hip fracture and more than 1,300 to prevent 1 vertebral fracture. For women older than 60, the number needed to screen to prevent 1 hip fracture is 1,856 for women aged 60-64, 731 for women aged 65-69, and 143 for women

aged 75-79. The benefits of screening improve substantially in older women because osteoporosis is both more prevalent and more likely to lead to a fracture in older women.

In all age groups, the number needed to screen to prevent fractures is lower in women with important risk factors than it is in women who do not have risk factors. For women aged 60-64 who have a risk factor that increases the risk of osteoporosis by 100% and fracture by 70%, the number needed to screen is 1,092 and the number need to treat is 72 to prevent 1 hip fracture. These numbers are comparable to those of women aged 65-69 without risk factors.[2] These estimates rely on many assumptions that may not apply for specific populations.

Potential Adverse Effects of Screening and Treatment

There are several potential harms of screening, although the empirical data for them are few. Women who undergo screening with bone density tests are more likely to begin hormone replacement therapy than women who do not. However, women who were diagnosed with osteoporosis after screening reported increased fears and anxiety in one study. Other potential harms may arise from inaccuracies and misinterpretations of bone density tests. Clinicians may have difficulty in using test results to provide accurate information to the patients because techniques used to measure bone density vary, test results are reported as T-scores, and information on how to integrate bone density results with other clinical predictors has not been clearly defined.[2]

In the alendronate treatment trials, gastrointestinal side effects occurred in about 25% of patients taking alendronate, but this was usually not higher (or only slightly higher) than the rate for placebo. Higher rates were observed among Medicare enrollees taking alendronate. In the FIT-II trial, the rates of ulcer disease were higher in the alendronate treatment group, with 2.2 percent developing ulcer disease, as opposed to 1.2 percent in the placebo group ($P<0.05$).[30] The long-term adverse effects of alendronate are unknown. Harms of hormone replacement therapy include venous thromboembolic events, endometrial cancer, and cholecystitis, all with relative risks of approximately 2.0.[12] Both raloxifene and tamoxifen are associated with thromboembolic events, leg cramps, and hot flashes.[2]

Recommendations of Others

In 1998, the National Osteoporosis Foundation, in collaboration with other professional organizations, issued screening guidelines recommending bone density testing for all women aged 65 or older and younger postmenopausal women who have had a fracture or who have one or more risk factors for osteoporosis.[31] Collaborating groups included the American Academy of Orthopaedic Surgeons, the American College of Obstetricians and Gynecologists, the American Geriatrics Society, the American College of Radiology, the American College of Rheumatology, the American Academy of Physical Medicine and Rehabilitation, the American Association of Clinical Endocrinologists, the Endocrine Society, and the American Society of Bone and Mineral Research. The American Association of Clinical Endocrinologists released revised guidelines in 2001.[32] A 2000 Consensus Development Conference sponsored by the U.S. National Institutes of Health concluded that the value of universal osteoporosis screening was not yet established.[33] The conference panel recommended an individualized approach to screening, noting that bone density measurement is appropriate when it will aid the patient's decision to institute treatment. The Canadian Task Force on Preventive Health Care is currently revising its recommendations on screening for osteoporosis.

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Appendix A
U.S. Preventive Services Task Force - Recommendations and Ratings

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

A. The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B. The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*

C. The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*

D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

Appendix B
U.S. Preventive Services Task Force - Strength of Overall Evidence

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.Epidemiology

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Screening to Prevent Osteoporotic Fractures: An Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To review evidence about screening to prevent osteoporotic fractures for the U.S. Preventive Services Task Force (USPSTF).

Data Sources: PubMed, the Cochrane Library, Embase, and trial registries from November 1, 2009, through October 1, 2016, and surveillance of the literature through March 23, 2018; bibliographies from retrieved articles.

Study Selection: Two investigators independently selected studies using a priori inclusion and exclusion criteria. We selected studies with a majority of adults age 40 years or older conducted in countries with a very high human development index. For screening studies, we required that studies include a majority of participants without prevalent low-trauma fractures. For treatment studies, we required that studies include a majority of participants with increased fracture risk. We selected studies of screening tests (fracture risk prediction instruments, bone measurement testing, or a combination of fracture risk prediction instruments and bone measurement testing) that were feasible for primary care settings and available in the United States. We selected studies of treatment approved by the U.S. Food and Drug Administration for synthesis of benefits and harms. We excluded studies of poor quality and of fracture risk prediction instruments without external validation.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality for included studies using predefined criteria.

Data Synthesis: One fair-quality trial demonstrated reduction in hip fractures when comparing screening with no screening (2.6% v 3.5%, Hazard rate [HR] 0.72; 95% confidence interval [CI], 0.59 to 0.89). The study reported no other statistically significant benefits (osteoporotic or clinical fractures, mortality) or harms (anxiety, quality of life). We included 168 articles of fair or good quality; 105 articles assessed screening accuracy and 65 articles assessed benefits and harms of treatment. Using centrally measured dual-energy X-ray absorptiometry (DXA) as the reference standard for identifying osteoporosis, the pooled estimate of accuracy as measured by the area under the curve (AUC) for clinical risk assessment instruments for women ranges from 0.65 to 0.76 and for men from 0.76 to 0.80. AUCs for the accuracy of calcaneal quantitative ultrasound in identifying central DXA–measured osteoporosis for women is 0.77 (95% CI, 0.72 to 0.82, 7 studies) and for men is 0.80 (95% CI, 0.67 to 0.94, 3 studies). The AUCs of machine-based tests, including centrally measured DXA (areal bone mineral density and trabecular bone score) and calcaneal quantitative ultrasound, for predicting fractures ranged from 0.59 to 0.86 (21 studies). The AUCs for instruments predicting fractures, some of which incorporate machine-based tests, have similar accuracy (pooled AUC range for the Fracture Risk Assessment Tool: 0.62 to 0.79; 24 studies). Available but limited evidence in studies including participants with a wide spectrum of baseline bone mineral density from normal to osteoporosis suggests no benefit from repeating a bone measurement test between 4 and 8 years after the initial screen. Evidence from placebo-controlled trials demonstrates the following benefits. For women, the risk of vertebral fractures can be reduced by bisphosphonates, parathyroid hormone, raloxifene, and denosumab by 36 percent to 68 percent. Relative risks (RRs) range from 0.32 (parathyroid hormone or denosumab) to 0.64 (raloxifene). The risk of nonvertebral fractures can

be reduced by 16 percent to 20 percent by bisphosphonates and denosumab (RR, 0.84 and 0.80, respectively). The risk of hip fractures can be reduced by 40 percent by denosumab (RR, 0.60). Evidence from bisphosphonates does not demonstrate benefit for hip fractures. Evidence is very limited for men. The risk of morphometric vertebral fractures can be reduced by 67 percent by zoledronic acid (RR, 0.33). No studies demonstrate reductions in risk of clinical vertebral fractures or hip fractures for men. Evidence on variations in effectiveness for subgroups is also limited; a single trial each for five drugs suggests no differences in effectiveness by age, baseline bone mineral density, prior fractures, or a combination of risk factors. Bisphosphonates are not consistently associated with discontinuations, serious adverse events, gastrointestinal events, or cardiovascular events. No included studies reported cases of osteonecrosis of the jaw or atypical femur fracture, although evidence from excluded studies (including active comparisons, case series, and secondary prevention populations) suggests an increased but rare risk of these outcomes. Raloxifene increases the risk of deep vein thrombosis (0.7% vs. 0.3%, RR, 2.14; 95% CI, 0.99 to 4.66; I^2=0%, 3 studies, N=5,839) and hot flashes (11.2% vs. 7.6%, RR, 1.42; 95% CI, 1.22 to 1.66; I^2=0%, 5 trials; N=6,249) when compared with placebo.

Limitations: The evidence is limited on the direct question of the benefits and harms of screening for elevated osteoporotic fracture risk. The indirect evidence pathway rests on studies evaluating (1) the accuracy of screening approaches in identifying osteoporosis and predicting fractures and (2) the benefits of treatment among those with osteoporosis or at high risk for fractures. Other limitations of the evidence base relate to underlying heterogeneity in baseline risk, prior fractures, prior treatment, and duration of followup.

Conclusions: Evidence from one trial of screening to prevent osteoporotic fractures suggests a reduction in hip fractures. The accuracy of clinical risk assessment tools for identifying osteoporosis or predicting fractures generally ranges from very poor (0.50) to good (0.90). Treatments reduce the risk of vertebral and nonvertebral fractures. Studies do not consistently demonstrate an increased risk of harms for drugs, although studies of raloxifene suggest a trend toward higher risk of deep vein thrombosis. Rare harms, such as osteonecrosis of the jaw and atypical femur fractures were not reported in this body of evidence but they may occur. The evidence is limited for subpopulations characterized by age, sex, baseline bone mineral density, and baseline fracture risk.

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2019 ISCD Official Position

Dual-energy X-ray Absorptiometry Monitoring with Trabecular Bone Score: 2019 ISCD Official Position

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Abstract

Trabecular bone score (TBS) is a textural index that evaluates pixel gray–level variations in the lumbar spine image by dual-energy X-ray absorptiometry. It provides an indirect assessment of trabecular microarchitecture that is an independent predictor of fracture risk. TBS does not appear to be clinically useful to monitor the skeletal effects of bisphosphonates and denosumab, but is potentially useful as a component of monitoring the skeletal effects of teriparatide and abaloparatide. The least significant change (LSC) for TBS can be conservatively estimated to be about 5.8% (the largest LSC in published data) or calculated by a dual-energy X-ray absorptiometry facility using the same methodology that is used for bone mineral density (BMD) precision assessment to calculate BMD LSC. A review of the best available evidence at the 2019 ISCD Position Development Conference concluded that the role of TBS in monitoring antiresorptive therapy is unclear and that TBS is potentially useful for monitoring anabolic therapy. For patients treated with teriparatide or abaloparatide, a statistically significant increase in TBS may represent a clinically meaningful improvement in trabecular structure. A significant decrease of TBS may represent a worsening of trabecular structure, suggesting the need for further clinical assessment and possible change in treatment strategies. Since BMD measures bone quantity and TBS measures bone quality, these tests can be considered complementary in assessing fracture risk and response to therapy in appropriate patients.

Key Words: Osteoporosis; TBS; monitor; DXA; fracture; treatment.

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Conflicts of interest: KK has served on scientific advisory boards or consulted for Radius and Alexion. He serves on the speaker's bureau for Radius and Alexion. He receives a retirement pension from Lilly USA.

Y-SC has received institutional grant from Maeil Daires; he has served on scientific advisory boards or consulted for Eli Lilly, Amgen, Samsung Bioepis, and Yuyu; he serves on the speakers' bureau for Pfizer, Hanmi, Handok, and Hanall; he is a board member of the Korea Women's Health and Osteoporosis Foundation.

ES has served on scientific advisory boards or consulted for Radius. He serves on the speaker's bureau for Radius.

EML has received no direct income from potentially conflicting entities. His employer, New Mexico Clinical Research & Osteoporosis Center, has received research grants from Radius, Amgen, Mereo, Bindex; income for service on scientific advisory boards or consulting for Amgen, Radius, Alexion, Sandoz, Samsung Bioepis; service on speakers' bureaus for Radius, Alexion; project development for University of New Mexico; and royalties from UpToDate for sections on DXA, fracture risk assessment, and prevention of osteoporosis. He is a board member of the National Osteoporosis Foundation, International Society for Clinical Densitometry, and Osteoporosis Foundation of New Mexico.

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2022 CPT Code Review
Genetics Related Codes

1) **81349**: Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
    a. Similar codes
        i. DIAGNOSTIC PROCEDURES file
            1. 81228: Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
            2. 81229: Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
            3. Note: entry in Diagnostic Guideline D1, NON-PRENATAL GENETIC TESTING GUIDELINE
                a. Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index <70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:
                    i. CPT 81228 and 81229, Cytogenomic constitutional microarray analysis: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies
            4. Note: entry in Diagnostic Guideline D17 PRENATAL GENETIC TESTING
                a. H) Array CGH (CPT 81228, 81229) when major fetal congenital anomalies are apparent on imaging, or with normal imaging when array CGH would replace karyotyping performed with CVS or amniocentesis in (G) above
        ii. On line 662/GN173
            1. 81277: Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
                a. Note: this is an oncology test on cancer tissue
            2. 81425-81427: Whole genome sequencing
    b. GAP input:
        i. 81228 (DMAP fee $630) and 81229 (DMAP fee $812) are performed using cytogenetic microarrays, to detect copy number variants (CNVs, deletions and duplications not detectable on karyotype),and loss of heterozygosity across the whole genome. Coverage for these services is currently addressed in GN D1 for

intellectual disabilities, and in D17 for use on fetal tissue from amniocentesis or chorionic villi, when fetal anomalies are seen on ultrasound. In practice, I have not seen a request for 81228 for a few years, it seems to have been entirely replaced by the higher resolution 81229 which can detect single nucleotide polymorphisms (SNPs). I guess this is because of advances in chip design and processing hardware and software. I suppose its okay to leave both codes in place, though one is seldom used. Thermo-Fisher is a major vendor in the microarray space. Early iterations of Next Generation Sequencing could not reliably detect CNVs, so a microarray was needed in addition, usually performed first and then sequencing if the microarray did not answer the clinical question. My impression is that now the bioinformatics have evolved to the point where CNVs can be detected in genome sequence data. My question about the new 81349 code is whether it represents CNV testing using microarray, like 81228 and 81229, or if it pulls CNV, loss of heterozygosity, etc off of NGS data

ii. Despite several staff attempts to get input from the OHSU genetics lab, no input was received.

a. <u>HERC staff recommendation</u>

iii. Place CPT 81349 on the DIAGNOSTIC PROCEDURES file

iv. Modify Diagnostic Guideline D1 as shown below (note other changes to this guideline as proposed in other issues at this meeting)

v. Modify Diagnostic Guideline D17 as shown below (note other changes to this guideline as proposed in other issues at this meeting)

DIAGNOSTIC GUIDELINE D1, NON-PRENATAL GENETIC TESTING GUIDELINE

A) Genetic tests are covered as diagnostic, unless they are listed below in section E1 as excluded or have other restrictions listed in this guideline. To be covered, initial screening (e.g. physical exam, medical history, family history, laboratory studies, imaging studies) must indicate that the chance of genetic abnormality is > 10% and results would do at least one of the following:
   1) Change treatment,
   2) Change health monitoring,
   3) Provide prognosis, or
   4) Provide information needed for genetic counseling for patient; or patient's parents, siblings, or children

B) Pretest and posttest genetic counseling is required for presymptomatic and predisposition genetic testing. Pretest and posttest genetic evaluation (which includes genetic counseling) is covered when provided by a suitable trained health professional with expertise and experience in genetics.
   1) "Suitably trained" is defined as board certified or active candidate status from the American Board of Medical Genetics, American Board of Genetic Counseling, or Genetic Nursing Credentialing Commission.

C) A more expensive genetic test (generally one with a wider scope or more detailed testing) is not covered if a cheaper (smaller scope) test is available and has, in this clinical context, a substantially similar sensitivity. For example, do not cover CFTR gene sequencing as the first test in a person of Northern European Caucasian ancestry because the gene panels are less expensive and provide substantially similar sensitivity in that context.

D) Related to diagnostic evaluation of individuals with intellectual disability (defined as a full scale or verbal IQ < 70 in an individual > age 5), developmental delay (defined as a cognitive index <70 on a standardized test appropriate for children < 5 years of age), Autism Spectrum Disorder, or multiple congenital anomalies:
   1) CPT 81228, ~~and~~ 81229 and 81349, Cytogenomic constitutional microarray analysis: Cover for diagnostic evaluation of individuals with intellectual disability/developmental delay; multiple congenital anomalies; or, Autism Spectrum Disorder accompanied by at least one of the following: dysmorphic features including macro or microcephaly, congenital anomalies, or intellectual disability/developmental delay in addition to those required to diagnose Autism Spectrum Disorder.
   2) CPT 81243, 81244, 81171,81172 Fragile X genetic testing is covered for individuals with intellectual disability/developmental delay. Although the yield of Fragile X is 3.5-10%, this is included because of additional reproductive implications.

E) A visit with the appropriate specialist (often genetics, developmental pediatrics, or child neurology), including physical exam, medical history, and family history is covered. Physical exam, medical history, and family history by the appropriate specialist, prior to any genetic testing is often the most cost-effective strategy and is encouraged. Related to other tests with specific CPT codes:
   1) Certain genetic tests have not been found to have proven clinical benefit. These tests are listed in Guideline Note 173, INTERVENTIONS THAT HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS; UNPROVEN INTERVENTIONS
   2) The following tests are covered only if they meet the criteria in section A above AND the specified situations:
      a) CPT 81205, BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X): Cover only when the newborn screening test is abnormal and serum amino acids are normal
      b) Diagnostic testing for cystic fibrosis (CF)
         i) CFTR, cystic fibrosis transmembrane conductance regulator tests. CPT 81220, 81221, 81222, 81223: For infants with a positive newborn screen for cystic fibrosis or who are symptomatic for cystic fibrosis, or for clients that have previously been diagnosed with cystic fibrosis but have not had genetic testing, CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220) is covered. If two mutations are not identified, CFTR full gene sequencing (CPT 81223) is covered. If two mutations are still not identified, duplication/deletion testing (CPT 81222) is covered. These tests may be ordered as reflex testing on the same specimen.
      c) Carrier testing for cystic fibrosis
         i) CFTR gene analysis of a panel containing at least the mutations recommended by the American College of Medical Genetics* (CPT 81220-81224) is covered once in a lifetime.
      d) CPT 81224, CFTR (cystic fibrosis transmembrane conductance regulator) (eg. cystic fibrosis) gene analysis; introm 8 poly-T analysis (eg. male infertility): Covered only after genetic counseling.

e) CPT 81225-81227, 81230-81231 (cytochrome P450). Covered only for determining eligibility for medication therapy if required or recommended in the FDA labelling for that medication. These tests have unproven clinical utility for decisions regarding medications when not required in the FDA labeling (e.g. psychiatric, anticoagulant, opioids).

f) CPT 81240. F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant: Factor 2 20210G>A testing should not be covered for adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

g) CPT 81241. F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant: Factor V Leiden testing should not be covered for: adults with idiopathic venous thromoboembolism; for asymptomatic family members of patients with venous thromboembolism and a Factor V Leiden or Prothrombin 20210G>A mutation; or for determining the etiology of recurrent fetal loss or placental abruption.

h) CPT 81247. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-) should only be covered
   i) After G6PD enzyme activity testing is done and found to be normal; AND either
      (a) There is an urgent clinical reason to know if a deficiency is present, e.g. in a case of acute hemolysis; OR
      (b) In situations where the enzyme activity could be unreliable, e.g. female carrier with extreme Lyonization.

i) CPT 81248. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s) is only covered when the information is required for genetic counseling.

j) CPT 81249. G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence is only covered
   i) after G6PD enzyme activity has been tested, and
   ii) the requirements under CPT 81247 above have been met, and
   iii) common variants (CPT 81247) have been tested for and not found.

k) CPT 81256, HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D): Covered for diagnostic testing of patients with elevated transferrin saturation or ferritin levels. Covered for predictive testing ONLY when a first degree family member has treatable iron overload from HFE.

l) CPT 81332, SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z): The alpha-1-antitrypsin protein level should be the first line test for a suspected diagnosis of AAT deficiency in symptomatic individuals with unexplained liver disease or obstructive lung disease that is not asthma or in a middle age individual with unexplained dyspnea. Genetic testing of the anpha-1 phenotype test is appropriate if the protein test is abnormal or borderline. The genetic test is appropriate for siblings of people with AAT deficiency regardless of the AAT protein test results.

m) CPT 81329, Screening for spinal muscular atrophy: is covered once in a lifetime for preconception testing or testing of the male partner of a pregnant female carrier

n) CPT 81415-81416, exome testing: A genetic counseling/geneticist consultation is required prior to ordering test
o) CPT 81430-81431, Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel: Testing for mutations in GJB2 and GJB6 need to be done first and be negative in non-syndromic patients prior to panel testing.
p) CPT 81440, 81460, 81465, mitochondrial genome testing: A genetic counseling/geneticist or metabolic consultation is required prior to ordering test.
q) CPT 81412 Ashkenazi Jewish carrier testing panel: panel testing is only covered when the panel would replace and would be similar or lower cost than individual gene testing including CF carrier testing.

* American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories. 2008 Edition, Revised 7/2018 and found at http://www.acmg.net/PDFLibrary/Cystic-Fibrosis-Population-Based-Carrier-Screening-Standards.pdf

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING
The following types of prenatal genetic testing and genetic counseling are covered for pregnant women:

A) Genetic counseling (CPT 96040, HPCPS S0265) for high-risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect.
B) Genetic counseling (CPT 96040, HPCPS S0265) prior to consideration of chorionic villus sampling (CVS), amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
C) Validated questionnaire to assess genetic risk in all pregnant women
D) Screening for hemoglobinopathies (CPT 83020, 83021)
E) Screening for aneuploidy with any of six screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, contingency, and cell free fetal DNA testing] (CPT 76813, 76814, 81508, 81510, 81511, 81420, 81507, 81512, 82105, 82677, 84163)
F) Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)
G) CVS or amniocentesis (CPT 59000, 59015, 76945,76946, 82106, 88235, 88261-88264, 88267, 88269, 88280, 88283, 88285, 88289,88291) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect
H) Array CGH (CPT 81228, 81229, 81349) when major fetal congenital anomalies are apparent on imaging, or with normal imaging when array CGH would replace karyotyping performed with CVS or amniocentesis in (G) above
I) FISH testing (CPT 88271, 88272, 88274, 88275, 81171, 81172) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
J) Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-81224)
K) Screening for fragile X status (CPT 81243, 81244, 81171, 81172) once in a lifetime
L) Screening for spinal muscular atrophy (CPT 81329) once in a lifetime
M) Screening for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255) once in a lifetime. Ashkenazi Jewish carrier panel testing (CPT 81412)

is covered if the panel would replace and would be of similar or lower cost than individual gene testing including CF carrier testing

N) Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

A) Serum triple screen
B) Expanded carrier screening which includes results for conditions not explicitly recommended for coverage

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

2022 CPT Code Review
Laboratory Test Codes

1) **81560** Transplantation medicine (allograft rejection, pediatric liver and small bowel), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score
    a. Similar codes: none
    b. Description: This code represents the Pleximmune test, which predicts acute cellular rejection in children with liver- or intestine transplantation and is intended to assist in the management of immunosuppression
    c. Evidence
        i. **Sindhi 2015**, profile of Pleximmune
            1. Pleximmune test sensitivity and specificity for predicting acute cellular rejection is 84% and 81% respectively in training set–validation set testing of 214 children
        ii. **Kohut 2020**, review of biomarkers for liver transplant rejection
            1. Honorable mention should be made to the development of a cell-based assay measuring allospecific CD154+T-cytotoxic memory cells expressed as an immunoreactivity index to predict ACR. This test, Pleximmune (Plexision Inc., Pittsburgh, PA), is the first cell-based test approved by the US Food and Drug Administration that predicts ACR in children who received LT or intestine transplantation. This test while holding tremendous potential has not been widely adopted into clinical practice.
    d. Other payer policies:
        i. **Aetna 2021**: Aetna considers the Pleximmune test experimental and investigational for prediction of acute cellular rejection in children with liver or intestine transplantation and all other indications because its clinical value has not been established.
    e. HERC staff summary: appears to be experimental
    f. HERC staff recommendation:
        i. Add CPT **87154:** to line 662 and add an entry to GN173 as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 662
The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
81560	Transplantation medicine (allograft rejection, pediatric liver and small bowel), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells,	Insufficient evidence of effectiveness	November 2021

	utilizing whole peripheral blood, algorithm reported as a rejection risk score		

2) **82653:** Elastase, pancreatic (EL-1), fecal; quantitative:
    a. Similar code: 82656 (Elastase, pancreatic (EL-1), fecal, qualitative or semi-quantitative) is Diagnostic
    b. Description: Measurement of the pancreatic enzyme elastase, which is a measure of exogenous pancreatic enzyme function. If low, a patient may need enzyme supplementation. This occurs frequently in diseases such as cystic fibrosis
    c. HERC staff recommendation: DIAGNOSTIC PROCEDURES

3) **83521:** Immunoglobulin light chains (ie, kappa, lambda), free, each
    a. Similar code: currently uses the genetic code 83520 (Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified)
    b. Description: test for diseases such as multiple myeloma, amyloidosis, and Waldenstrom macroglobulinemia
    c. HERC staff recommendation: DIAGNOSTIC PROCEDURES

4) **83529**: Interleukin-6 (IL-6)
    a. Similar code(s): none
    b. Description: pro-inflammatory cytokine being studied for use as an inflammatory marker for autoimmune and inflammatory diseases such as multiple sclerosis, atherosclerosis, lupus, etc. The drug tocilizumab is an interleukin-6 receptor antagonist
    c. Evidence
        i. **Franco 2019**, Cochrane review of IL-6 for diagnosis of sepsis in critically ill adults
            1. N=23 studies (4192 patients) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6490303/pdf/CD011811.pdf
            2. Using a fixed prevalence of sepsis of 50% and a fixed specificity of 74%, we found a sensitivity of 66% (95% confidence interval 60 to 72).
            3. Our evidence assessment of plasma interleukin-6 concentrations for the diagnosis of sepsis in critically ill adults reveals several limitations. High heterogeneity of collected evidence regarding the main diagnosis, setting, country, positivity threshold, sepsis criteria, year of publication, and the origin of infection, among other factors, along with the potential number of misclassifications, remain significant constraints for its implementation
        ii. **Wang 2013**, systematic review and meta-analysis of inflammatory markers and risk of type 2 diabetes
            1. N=10 prospective cohort studies (19,709 patients)
            2. detected a significant dose-response association of IL-6 levels with type 2 diabetes risk (relative risk [RR] 1.31 [95%CI 1.17–1.46]).

3. CONCLUSIONS: This meta-analysis provides further evidence that elevated levels of IL-6 and CRP are significantly associated with increased risk of type 2 diabetes.

d. Other payer policies:
   i. **Aetna 2021:** IL-6 is experimental for the diagnosis of inflammatory bowel disease and rheumatic diseases
e. HERC staff summary: IL-6 testing appears to be experimental
f. HERC staff recommendation:
   i. Add CPT 83529 to line 662 and add an entry to GN173 as shown below

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Procedure Code	Intervention Description	Rationale	Last Review
83529	Interleukin-6 (IL-6)	Insufficient evidence of effectiveness	November 2021

5) **86015**: Actin (smooth muscle) antibody (ASMA), each
   a. Similar code(s): none
   b. Description: used as a diagnostic test for autoimmune hepatitis
   c. Other payer policies:
      i. Aetna 2021: ASMA is experimental for the diagnosis of inflammatory bowel disease but may be medically necessary to diagnose autoimmune hepatitis
   d. HERC staff recommendation: DIAGNOSTIC PROCEDURES

6) **86036**: Antineutrophil cytoplasmic antibody (ANCA); screen, each antibody and **86037**: Antineutrophil cytoplasmic antibody (ANCA); titer, each antibody
   a. Similar code(s): none
   b. Description: used to diagnose polyarteritis nodosa, microscopic polyangiitis, and similar autoimmune vasculitis disorders
   c. HERC staff recommendation: DIAGNOSTIC PROCEDURES

7) **86051**: Aquaporin-4 (neuromyelitis optica [NMO]) antibody; enzyme-linked immunosorbent immunoassay (ELISA); **86052**: Aquaporin-4 (neuromyelitis optica [NMO]) antibody; cell-based immunofluorescence assay (CBA), each; **86053**: Aquaporin-4 (neuromyelitis optica [NMO]) antibody; flow cytometry (ie, fluorescence-activated cell sorting [FACS]), each
   a. Similar code(s): none
   b. Description: NMO antibodies help to diagnose neuromyelitis optica, an autoimmune disease of the CNS, and to distinguish this condition from multiple sclerosis
   c. HERC staff recommendation: DIAGNOSTIC PROCEDURES

8) **86231**: Endomysial antibody (EMA), each immunoglobulin (Ig) class; **86258:** Gliadin (deamidated) (DGP) antibody, each immunoglobulin (Ig) class; **86364**: Tissue transglutaminase, each immunoglobulin (Ig) class
    a. Similar code(s): none
    b. Description: serum tests used in the diagnosis of celiac disease and to determine the adherence to a gluten free diet
    c. Expert guidelines:
        i. **American College of Gastroenterology 2013**, guideline for the diagnosis and management of celiac disease
            1. Immunoglobulin A (IgA) anti-tissue transglutaminase (TTG) antibody is the preferred single test for detection of CD in individuals over the age of 2 years. (Strong recommendation, high level of evidence)
            2. In patients in whom low IgA or selective IgA deficiency is identified, IgG-based testing (IgG DGPs and IgG TTG) should be performed. (Strong recommendation, moderate level of evidence)
            3. EMA IgG is not widely available
            4. A positive CD-specific serology (TTG, DGP, and EMA) in patients with villous atrophy confirms the diagnosis of CD
            5. Both EMA and DGP are listed in their diagnostic flowchart for evaluation of suspected celiac disease
        ii. **NICE 2015**, assessment and management of celiac disease https://www.nice.org.uk/guidance/ng20/resources/coeliac-disease-recognition-assessment-and-management-pdf-1837325178565
            1. When healthcare professionals request serological tests to investigate suspected coeliac disease in young people and adults, laboratories should:
                a. test for total immunoglobulin A (IgA) and IgA tissue transglutaminase (tTG) as the first choice
                b. use IgA endomysial antibodies (EMA) if IgA tTG is weakly positive
                c. consider using IgG EMA, IgG deamidated gliadin peptide (DGP) or IgG tTG if IgA is deficient
    d. HERC staff recommendation: DIAGNOSTIC PROCEDURES

9) **86362**: Myelin oligodendrocyte glycoprotein (MOG-IgG1) antibody; cell-based immunofluorescence assay (CBA), each; **86363**: Myelin oligodendrocyte glycoprotein (MOG-IgG1) antibody; flow cytometry (ie, fluorescence-activated cell sorting [FACS]), each
    a. Similar code(s): none
    b. Description: Myelin oligodendrocyte glycoprotein antibody disorders (MOGAD) is an idiopathic, inflammatory, demyelinating disease of the central nervous system (CNS). Diagnostic criteria for MOGAD include serum positive MOG-IgG by cell based assay, as well as clinical findings such as optic neuropathy or transverse myelitis
    c. HERC staff recommendation: DIAGNOSTIC PROCEDURES

10) **86381**: Mitochondrial antibody (eg, M2), each
    a. Similar code(s): none
    b. Description: test used to diagnostic primary biliary cholangitis
    c. HERC staff recommendation: DIAGNOSTIC PROCEDURES

11) **86596**: Voltage-gated calcium channel antibody, each
    a. Similar code(s): none
    b. Description: used to diagnose Lambert-Eaton myasthenic syndrome, a rare autoimmune disorder of the neuromuscular junction. This testing is required by many insurers prior to treatment with Firdapse or Ruzurgi
    c. HERC staff recommendation: DIAGNOSTIC PROCEDURES

12) **87154:** Culture, typing; identification of blood pathogen and resistance typing, when performed, by nucleic acid (DNA or RNA) probe, multiplexed amplified probe technique including multiplex reverse transcription, when performed, per culture or isolate, 6 or more targets
    a. Similar code(s): none
    b. Description: Several proprietary tests are on the market (e.g. FilmArray, BioFire, Sepsityper) which identify multiple pathogens and test for antibiotic resistance genes. These tests allow rapid identification of pathogens in patients with sepsis compared to the normal 2 day blood culture and sensitivity tests.
    c. Evidence
        i. **Robinson 2021,** clinical impact of rapid species identification
            1. Pre-post observational study
            2. N=514 patients
            3. Median time to antimicrobial susceptibility testing (AST) results decreased 29.4 hours ($P < .001$) post-intervention, Utilization (days of therapy [DOTs]/1000 days present) of broad-spectrum agents decreased (PRE 655.2 vs POST 585.8; $P = .043$) and narrow-spectrum beta-lactams increased (69.1 vs 141.7; $P < .001$). Discrepant results occurred in 69/250 (28%) post-intervention episodes, resulting in incorrect antibiotic stewardship program recommendations in 10/69 (14%).
            4. No significant differences in secondary clinical outcomes including in-hospital and 30-day mortality, length of stay, C difficile infection, readmission, or relapse of BSI were observed
        ii. **Ehren 2020**, clinical impact of rapid species identification
            1. Before-after observational study
            2. N=264 patients (64 conventional testing, 68 conventional testing + rapid testing, 72 rapid diagnostics)
            3. Time to identification of species significant reduced, as well as time to step-down antimicrobial therapy. However, groups did not differ in antimicrobial consumption, duration of antimicrobial therapy, mortality, length of stay, or incidence of C difficile infection.
    d. Expert guidelines

i. **Barlam 2015**, IDSA guideline on implementing an antibiotic stewardship program
   1. Should ASPs Advocate for Rapid Diagnostic Testing on Blood Specimens to Optimize Antibiotic Therapy and Improve Clinical Outcomes?
      a. We suggest rapid diagnostic testing in addition to conventional culture and routine reporting on blood specimens if combined with active ASP support and interpretation (weak recommendation, moderate-quality evidence).
      b. Comment: Availability of rapid diagnostic tests is expected to increase; thus, ASPs must develop processes and interventions to assist clinicians in interpreting and responding appropriately to results.

e. Expert input: John Townes, OHSU head of infectious disease felt that these tests might be beneficial from an infection control and antibiotic stewardship perspective
f. HERC staff summary: rapid pathogen testing appears to be a promising technology for antibiotic stewardship; however, the evidence to date does not appear to show that these tests affect clinical outcomes. These tests have a weak recommendation for coverage by the IDSA.
g. HERC staff recommendation:
   i. Add CPT **87154:** to line 662 and add an entry to GN173 as shown below
      1. Alternative: place on the Diagnostic Procedures File as likely only to be used in ICU situations where they would be covered as part of DRG

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
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Procedure Code	Intervention Description	Rationale	Last Review
87154	Culture, typing; identification of blood pathogen and resistance typing, when performed, by nucleic acid (DNA or RNA) probe, multiplexed amplified probe technique including multiplex reverse transcription, when performed, per culture or isolate, 6 or more targets	Insufficient evidence of effectiveness	November 2021

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Profile of the Pleximmune blood test for transplant rejection risk prediction

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Summary

The Pleximmune™ test (Plexision Inc., Pittsburgh, PA, USA) is the first cell-based test approved by the US FDA, which predicts acute cellular rejection in children with liver- or intestine transplantation. The test addresses an unmet need to improve management of immunosuppression, which incurs greater risks of opportunistic infections and Epstein–Barr virus-induced malignancy during childhood. High-dose immunosuppression and recurrent rejection after intestine transplantation also result in a 5-year graft loss rate of up to 50%. Such outcomes seem increasingly unacceptable because children can experience rejection-free survival with reduced immunosuppression. Pleximmune test sensitivity and specificity for predicting acute cellular rejection is 84% and 81% respectively in training set–validation set testing of 214 children. Among existing gold standards, the biopsy detects but cannot predict rejection. Anti-donor antibodies, which presage antibody-mediated injury, reflect late-stage allosensitization as a downstream effect of engagement between recipient and donor cells. Therefore, durable graft and patient outcomes also require an accurate management of cellular immune responses in clinical practice.

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Financial & competing interests disclosure

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Genomics and Liver Transplantation: Genomic Biomarkers for the Diagnosis of Acute Cellular Rejection

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Acute cellular rejection (ACR) is a common complication in liver transplantation recipients (LTRs), especially within the first 12 months, and it is associated with increased morbidity and mortality. Although abnormalities in standard liver biochemistries may raise the clinical suspicion for ACR, it lacks specificity, and invasive liver biopsies, which are associated with numerous risks, are required for definitive diagnoses. Biomarker discovery for minimally invasive tools for diagnosis and prognostication of ACR after liver transplantation (LT) has become a rapidly evolving field of research with a recent shift in focus to omics-based biomarker discovery. Although none are yet ready to replace the standard of care, there are several promising minimally invasive, blood-derived biomarkers that are under intensive research for the diagnosis of ACR in LTRs. These omics-based biomarkers, encompassing DNA, RNA, proteins, and metabolites, hold tremendous potential. Some are likely to become integrated into ACR diagnostic algorithms to assist clinical decision making with a high degree of accuracy that is cost-effective and reduces or even obviates the need for an invasive liver biopsy.

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Although outcomes after liver transplantation (LT) have significantly improved, acute cellular rejection (ACR) still remains a common complication, occurring in up to 30.0% of liver transplantation recipients (LTRs) within the first 12 months.[1] The occurrence of ACR after LT is associated with increased risk of graft failure, graft failure-related death, and all-cause mortality.[1] A clinical suspicion of ACR is raised in the face of elevated serum liver biochemistry, but these tests lack specificity for ACR,[2] especially because other common pathological states, such as cholestasis, infection, and vascular thrombosis, can also result in liver biochemistry abnormalities. An invasive liver biopsy is performed to establish a definitive diagnosis of ACR, and it can be associated with risks of pain, bleeding, bile leak, and sampling issues.[3] As such, there is a compelling need for minimally invasive assays with high sensitivity and specificity to diagnose and prognosticate ACR and for surveillance of graft health to impact allograft survival. Here, several promising minimally invasive, blood-derived biomarkers for the diagnosis and, to a lesser degree, the prognosis of ACR are reviewed, with a strong focus on omics-based biomarker discovery.

Abbreviations: ACR, acute cellular rejection; AGO, argonaute; ALT, alanine aminotransferase; AMR, antibody-mediated rejection; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; cfDNA, cell-free DNA; CR, chronic rejection; CXCL, chemokine (C-X-C motif) ligand; ddcfDNA, donor-derived cell-free DNA; ddPCR, droplet digital polymerase chain reaction; dnDSA, de novo donor-specific antibodies; DOA, class II region, family, alpha chain; DSA, donor-specific antibodies; FOXP3, forkhead box P3; GATA3, GATA-Binding Protein 3; GWAS, genome-wide association study; HCV, hepatitis C virus; HDL, high-density lipoprotein; HLA, human leukocyte antigen; HLA-1, human leukocyte antigen class 1; HLA-2, human leukocyte antigen class 2; I/D, insertion/deletion; iGeneTRAiN, International Genetics and Translational Research in Transplantation Network; IgG4, immunoglobulin G subclass 4; IL, interleukin; IST, immunosuppression therapy; LIT, liver injury test; LT, liver transplantation; LTR, liver transplantation recipient; MFI, mean fluorescence intensity; MHC, major histocompatibility complex; miRNA, microRNA; mRNA, messenger RNA; NODAT, new-onset diabetes after transplantation; NPV, negative predictive value; PCR,

Liver Biochemistry

Clinicians have long recognized that conventional liver injury tests (LITs) are inadequate markers for the specific

Inflammatory Markers and Risk of Type 2 Diabetes

A systematic review and meta-analysis

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OBJECTIVE—There has been growing evidence that inflammatory markers play a role in the development of type 2 diabetes. We aimed to systematically review prospective studies on the associations of elevated levels of interleukin-6 (IL-6) and C-reactive protein (CRP) with increased risk of type 2 diabetes by conducting a meta-analysis.

RESEARCH DESIGN AND METHODS—A systematic search of the PubMed, EMBASE, ISI Web of Knowledge, and Cochrane Library databases up until 10 February 2012 was conducted to retrieve prospective studies matched to search terms. We used generalized least-squares trend estimation to assess dose-response relationships. The summary risk estimates were pooled using either fixed-effects or random-effects models to incorporate between-study variation.

RESULTS—The meta-analysis, including 10 prospective studies, with a total of 19,709 participants and 4,480 cases, detected a significant dose-response association of IL-6 levels with type 2 diabetes risk (relative risk [RR] 1.31 [95% CI 1.17–1.46]). For CRP, the meta-analysis involving 22 cohorts, with a total of 40,735 participants and 5,753 cases, showed that elevated CRP levels were significantly associated with increased risk of type 2 diabetes (1.26 [1.16–1.37]), with the absence of publication bias. Sensitivity and subgroup analyses further supported the associations.

CONCLUSIONS—This meta-analysis provides further evidence that elevated levels of IL-6 and CRP are significantly associated with increased risk of type 2 diabetes.

Diabetes Care 36:166–175, 2013

The rapid worldwide increase in the prevalence of type 2 diabetes has become a serious public health problem (1). Type 2 diabetes may be accompanied by long-term microvascular and macrovascular complications, which lead to both morbidity and mortality (2). In addition, as many as one-third of individuals with type 2 diabetes are undiagnosed. However, accumulating evidence shows that inflammation may play a crucial intermediary role in the pathogenesis of type 2 diabetes, thus relating diabetes to a number of commonly coexisting conditions thought to originate via inflammatory mechanisms (3). In this regard, more recent data suggest that interleukin-6 (IL-6) and C-reactive protein (CRP) are associated with type 2 diabetes (4–10). IL-6, a pleiotropic proinflammatory cytokine, is produced by a variety of cells, including activated leukocytes, endothelial cells, and adipocytes (11). CRP is an acute-phase plasma protein synthesized by the liver and has been shown to be a sensitive, systemic biomarker of inflammation (3). The stability of this protein during long-term frozen blood storage and the availability of inexpensive, precise, and standardized assays have assisted studies of CRP (12).

One potential implication of the many studies suggesting a relation between inflammation and diabetes is that inflammatory markers may be used to refine diabetes risk prediction and thus better target individuals for lifestyle interventions. However, the results reported on the association between IL-6 and diabetes risk have varied across studies (13–16). To date, no systematic review has been performed to evaluate the available evidence on the association of IL-6 levels with the risk of type 2 diabetes. Two previous meta-analyses evaluating the association of CRP and diabetes risk have yielded contradictory results. One previous meta-analysis (17) suggested that a positive association exists between CRP and diabetes risk. In contrast, another meta-analysis (18) concluded that CRP may not be an independent risk factor for the development of diabetes.

The objective of the current study was to estimate the magnitude of the relationships between IL-6 and CRP levels and the risk of type 2 diabetes in prospective studies and to quantify these relationships in a meta-analysis.

RESEARCH DESIGN AND METHODS

Search strategy

We conducted the present meta-analysis in accordance with the guidelines of the Meta-analysis of Observation Studies in Epidemiology Group (19). A systematic literature search was performed to identify all studies published before 10 February 2012 that investigated the association between inflammatory markers and the risk of type 2 diabetes. Electronic

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CME

ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease

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This guideline presents recommendations for the diagnosis and management of patients with celiac disease. Celiac disease is an immune-based reaction to dietary gluten (storage protein for wheat, barley, and rye) that primarily affects the small intestine in those with a genetic predisposition and resolves with exclusion of gluten from the diet. There has been a substantial increase in the prevalence of celiac disease over the last 50 years and an increase in the rate of diagnosis in the last 10 years. Celiac disease can present with many symptoms, including typical gastrointestinal symptoms (e.g., diarrhea, steatorrhea, weight loss, bloating, flatulence, abdominal pain) and also non-gastrointestinal abnormalities (e.g., abnormal liver function tests, iron deficiency anemia, bone disease, skin disorders, and many other protean manifestations). Indeed, many individuals with celiac disease may have no symptoms at all. Celiac disease is usually detected by serologic testing of celiac-specific antibodies. The diagnosis is confirmed by duodenal mucosal biopsies. Both serology and biopsy should be performed on a gluten-containing diet. The treatment for celiac disease is primarily a gluten-free diet (GFD), which requires significant patient education, motivation, and follow-up. Non-responsive celiac disease occurs frequently, particularly in those diagnosed in adulthood. Persistent or recurring symptoms should lead to a review of the patient's original diagnosis to exclude alternative diagnoses, a review of the GFD to ensure there is no obvious gluten contamination, and serologic testing to confirm adherence with the GFD. In addition, evaluation for disorders associated with celiac disease that could cause persistent symptoms, such as microscopic colitis, pancreatic exocrine dysfunction, and complications of celiac disease, such as enteropathy-associated lymphoma or refractory celiac disease, should be entertained. Newer therapeutic modalities are being studied in clinical trials, but are not yet approved for use in practice. Given the incomplete response of many patients to a GFD-free diet as well as the difficulty of adherence to the GFD over the long term, development of new effective therapies for symptom control and reversal of inflammation and organ damage are needed. The prevalence of celiac disease is increasing worldwide and many patients with celiac disease remain undiagnosed, highlighting the need for improved strategies in the future for the optimal detection of patients.

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INTRODUCTION

This clinical guideline addresses the diagnosis, treatment, and overall management of patients with celiac disease (CD), including an approach to the evaluation of non-responsive CD. While it is primarily directed at the care of adult patients, variations pertinent to the pediatric population have been included.

Each section will provide specific recommendations based on the current literature and a summary of the evidence supporting those recommendations. The GRADE system was used to evaluate the quality of supporting evidence (1) (**Table 1**). A "strong" recommendation is made when the benefits clearly outweigh the negatives and the result of no action. "Conditional" is used when some uncertainty remains about the balance of benefit/potential harm. The quality of the evidence is graded from high to low. "High"-quality evidence indicates that further research is unlikely to change the authors' confidence in the estimate of effect. "Moderate"-quality evidence indicates that further research would be likely to have an impact on the confidence of the estimate, whereas "Low"-quality evidence indicates that further study would likely have an important impact on the confidence in the estimate of the effect and would likely change the estimate.

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Clinical Infectious Diseases

MAJOR ARTICLE

Implementation of a Rapid Phenotypic Susceptibility Platform for Gram-Negative Bloodstream Infections With Paired Antimicrobial Stewardship Intervention: Is the Juice Worth the Squeeze?

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Background. Implementation of the Accelerate Pheno™ Gram-negative platform (RDT) paired with antimicrobial stewardship program (ASP) intervention projects to improve time to institutional-preferred antimicrobial therapy (IPT) for Gram-negative bacilli (GNB) bloodstream infections (BSIs). However, few data describe the impact of discrepant RDT results from standard of care (SOC) methods on antimicrobial prescribing.

Methods. A single-center, pre-/post-intervention study of consecutive, nonduplicate blood cultures for adult inpatients with GNB BSI following combined RDT + ASP intervention was performed. The primary outcome was time to IPT. An a priori definition of IPT was utilized to limit bias and to allow for an assessment of the impact of discrepant RDT results with the SOC reference standard.

Results. Five hundred fourteen patients (PRE 264; POST 250) were included. Median time to antimicrobial susceptibility testing (AST) results decreased 29.4 hours ($P < .001$) post-intervention, and median time to IPT was reduced by 21.2 hours ($P < .001$). Utilization (days of therapy [DOTs]/1000 days present) of broad-spectrum agents decreased (PRE 655.2 vs POST 585.8; $P = .043$) and narrow-spectrum beta-lactams increased (69.1 vs 141.7; $P < .001$). Discrepant results occurred in 69/250 (28%) post-intervention episodes, resulting in incorrect ASP recommendations in 10/69 (14%). No differences in clinical outcomes were observed.

Conclusions. While implementation of a phenotypic RDT + ASP can improve time to IPT, close coordination with Clinical Microbiology and continued ASP follow up are needed to optimize therapy. Although uncommon, the potential for erroneous ASP recommendations to de-escalate to inactive therapy following RDT results warrants further investigation.

Keywords. antimicrobial stewardship; rapid diagnostics; bloodstream infections; susceptibility testing.

Bloodstream infections (BSIs) with Gram-negative bacilli (GNB) are associated with significant mortality, with delay in active therapy associated with worsened prognosis [1–3]. Administration of timely active therapy has been further complicated by increasing rates of antimicrobial resistance [4], along with increasing recognition of the need to avoid overuse of broad-spectrum agents [5, 6]. Rapid diagnostic tests (RDTs) have emerged as a promising tool in targeting appropriate therapy to patients earlier, and when paired with an antimicrobial stewardship program (ASP) have been associated with improved outcomes, including mortality [7].

Until recently, rapid diagnostics for GNB BSIs have primarily utilized genotypic approaches that provide rapid identification with limited resistance targets [8, 9]. However, the complexity of Gram-negative resistance mechanisms limits the ability of these methods to effectively support modification to definitive therapy. As broad-spectrum empiric therapies are often prescribed, early phenotypic susceptibility information is not only needed to guide timely active therapy, but also help drive prompt elimination of unnecessary antimicrobial spectrum, a fundamental goal of any ASP [5].

The Accelerate Pheno™ system (Accelerate Diagnostics, Tucson, AZ) is a novel RDT which uses fluorescence in-situ

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Nonstandard Abbreviations. ASP, antimicrobial stewardship program; ARLG, Antibacterial Resistance Leadership Group; AST, antimicrobial susceptibility testing; BSI, bloodstream infections; CDC, Centers for Disease Control and Prevention; CDI, *Clostridioides difficile* infection; CLSI, Clinical and Laborataory Standards Institute; DOT, days of therapy; EMR, electronic medical record; GNB, Gram-negative bacilli; IPT, institutional-preferred antimicrobial therapy; LOS, length of stay; OPAT, outpatient parenteral antimicrobial therapy; POST, intervention period; PRE, historical period; RDT, rapid diagnostic test; SAAR, Standardized Antimicrobial Administration Ratio; SNF, skilled-nursing facility; SOC, standard of care.

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Clinical Infectious Diseases

MAJOR ARTICLE

Clinical Impact of Rapid Species Identification From Positive Blood Cultures With Same-day Phenotypic Antimicrobial Susceptibility Testing on the Management and Outcome of Bloodstream Infections

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Background. Timely availability of microbiological results from positive blood cultures is essential to enable early pathogen-directed therapy. The Accelerate Pheno system (ADX) is a novel technology using fluorescence in situ hybridization for rapid species identification (ID) and morphokinetic bacterial analysis for phenotypic antimicrobial susceptibility testing (AST), with promising results. Yet the impact of this technology on clinical management and patient outcome remains unclear.

Methods. We conducted a quasiexperimental before-and-after observational study and analyzed 3 groups with different diagnostic and therapeutic pathways following recent integration of ADX: conventional microbiological diagnostics with and without antimicrobial stewardship program (ASP) intervention, and rapid diagnostics (ADX in addition to conventional standard) with ASP intervention. Primary endpoints were time to adequate, to optimal and to step-down antimicrobial therapy. Secondary endpoints were antimicrobial consumption, in-hospital mortality, length of stay (LOS), and the incidence of *Clostridioides difficile* infection (CDI).

Results. Two hundred four patients (conventional diagnostics, n = 64; conventional diagnostics + ASP, n = 68; rapid diagnostics + ASP; n = 72) were evaluated. The use of ADX significantly decreased time from Gram stain to ID (median, 23 vs 2.2 hours, $P < .001$) and AST (median, 23 vs 7.4 hours, $P < .001$), from Gram stain to optimal therapy (median, 11 vs 7 hours, $P = .024$) and to step-down antimicrobial therapy (median, 27.8 vs 12 hours, $P = .019$). However, groups did not differ in antimicrobial consumption, duration of antimicrobial therapy, mortality, LOS, or incidence of CDI.

Conclusions. Use of ADX significantly reduced time to ID and AST as well as time to optimal antimicrobial therapy but did not affect antimicrobial consumption and clinical outcome.

Keywords. rapid diagnostic tests; antimicrobial stewardship; bacteremia; Accelerate Pheno system.

Rapid initiation of appropriate antimicrobial therapy is crucial in managing bloodstream infections (BSIs), and delay can result in a substantial increase of mortality [1]. As species identification (ID) and antimicrobial susceptibility testing (AST) using conventional methods may take up to 72 hours after sample collection [2], broad-spectrum antimicrobials are often used as empiric therapy [3]. Prolonged treatment with these compounds, however, may lead to adverse events including *Clostridioides difficile* infection (CDI), may incur higher costs, and may facilitate the emergence of resistance [4, 5]. Timely availability of microbiological results allows for early targeted therapy, a key component of an effective antimicrobial stewardship program (ASP) [6–8].

The advent of molecular methods for same-day identification of bloodstream pathogens and their resistance genes directly from positive blood cultures have brought their potential usefulness for the management of BSI into focus, and results can be made available 1–2 days earlier compared to conventional diagnostic methods [9–12]. Other technologies can be applied directly to whole blood samples without prior incubation [12].

The Accelerate Pheno system (ADX; Accelerate Diagnostics, Tucson, Arizona) is a new technology that allows rapid identification of microorganisms from a positive blood culture within 90 minutes based on fluorescence in situ hybridization as well as phenotypic AST within 7 hours using automated microscopic imaging of live, growing bacterial cells in the presence of antimicrobial agents [13, 14]. While rapid genotypic testing

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Clinical Infectious Diseases

IDSA GUIDELINE

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

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Evidence-based guidelines for implementation and measurement of antibiotic stewardship interventions in inpatient populations including long-term care were prepared by a multidisciplinary expert panel of the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. The panel included clinicians and investigators representing internal medicine, emergency medicine, microbiology, critical care, surgery, epidemiology, pharmacy, and adult and pediatric infectious diseases specialties. These recommendations address the best approaches for antibiotic stewardship programs to influence the optimal use of antibiotics.

Keywords. antibiotic stewardship; antibiotic stewardship programs; antibiotics; implementation.

EXECUTIVE SUMMARY

Antibiotic stewardship has been defined in a consensus statement from the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) as "coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration" [1]. The benefits of antibiotic stewardship include improved patient outcomes, reduced adverse events including *Clostridium difficile* infection (CDI), improvement in rates of antibiotic susceptibilities to targeted antibiotics, and optimization of resource utilization across the continuum of care. IDSA and SHEA strongly believe that antibiotic stewardship programs (ASPs) are best led by infectious disease physicians with additional stewardship training.

Summarized below are the IDSA/SHEA recommendations for implementing an ASP. The expert panel followed a process used in the development of other IDSA guidelines, which included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (Figure 1) [2–5]. A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found online in the full text of the guidelines. For the purposes of this guideline, the term antibiotic will be used instead of antimicrobial and should be considered synonymous.

RECOMMENDATIONS FOR IMPLEMENTING AN ANTIBIOTIC STEWARDSHIP PROGRAM

Interventions

I. Does the Use of Preauthorization and/or Prospective Audit and Feedback Interventions by ASPs Improve Antibiotic Utilization and Patient Outcomes?

Recommendation

1. We recommend preauthorization and/or prospective audit and feedback over no such interventions *(strong recommendation, moderate-quality evidence)*.

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[a]T. F. B. and S. E. C. contributed equally to this work as co-chairs.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant clinician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the clinician in the light of each patient's individual circumstances.

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Remote Therapeutic Monitoring

Codes:

1) **98975**: Remote therapeutic monitoring (eg, respiratory system status, musculoskeletal system status, therapy adherence, therapy response); initial set-up and patient education on use of equipment
2) **98976**: Remote therapeutic monitoring (eg, respiratory system status, musculoskeletal system status, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor respiratory system, each 30 days
3) **98977**: Remote therapeutic monitoring (eg, respiratory system status, musculoskeletal system status, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor musculoskeletal system, each 30 days
4) **98980**: Remote therapeutic monitoring treatment management services, physician or other qualified health care professional time in a calendar month requiring at least one interactive communication with the patient or caregiver during the calendar month; first 20 minutes
5) **98981**: Remote therapeutic monitoring treatment management services, physician or other qualified health care professional time in a calendar month requiring at least one interactive communication with the patient or caregiver during the calendar month; each additional 20 minutes

Similar codes:

1) Remote monitoring on lines 9,20,48,58,69,75,81,97,98,110,172,189,202,213,219,222, 223, 225, 233, 257, 264, 281, 283, 304, 341, 347,366,464,566,635,647,653,657
    a. 99453: Remote monitoring of physiologic parameter(s) (eg, weight, blood pressure, pulse oximetry, respiratory flow rate), initial; set-up and patient education on use of equipment
    b. 99457: Remote physiologic monitoring treatment management services, clinical staff/physician/other qualified health care professional time in a calendar month requiring interactive communication with the patient/caregiver during the month; first 20 minutes
    c. 99458: Remote physiologic monitoring treatment management services, clinical staff/physician/other qualified health care professional time in a calendar month requiring interactive communication with the patient/caregiver during the month; each additional 20 minutes (List separately in addition to code for primary procedure)
2) Remote monitoring on line 502 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS
    a. 99454: Remote monitoring of physiologic parameter(s) (eg, weight, blood pressure, pulse oximetry, respiratory flow rate), initial; device(s) supply with daily recording(s) or programmed alert(s) transmission, each 30 days

Description: CMS recently created remote therapeutic monitoring (RTM) codes, which are very similar to the remote physiologic monitoring (RPM) codes that were published in 2020.

CMS has identified some key differences between these codes.

1) RTM codes allow collection of non-physiologic data such as therapy adherence and response that are not included in the RPM codes.

2) RTM codes allow only for monitoring of respiratory and musculoskeletal system data, where RPM codes do not specify systems and could be used for cardiovascular, endocrine, and other system data
3) RTM allow data to be self-reported by the patient or reported by a device, while RPM codes require data to be reported by a device
4) Three of the RTM codes (98975-98977) are intended to be reported by nurses, speech therapists, nurse practictioners, physical therapists, and other providers who cannot report RPM codes. These are considered Practice Expense (PE) codes.

In July 2021, CMS published a proposed rule stating: "primary billers of RTM codes are projected to be nurses and physical therapists… In our review of the new codes, we identified an issue that disallows physical therapists and other practitioners, who are not physicians or NPPs, to bill the RTM codes." CMS considers all five codes to be "incident to" services.

In November 2021, according to the final rule published by CMS, primary billers for these codes have been finalized as "therapists and other qualified healthcare professionals to bill the RTM codes as described. However, where the practitioner's Medicare benefit does not include services furnished incident to their professional services, the items and services described by these codes must be furnished directly by the billing practitioner or, in the case of a PT or OT, by a therapy assistant under the PT's or OT's supervision."

CMS finalized RVUs for these five codes, designating CPT 98980 and 98981 to have similar RVUs to CPT 99457 and 99458 to maintain parity between RTM and RPM. However, CMS notes "The treatment management RTM codes (CPT codes 98980 and 98981), because they are not E/M codes, cannot be designated as care management services." Code 98975 was cross-walked to the PE RVU of CPT 99453 and codes 98976-77 were cross-walked to the PE RVU of 99454.

However, CMS is unclear on what types of devices or equipment are meant to be represented by these codes. Their proposed rule stated they are "seeking comment on the typical type of device(s) and associated costs of the device(s) that might be used to collect the various kinds of data included in the code descriptors (for example, respiratory system status, musculoskeletal status, medication adherence, pain) for the RTM services." CMS notes that for these codes a "device used must meet the FDA definition of a medical device." There was no clarification provided in the final rule released on 11/3/2021.

HERC staff recommendations:

1) Advise HSD to place the following codes on the EXLCUDED filed until CMS clarifies utilization and definition of included devices
    a. **98975**: Remote therapeutic monitoring (eg, respiratory system status, musculoskeletal system status, therapy adherence, therapy response); initial set-up and patient education on use of equipment
    b. **98976**: Remote therapeutic monitoring (eg, respiratory system status, musculoskeletal system status, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor respiratory system, each 30 days
    c. **98977**: Remote therapeutic monitoring (eg, respiratory system status, musculoskeletal system status, therapy adherence, therapy response); device(s) supply with scheduled

(eg, daily) recording(s) and/or programmed alert(s) transmission to monitor musculoskeletal system, each 30 days

d. **98980**: Remote therapeutic monitoring treatment management services, physician or other qualified health care professional time in a calendar month requiring at least one interactive communication with the patient or caregiver during the calendar month; first 20 minutes
e. **98981**: Remote therapeutic monitoring treatment management services, physician or other qualified health care professional time in a calendar month requiring at least one interactive communication with the patient or caregiver during the calendar month; each additional 20 minutes

2022 CPT Code Review
New Vaccine Codes

Codes

1) **90626**: Tick-borne encephalitis virus vaccine, inactivated; 0.25 mL dosage
2) **90627**: Tick-borne encephalitis virus vaccine, inactivated; 0.5 mL dosage
3) **90671:** Pneumococcal conjugate vaccine, 15 valent (PCV15)
4) **90677**: Pneumococcal conjugate vaccine, 20 valent (PCV20)
5) **90758**: Zaire ebolavirus vaccine, live,
6) **90759**: Hepatitis B vaccine (HepB), 3-antigen (S, Pre-S1, Pre-S2), 10 mcg dosage, 3 dose schedule

Information

1) Tick borne encephalitis virus vaccine
    a. Information from the CDC website (accessed October 11, 2021):
        i. Tick-borne encephalitis, or TBE, is a human viral infectious disease involving the central nervous system. TBE is caused by the tick-borne encephalitis virus (TBEV), a member of the family *Flaviviridae*. Three virus sub-types are described: European or Western tick-borne encephalitis virus, Siberian tick-borne encephalitis virus, and Far eastern Tick-borne encephalitis virus (formerly known as Russian Spring Summer encephalitis virus, RSSEV).
        ii. On August 13, 2021, the Food and Drug Administration approved a tick-borne encephalitis (TBE) vaccine, TICOVAC™, manufactured by Pfizer. The vaccine is an inactivated vaccine that has been licensed and used in Europe for about 20 years. The vaccine has both pediatric and adult formulations and is the only one currently licensed in the United States. An Advisory Committee on Immunization Practices (ACIP) Work Group was formed in 2020 to discuss the use of TBE vaccine in children and adults traveling to or residing in areas at risk and in laboratory workers. The Work Group is currently reviewing the epidemiology of TBE among travelers and laboratory workers, and data on the safety and effectiveness of the TBE vaccine. The Work Group is developing evidence-based recommendations for consideration by ACIP which will likely be approved in 2022
    b. 15 and 20 valent pneumococcal conjugate vaccines
        i. Two new pneumococcal vaccines received FDA approval in July 2021.
            1. PCV20 is a Pfizer product
            2. PCV15 is a Merck product
        ii. According to the ACIP website, these vaccines were initially scheduled to be reviewed at the February, June and October 2021 ACIP meetings. However, no discussion has actually occurred to date at ACIP.
        iii. The official ACIP vaccine recommendations remain only for the 13 and 23 valent vaccines.
    c. Ebola vaccine
        i. This is considered a travel vaccine due to the fact that Ebola is only currently found in certain areas of Africa
        ii. According to the CDC (webpage accessed October 10, 2021), the Ebola vaccine is only for health care providers caring for Ebola patients at federally designated Ebola Treatment centers and biosafety level 4 workers
    d. Hepatitis B vaccine (HepB), 3-antigen (S, Pre-S1, Pre-S2)
        i. VBI product

ii. Currently ACIP only recommends Engerix, Hepisav-B, Recombivax HB (all appear to be single antigen vaccines) as well as Pediarix and Twinrix (combination vaccines)

HERC staff recommendation:

1) Place all of the following codes on the EXCLUDED FILE
    a. **90626**: Tick-borne encephalitis virus vaccine, inactivated; 0.25 mL dosage
    b. **90627**: Tick-borne encephalitis virus vaccine, inactivated; 0.5 mL dosage
    c. **90671:** Pneumococcal conjugate vaccine, 15 valent (PCV15)
    d. **90677**: Pneumococcal conjugate vaccine, 20 valent (PCV20)
    e. **90758**: Zaire ebolavirus vaccine, live
    f. **90759**: Hepatitis B vaccine (HepB), 3-antigen (S, Pre-S1, Pre-S2), 10 mcg dosage, 3 dose schedule
2) HSD can move to covered status if/when ACIP approval is received. HERC can then act to add the vaccine to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS
    a. Note: the Ebola vaccine is considered a travel vaccine and will remain on the EXCLUDED FILE

Section 6.0

New Codes

2022 HCPCS Code Review

1) HCPCS **C1832** Autograft suspension, including cell processing and application, and all system components
    a. Description: this HCPCS code describes the creation and application of epidermal autographs. This procedure is done with the RECELL® Autologous Cell Harvesting Device. Autologous skin cell suspension has been studied for the treatment of burns, diabetic foot ulcers, and venous ulcers. The purported advantage to autologous skin cell suspension is the reduction in donor site morbidity.
        i. From the FDA (2021):
            1. RECELL® is a single-use, stand-alone, battery-operated, autologous cell harvesting device containing enzymatic and delivery solutions, sterile surgical instruments, and actuators. The RECELL Device enables a thin split-thickness skin sample to be processed to produce a RES® Regenerative Epidermal Suspension for immediate delivery onto a prepared wound bed. The cell suspension contains a mixed population of cells, including keratinocytes, fibroblasts, and melanocytes, obtained from the disaggregation of the skin sample. The preservation of melanocytes is important for restoring natural pigmentation to the recipient area. Additionally, sub-populations of keratinocytes critical for re-epithelialization have been identified in RES including basal keratinocytes, suprabasal keratinocytes, and activated keratinocytes.
            2. The RECELL Autologous Cell Harvesting Device is indicated for the treatment of acute thermal burn wounds. The RECELL Device is used by an appropriately-licensed healthcare professional at the patient's point of care to prepare autologous RES® Regenerative Epidermal Suspension for direct application to acute partial-thickness thermal burn wounds in patients 18 years of age and older or application in combination with meshed autografting for acute full-thickness thermal burn wounds in pediatric and adult patients.
    b. Evidence
        i. NOTE: due to the limited FDA approval of this technology (autologous skin cell suspension is only FDA approved for treatment of burns and then only when used with split thickness skin grafts), only this limited indication was researched
        ii. **Barnett 2021,** a pilot study of autologous skin cell suspension for hand burns
            1. Retrospective cohort study, N=59 patients
                a. N=37 treated with autologous skin cell suspension ASCS) with split-thickness skin grafting (STSG)
                b. N=22 treated with split thickness skin grafting alone
            2. There was no difference in time to wound re-epithelialization between both groups (ASCS, 11 ± 4 days vs STSG, 11 ± 5 days). Mean length-of-stay was 23 ± 13 days compared to 10 ± 13 days ($P < .05$) between the ASCS and STSG groups, respectively. No patients in the ASCS group required reoperation, whereas 2 patients in the STSG group required such for an infection-related graft loss and a web space contracture release.
        iii. **Kowal 2019**, cost effectiveness of use of autologous cell harvesting devices compared to standard wound care in the US
            1. Modeling study

2. ASCS treatment is cost-saving or cost neutral (<2% difference) and results in lower LOS compared to SOC across expected patient profiles and scenarios. In aggregate, ASCS treatment saves a burn center 14–17.3% annually. Results are sensitive to, but remain robust across, changing assumptions for relative impact of ASCS use on LOS, procedure time, and number of procedures

c. HERC staff summary: autologous skin cell suspension is experimental for the FDA approved indication of treatment of burns

d. HERC staff recommendation

i. Place HCPCS C1832 on line 662/GN173 as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
C1832	Autograft suspension, including cell processing and application, and all system components	Insufficient evidence of effectiveness	November, 2021

2) HCPCS **C1833** Monitor, cardiac, including intracardiac lead and all system components (implantable)

a. Description: Implantable cardiac monitors utilize electrogram devices to record cardiac data and detect ischemic events in patients who have had prior acute coronary syndrome (ACS) events and who remain at high risk for recurrent ACS events. The devices are intended to provide an early warning of ischemic events and to minimize the time between ischemic event onset and medical care.

b. Evidence:

i. **Gibson 2019**, ALERTS trial

1. Industry sponsored randomized trail of implantable cardiac monitors
2. N=907 patients at high risk for acute cardiac events
    a. N=437 had the alarms activated immediately, N=446 had alarms activated after 6 months
3. Primary study safety endpoint was absence of system-related complications. Primary efficacy endpoint was a composite of cardiac/unexplained death, new Q-wave myocardial infarction, or detection to presentation time >2 hours
4. Safety: 31 system related complications were reported in 30 patients (3.3%). Complications included infections, pain, device malfunction, and device erosion
5. The efficacy endpoint for a confirmed occlusive event within 7 days was not significantly reduced in the treatment compared with control group (16 of 423 [3.8%] vs. 21 of 428 [4.9%], posterior probability ¼ 0.786).

Within a 90-day window, alarms significantly decreased detection to arrival time at a medical facility (51 min vs. 30.6 h; Pr [pt < pc] >0.999).

6. Conclusion: Overall, the implantable cardiac system was safe, and the rate of complications was low. However, the ALERTS trial failed to meet the pre-specified primary efficacy endpoint of the randomized trial.

c. Other payer policies: no private payer surveyed is covering this technology
d. HERC staff summary: intracardiac ischemia monitoring is experimental
e. HERC staff recommendation
    i. Place HCPCS C1833 on line 662/GN173 as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 662
The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
C1833	Monitor, cardiac, including intracardiac lead and all system components (implantable)	Insufficient evidence of effectiveness	November, 2021

3) HCPCS **G0465** Autologous platelet rich plasma (prp) for diabetic chronic wounds/ulcers, using an fda-cleared device (includes administration, dressings, phlebotomy, centrifugation, and all other preparatory procedures, per treatment)
    a. Similar code: G0460 (Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment)
    b. G0460 was reviewed in May, 2021. Based on that review, G0460 was placed on line 662/GN173.
        i. Staff summary: Platelet rich plasma has moderate evidence of effectiveness for increasing the healing rate and reducing the healing time for chronic lower extremity diabetic ulcers. Evidence is insufficient to estimate the effect of PRP on important outcomes such as pain, hospitalization, amputations and wound recurrence for diabetic ulcers. There is also insufficient evidence for the use of platelet rich plasma for non-diabetic chronic wounds. One highly regarded evidence-based source (AHRQ) found moderate SOE for use of PRP for diabetic lower extremity ulcers; however, another highly regarded evidence based source (NICE) does not recommend PRP for this indication. Currently, no private insurer surveyed is covering PRP for any indication, although this may change in the future based on the 2021 CMS decision.
    c. HERC staff summary: there is insufficient evidence regarding the efficacy of platelet rich plasma as a treatment for diabetic wounds/ulcers
    d. HERC staff recommendation:
        i. Place HCPCS G0465 on line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR

HAVE HARMS THAT OUTWEIGH BENEFITS and modify the GN173 entry for this technology as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
Line 662
The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
G0460 G0465	Autologous platelet rich plasma for diabetic or non-diabetic chronic wounds/ulcers including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment	Insufficient evidence of effectiveness	May, 2021

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Original Research

Use of Autologous Skin Cell Suspension for the Treatment of Hand Burns: A Pilot Study

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Key words:
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Purpose: Autologous skin cell suspension (ASCS) is a valid alternative and adjunct to split-thickness skin grafting (STSG) for treating burns. Limited data exists regarding the use of ASCS for hand burns. We hypothesized that using ASCS in hand burns shortens healing time with no difference in complications and less donor site morbidity.
Methods: This was a retrospective chart review of second- and third-degree hand burns treated at a level 1 Trauma and Burn Center from 2017 to 2019. Study groups included patients with hand burns treated with ASCS in combination with STSG and those treated with STSG alone. Outcomes included time to re-epithelialization, return to work, length of hospital stay, and complications including reoperation, graft failure, and infection.
Results: Fifty-nine patients aged 14 to 85 years (mean age 39 ± 15 years) met inclusion criteria. The ASCS treatment group comprised 37 patients; STSG comprised 22 patients. Mean follow-up time was 14 ± 7 months. The ASCS treatment group had a larger mean percent total body surface area (TBSA) (22% ± 14% vs 6% ± 8%; $P < .05$). There was no difference in time to wound re-epithelialization between both groups (ASCS, 11 ± 4 days vs STSG, 11 ± 5 days). Mean length-of-stay was 23 ± 13 days compared to 10 ± 13 days ($P < .05$) between the ASCS and STSG groups, respectively. No patients in the ASCS group required reoperation, whereas 2 patients in the STSG group required such for an infection-related graft loss and a web space contracture release. On multivariable analysis adjusting for TBSA, ASCS was associated with an earlier return to work ($P < .05$).
Conclusions: ASCS is safe and effective in treating hand burns. ASCS was associated with similar rates of re-epithelialization, earlier return to work, and no difference in complications compared with STSG.
Type of study/level of evidence: Therapeutic IV.

Deep dermal injuries involving the hand are potentially debilitating and benefit from tangential excision and skin grafting methods for hand reconstruction.[1] Early excision of burn wounds and prompt closure with autologous split-thickness skin grafts are the current standard of care.[2,3] Severe hand burns requiring skin grafting present unique challenges. To achieve a functional and aesthetic outcome, healing by secondary intention and scar formation should be minimized.[4] Delayed wound healing can result in scar contracture throughout the hand leading to a restricted range of motion, decreased functional strength, impaired work and daily activity performance, and the need for further surgery.[5] Inherent limitations of split-thickness skin grafting (STSG) include the risk of donor site morbidity and availability of noninvolved donor skin. Moreover, this treatment strategy is associated with pain, pruritis, infection, dyschromia, dyspigmentation, delayed healing, and hypertrophic scarring.[6–8]

Autologous skin cell suspension (ASCS) has been implemented as a valid alternative and adjunct to STSG for treating burns as less

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ORIGINAL RESEARCH

Cost-Effectiveness of the Use of Autologous Cell Harvesting Device Compared to Standard of Care for Treatment of Severe Burns in the United States

Stacey Kowal · Eliza Kruger · Pinar Bilir · James H. Holmes IV · William Hickerson · Kevin Foster · Scott Nystrom · Jeremiah Sparks · Narayan Iyer · Katie Bush · Andrew Quick

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ABSTRACT

Introduction: When introducing a new intervention into burn care, it is important to consider both clinical and economic impacts, as the financial burden of burns in the USA is significant. This study utilizes a health economic modeling approach to estimate cost-effectiveness and burn center budget-impact for the use of the RECELL® Autologous Cell Harvesting Device to prepare autologous skin cell suspension (ASCS) compared to standard of care (SOC) split-thickness skin graft (STSG) for the treatment of severe burn injuries requiring surgical intervention for definitive closure.

Methods: A hospital-perspective model using sequential decision trees depicts the acute burn care pathway (wound assessment, debridement/excision, temporary coverage, definitive closure) and predicts the relative differences between use of ASCS compared to SOC. Clinical inputs and ASCS impact on length of stay (LOS) were derived from clinical trials and real-world use data, American Burn Association National Burn Repository database analyses, and burn surgeon interviews. Hospital resource use and unit costs were derived from three US burn centers. A budget impact calculation leverages Monte Carlo simulation to estimate the overall impact to a burn center.

Results: ASCS treatment is cost-saving or cost-neutral (< 2% difference) and results in lower

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Implantable Cardiac Alert System for Early Recognition of ST-Segment Elevation Myocardial Infarction

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ABSTRACT

BACKGROUND Symptoms remain a poor prompt for acute coronary syndromes (ACS). Timely restoration of perfusion in ST-segment elevation myocardial infarction is associated with improved left ventricular function and survival.

OBJECTIVES This report details the results of ALERTS (AngelMed for Early Recognition and Treatment of STEMI), a multicenter, randomized trial of an implantable cardiac monitor that alerts patients with rapidly progressive ST-segment deviation.

METHODS High-risk ACS subjects (N = 907) were randomized to a control (alarms deactivated) or treatment group for 6 months, after which alarms were activated in all subjects. The primary safety endpoint was absence of system-related complications (>90%). The composite primary efficacy endpoint was cardiac/unexplained death, new Q-wave myocardial infarction, or detection to presentation time >2 h.

RESULTS Safety was met with 96.7% freedom from system-related complications (n = 30). The efficacy endpoint for a confirmed occlusive event within 7 days was not significantly reduced in the treatment compared with control group (16 of 423 [3.8%] vs. 21 of 428 [4.9%], posterior probability = 0.786). Within a 90-day window, alarms significantly decreased detection to arrival time at a medical facility (51 min vs. 30.6 h; Pr [pt < pc] >0.999). In an expanded analysis using data after the randomized period, positive predictive value was higher (25.8% vs. 18.2%) and false positive rate significantly lower in the ALARMS ON group (0.164 vs. 0.678 false positives per patient-year; p < 0.001).

CONCLUSIONS The implantable cardiac system detects early ST-segment deviation and alerts patients of a potential occlusive event. Although the trial did not meet its pre-specified primary efficacy endpoint, results suggest that the device may be beneficial among high-risk subjects in potentially identifying asymptomatic events. (AngelMed for Early Recognition and Treatment of STEMI [ALERTS]; NCT00781118) (J Am Coll Cardiol 2019;73:1919–27)

Improvements in total ischemic time (symptom-to-door + door-to-balloon or door-to-needle times) in the setting of ST-segment elevation myocardial infarction (STEMI) are associated with improved survival (1-6). Despite the well-recognized time dependency of myocardial salvage in STEMI (7), improvements in door-to-balloon time from 90 to 75 min have not improved survival (8). Additional improvements in survival are likely dependent on decreasing symptom-to-door time (9). The lengthy

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

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Section 7.0

New Discussion Items

Biennial Review 2024
Angioedema Line Removal

Question: Should the redundant angioedema line be struck through until the next biennial review?

Question source: Dr. Ben Hoffman, HERC staff

Issue: Dr. Ben Hoffman brought concerns to HERC staff that angioedema and biotinidase deficiency were both below the funding line. Biotinidase deficiency is an inborn error of metabolism that leads to severe developmental issues unless treated with a supplement. Angioedema is a condition in which medications, foods, or other triggers can cause swelling of the mucous membranes, airway, and GI tract. Angioedema can be life threatening when it causes airway obstruction.

On researching this question, HERC staff discovered that the lower line was completely redundant to another, covered line. Line 192 HEREDITARY ANGIOEDEMA contains all the diagnosis codes and all of the treatment codes included on line 487 ANGIOEDEMA. There is no guideline or other indication of when one of these diagnoses would be on a covered vs an uncovered line.

Lines 192 and 487 were created out of a split line (then line 343) during the 2012 ICD-10 review. The allergists who reviewed that line felt that hereditary angioedema was much more serious than angioneurotic edema and should be prioritized on separate lines. However, there is a single ICD-10 code for all forms of angioedema (ICD-10-CM T78.3XXA-T78.3XXD Angioneurotic edema). ICD-10 D84.1 (Defects in the complement system) also lists hereditary angioneurotic edema as a subdiagnosis. During the ICD-10 Allergy review, the allergists did note that angioneurotic edema has a variety of manifestations, including death.

Current Prioritized List status

ICD-10 Code	**Code Description**	**Current Placement**
D81.810	Biotinidase deficiency	60 METABOLIC DISORDERS 192 HEREDITARY ANGIOEDEMA 241 ACUTE AND SUBACUTE NECROSIS OF LIVER; SPECIFIED INBORN ERRORS OF METABOLISM (E.G., MAPLE SYRUP URINE DISEASE, TYROSINEMIA) 487 ANGIOEDEMA
D84.1	Defects in the complement system [hereditary angioneurotic edema listed as a subdiagnosis]	60,192,241 313 DISORDERS INVOLVING THE IMMUNE SYSTEM
T78.3	Angioneurotic edema	192, 487 Dysfunction lines (71, 292, 345, 377)

Biennial Review 2024
Angioedema Line Removal

Line: 192
Condition: HEREDITARY ANGIOEDEMA
Treatment: MEDICAL THERAPY
ICD-10: D81.810,D84.1,T78.3XXA-T78.3XXD
CPT: 98966-98972,99051,99060,99070,99078,99184,99202-99239,99281-99285,99291-99366, 99374-99404,99411-99416,99421-99429,99441-99449,99451,99452,99468-99472,99475-99480,99487-99491,99495-99498,99605-99607
HCPCS: G0068,G0071,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427,G0463-G0467, G0490,G0508-G0511,G2011,G2012,G2064,G2065

Line: 487
Condition: ANGIOEDEMA
Treatment: MEDICAL THERAPY
ICD-10: D81.810,T78.3XXA-T78.3XXD
CPT: 98966-98972,99051,99060,99070,99078,99184,99202-99239,99281-99285,99291-99404, 99411-99449,99451,99452,99468-99472,99475-99480,99487-99491,99495-99498,99605-99607
HCPCS: G0068,G0071,G0088-G0090,G0248-G0250,G0396,G0397,G0406-G0408,G0425-G0427, G0463-G0467,G0490,G0508-G0511,G2011,G2012,G2064,G2065,G2211,G2212,G2214, G2251,G2252

HERC staff summary
Based on the ICD-10 Allergy review, two angioedema lines were created. However, these lines are completely redundant in terms of coding. In order to continue to have two lines, a guideline with extensive descriptions of the types of angioedema that are not covered would need to be created. HERC staff feels that as angioedema in some forms has the ability to cause death, it should be prioritized above the funding line. As a result, staff is recommending striking the lower line. This should have no effect on coverage, as the diagnosis and procedure code pairings on line 487 are all reproduced on line 192. Additionally, it can cause confusion to have a potentially life threatening condition appear to be non-funded.

Additionally, biotinidase deficiency has nothing to do with angioedema and should be removed from these lines and left only on the lines for inborn errors of metabolism.

HERC staff recommendations:
1) For the January 1, 2022 Prioritized List:
    a. Strike through line 487 ANGIOEDEMA
    b. Rename line 192 ~~HEREDITARY~~ ANGIOEDEMA
    c. Delete ICD-10-CM D81.810 (Biotinidase deficiency) from line 192 HEREDITARY ANGIOEDEMA
        i. Keep on the metabolic disorders lines
2) For the January 1, 2024 Prioritized List:
    a. Delete line 487

Platelet Rich Plasma

Question: Is platelet rich plasma covered for any indication on the Prioritized List?

Question source: Holly Jo Hodges, CCO medical director

Issue: Platelet-rich plasma (PRP) therapy uses injections of a concentration of a patient's own platelets to accelerate the healing of injured tendons, ligaments, muscles and joints. The mechanism of action of PRP is unclear.

Platelet rich plasma for treatment of knee osteoarthritis was reviewed as part of a coverage guidance and wording excluding it from use for this indication was put into a guideline. PRP for treatment of spinal conditions was added to Guideline Note 37 at the October, 2021 meeting. PRP for treatment of ulcers and wounds was discussed in May, 2021 but left on line 662/GN 173.

CCOs would like further direction on coverage, as they get frequent requests for coverage of PRP for a wide variety of indications. Currently, the only code for general PRP is a level III CPT code, 0232T INJECTION(S), PLATELET RICH PLASMA, ANY SITE, INCL. These types of codes are generally considered experimental by Medicaid and not placed on the Prioritized List.

PRP can be used to treat a wide variety of tendinopathies, tendon tears, joint inflammation, plantar fasciitis, osteoarthritis, low back pain, and other musculoskeletal conditions.

Current Prioritized List status

GUIDELINE NOTE 37, SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS

Lines 346,529

Spine surgery is included on Line 346 only in the following circumstances:

A) Decompressive surgery is included on Line 346 to treat debilitating symptoms due to central or foraminal spinal stenosis, and only when the patient meets the following criteria:
   1) Has MRI evidence of moderate or severe central or foraminal spinal stenosis AND
   2) Has neurogenic claudication OR
   3) Has objective neurologic impairment consistent with the MRI findings. Neurologic impairment is defined as objective evidence of one or more of the following:
      a) Markedly abnormal reflexes
      b) Segmental muscle weakness
      c) Segmental sensory loss
      d) EMG or NCV evidence of nerve root impingement
      e) Cauda equina syndrome
      f) Neurogenic bowel or bladder
      g) Long tract abnormalities

   Foraminal or central spinal stenosis causing only radiating pain (e.g. radiculopathic pain) is included only on Line 529.

B) Spinal fusion procedures are included on Line 346 for patients with MRI evidence of moderate or severe central spinal stenosis only when one of the following conditions are met:
   1) spinal stenosis in the cervical spine (with or without spondylolisthesis) which results in objective neurologic impairment as defined above OR

2) spinal stenosis in the thoracic or lumbar spine caused by spondylolisthesis resulting in signs and symptoms of neurogenic claudication and which correlate with xray flexion/extension films showing at least a 5 mm translation OR
3) pre-existing or expected post-surgical spinal instability (e.g. degenerative scoliosis >10 deg, >50% of facet joints per level expected to be resected)

For all other indications, spine surgery is included on Line 529.

The following interventions are not included on these lines due to lack of evidence of effectiveness for the treatment of conditions on these lines, including cervical, thoracic, lumbar, and sacral conditions:

- local injections (including ozone therapy injections)
- botulinum toxin injection
- intradiscal electrothermal therapy
- therapeutic medial branch block
- coblation nucleoplasty
- percutaneous intradiscal radiofrequency thermocoagulation
- percutaneous laser disc decompression
- radiofrequency denervation
- corticosteroid injections for cervical pain
- intradiscal injections, including platelet rich plasma, stem cells, methylene blue, or ozone

Corticosteroid injections for low back pain with or without radiculopathy are only included on Line 529. Diagnostic anesthetic injections for selective nerve root blocks are included on Line 529 for lumbar or sacral symptoms.

The development of this guideline note was informed by HERC coverage guidances on Percutaneous Interventions for Low Back Pain, Percutaneous Interventions for Cervical Spine Pain, Low Back Pain: Corticosteroid Injections and Low Back Pain: Minimally Invasive and Non-Cordicosteroid Percutaneous Interventions. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

GUIDELINE NOTE 104, NEWER INTERVENTIONS FOR OSTEOARTHRITIS OF THE KNEE

Lines 431,463

The following treatments are not included on this line for osteoarthritis of the knee:

- Whole body vibration
- Glucosamine/chondrioitin (alone, or in combination)
- Platelet rich plasma
- Viscosupplementation
- Transcutaneous electrical stimulation (TENS)

CPT 20610 and 20611 are included on these lines only for interventions other than viscosupplementation for osteoarthritis of the knee.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
G0460	Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment	Insufficient evidence of effectiveness	May 2021

Evidence

1) **Nazaroff 2021,** systematic review of level I and II studies of platelet rich plasma therapy
    a. N=132 articles
        i. 28 different conditions across eight medical fields. Studies investigating PRP treatment for musculoskeletal (MSK) conditions comprised 74% of all studies. Tendinopathy (n = 29) and osteoarthritis (n = 28) were the two most commonly studied conditions. MSK studies were 76% level 1 evidence while 57% of all other studies were level 1 evidence ($p<0.05$). Cosmetic studies comprised 14% (n = 19) of all studies, and 53% of these were level I evidence.
        ii. Majority of studies were assessed using the Cochranes Risk of Bias Tool, 80% (n = 106). Among these studies, 30% (n = 32) were assessed to be "Low" risk of bias, 25% (n = 26) were found to have "Some Concerns", and 45% (n = 48) were assessed to be "High" risk of bias
    b. Overall, 61% of the studies found PRP to be favorable over control treatment, with no difference in favorable reporting between MSK and other medical specialties.
    c. Conclusions: In summary, the vast majority of level I and II clinical studies investigating PRP have been conducted for MSK injuries, with only a handful of studies conducted for conditions in other medical specialties. Studies that reported details on PRP processing and composition were in the minority, and PROMs were not often used as an outcome measure in non-MSK studies. Rigorous reporting in human clinical studies across all medical specialties is crucial for evaluating the effects of PRP and moving towards disease-specific and individualized treatment.
2) **Gato-Calvo 2019**, evidence review of platelet rich plasma for treatment of osteoarthritis
    a. N=5 systematic reviews and meta-analyses
        i. A total of 19 individual trials were identified in the five reviews but only 9 were level of evidence I RCTs, and many had moderate or high risks of bias.
    b. At present, results from these RCTs seem to favor PRP use over other intraarticular treatments to improve pain scales in the short and medium term (6–12months), but the overall level of evidence is low. As a result, clinical effectiveness of PRP for knee osteoarthritis treatment is still under debate. This is, prominently, the result of a lack of standardization of PRP products, scarceness of high quality RCTs not showing high risks of bias, and poor patient stratification for inclusion in the RCTs.
3) **Chen 2018**, systematic review and meta-analysis of platelet rich plasma on tendon and ligament healing
    a. N=21 studies (1031 patients)
        i. The majority of studies published investigated rotator cuff (38.1%) or lateral epicondylitis (38.1%).
        ii. Other included conditions: patellar tendinopathy (PT), achilles tendinopathy (AT), anterior cruciate ligament injury (ACL), and hamstring tendinopathy (HT).
    b. 17 studies (844 participants) reported short-term VAS data and 14 studies (771 participants) reported long-term VAS data. Overall, long-term follow-up results showed significantly less pain in the PRP group compared to control (WMD: −0.84; 95% CI: −1.23, −0.44; $p<0.01$). Patients treated for rotator cuff injury (WMD: −0.53; 95% CI: −0.98, −0.09; $p=0.02$) and lateral epicondylitis (WMD: −1.39; 95% CI: −2.49, −0.29; $p=0.01$) both reported significantly less pain in the long-term. Substantial heterogeneity was reported at baseline ($I2: 72.0\%$, $p<0.01$), short term follow-up ($I2: 72.5\%$, $p<0.01$), long term follow-up ($I2: 76.1\%$, $p<0.01$), and overall ($I2: 75.8\%$, $p<0.01$). The funnel plot

appeared to be asymmetric, with some missingness at the lower right portion of the plot suggesting possible publication bias.

c. No study reported severe adverse events (SAEs).
d. **Conclusion:** This review shows that PRP may reduce the pain associated with lateral epicondylitis and rotator cuff pathology.

4) **Hussain 2017**, evidence based evaluation of platelet rich plasma in orthopedics
    a. Reviewed conditions:
        i. Knee osteoarthritis, rotator cuff repair, epicondylitis, patellar tendinopathy, Achilles tendinopathy, hamstring injuries and anterior cruciate ligament repair
    b. the evidence appears to suggest that PRP may provide some benefit in patients who present with knee osteoarthritis or lateral epicondylitis. On the other hand, evidence appears to be inconsistent or shows a minimal benefit for PRP usage in rotator cuff repair, patellar and Achilles tendinopathies, hamstring injuries, anterior cruciate ligament (ACL) repair, and medial epicondylitis. There is limited confidence in the conclusions from the published meta-analyses due to issues with statistical pooling, and limited subgroup analyses exploring the substantial heterogeneity across studies. Evidence-based clinicians considering the use of PRP in their patients with musculoskeletal injuries should be wary that the literature appears to be inconsistent and thus far, inconclusive.

<u>Other payer policies</u>

1) CMS LCD 2021: This is a NON-coverage policy for all platelet-rich plasma (PRP) injections and/or applications as a means of managing musculoskeletal injuries and/or joint conditions
    a. While promising, we believe that there is insufficient high-quality evidence to justify the use of PRP for the treatment of any condition except for within the confines of a well-designed clinical trial.
2) All private payers surveyed considered PRP to be experimental

Platelet Rich Plasma

HERC staff summary

General reviews of the effectiveness of platelet rich plasma for a wide variety of conditions finds that the literature is highly biased and inconclusive. CMS and all private payers consider PRP experimental, and Medicaid considers CPT level III codes, such as 0232T, to be experimental. HERC staff recommend placing CPT 0232T on line 662/GN173, with individual indications reviewed in the future as evidence matures.

HERC staff recommendation

1) Add CPT 0232T to line 662/GN173 as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed	Insufficient evidence of effectiveness	November 2021

PLOS ONE

RESEARCH ARTICLE

Reporting in clinical studies on platelet-rich plasma therapy among all medical specialties: A systematic review of Level I and II studies

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Abstract

Background

The clinical practice of platelet-rich plasma (PRP) therapy has grown significantly in recent years in multiple medical specialties. However, comparisons of PRP studies across medical fields remain challenging because of inconsistent reporting of protocols and characterization of the PRP being administered. The purpose of this systematic review was to determine the quantity of level I/II studies within each medical specialty and compare the level of study reporting across medical fields.

Methods

The Cochrane Database, PubMed, and EMBASE databases were queried for level I/II clinical studies on PRP injections across all medical specialties. From these studies, data including condition treated, PRP processing and characterization, delivery, control group, and assessed outcomes were collected.

Results

A total of 132 studies met the inclusion and exclusion criteria and involved 28 different conditions across 8 specialties (cardiothoracic surgery, cosmetic, dermatology, musculoskeletal (MSK), neurology, oral maxillofacial surgery, ophthalmology, and plastic surgery). Studies on PRP for MSK injuries made up the majority of the studies (74%), with knee osteoarthritis and tendinopathy being most commonly studied. Of the 132 studies, only 44 (33%) characterized the composition of PRP used, and only 23 (17%) reported the leukocyte component. MSK studies were more likely to use patient-reported outcome measures to assess outcomes, while studies from other specialties were more likely to use clinician- or imaging-based objective outcomes. Overall, 61% of the studies found PRP to be favorable over control treatment, with no difference in favorable reporting between MSK and other medical specialties.

Competing interests: The authors have declared that no competing interests exist.

Conclusions

The majority of level I/II clinical studies investigating PRP therapy across all medical specialties have been conducted for MSK injuries with knee osteoarthritis and tendinopathy being the most commonly studied conditions. Inconsistent reporting of PRP composition exists among all studies in medicine. Rigorous reporting in human clinical studies across all medical specialties is crucial for evaluating the effects of PRP and moving towards disease-specific and individualized treatment.

Introduction

The use of platelet-rich plasma (PRP) to treat a multitude of medical conditions has greatly increased over the past decade. As a strategy to deliver a higher concentration of growth factors and cytokines that initiate and regulate tissue healing, PRP therapy has been utilized for a wide range of orthopaedic injuries, including tendinopathies, osteoarthritis, and muscle injuries [1–3]. Recently, PRP has also been increasingly used for the treatment of cosmetic conditions, including hair restoration, breast augmentation, scar treatment, and dermatologic conditions [4–6]. Other reported applications of PRP therapy have included nerve regeneration, periodontal therapies, wound healing, and augmentation of surgical repairs [7–9].

Despite the widespread clinical practice of PRP in all areas of medicine, there remains uncertainty and skepticism among the medical community regarding its efficacy. Much of this skepticism can be attributed to the unawareness of the quantity and quality of evidence investigating PRP treatment, particularly across medical specialties. The practice of evidence-based medicine utilizes the strongest quality of evidence to make informed decisions on the care of individual patients. Although many randomized controlled trials investigating PRP have been conducted for musculoskeletal (MSK) conditions [1,3,10,11], the number of high-quality studies on PRP treatment from other medical specialties compared to orthopaedics, sports medicine, and other MSK fields is unknown. Furthermore, there remain deficiencies in the level of reporting in these studies, particularly regarding the processing and composition of PRP. This has led to calls within orthopaedics for minimal reporting standards in order to allow for reproducibility and comparison across studies [12–15]. Whether the level of reporting is similarly inconsistent within studies from other medical fields is unknown. Detailed reporting in clinical trials for PRP across all medical fields would be beneficial for identifying the key components of PRP and efficiently translating PRP therapy into clinically meaningful treatment.

The purpose of this systematic review was to review the current PRP literature across all medical specialties and determine 1) the quantity of level I and II studies within each medical specialty based on indication, and 2) the level of reporting in these studies with regards to PRP processing, composition, activation, delivery, and outcome assessment. Due to the majority of these studies being from the orthopaedic literature, comparisons in the level of reporting between MSK studies and those from other medical fields were performed.

Materials and methods

Article identification and selection process

A literature search was conducted in June 2019 to identify articles pertaining to PRP therapy according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Fig 1) [16]. The PubMed (including MEDLINE), Cochrane, and EMBASE

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Platelet-rich plasma in osteoarthritis treatment: review of current evidence

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Abstract: Platelet-rich plasma (PRP) is defined as a volume of plasma with a platelet concentration higher than the average in peripheral blood. Many basic, preclinical and even clinical case studies and trials report PRP's ability to improve musculoskeletal conditions including osteoarthritis, but paradoxically, just as many conclude it has no effect. The purpose of this narrative review is to discuss the available relevant evidence that supports the clinical use of PRP in osteoarthritis, highlighting those variables we perceive as critical. Here, recent systematic reviews and meta-analyses were used to identify the latest randomized controlled trials (RCTs) testing a PRP product as an intra-articular treatment for knee osteoarthritis, compared with an intra-articular control (mostly hyaluronic acid). Conclusions in the identified RCTs are examined and compared. In total, five recent meta-analyses and systematic reviews were found meeting the above criteria. A total of 19 individual trials were identified in the five reviews but only 9 were level of evidence I RCTs, and many had moderate or high risks of bias. At present, results from these RCTs seem to favor PRP use over other intra-articular treatments to improve pain scales in the short and medium term (6–12 months), but the overall level of evidence is low. As a result, clinical effectiveness of PRP for knee osteoarthritis treatment is still under debate. This is, prominently, the result of a lack of standardization of PRP products, scarceness of high quality RCTs not showing high risks of bias, and poor patient stratification for inclusion in the RCTs.

Keywords: allogenic products, anti-inflammatory intra-articular therapies, clinical evidence, clinical trials, knee osteoarthritis, patient stratification, platelet-rich plasma

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Introduction

Platelets, also known as thrombocytes, are small cytoplasmic fragments derived from bone marrow megakaryocytes. Most platelet functions are directly connected with platelet activation, a process that occurs naturally after an injury in the wall of a blood vessel. Platelets are then exposed to collagen and other extracellular matrix proteins that stimulate their activation, resulting in the release of the content of their cytoplasmic granules.[1] Overall, platelets contain over 800 proteins and molecules, comprising cytokines, chemokines, membrane proteins, metabolites, messenger molecules, growth factors (GFs) and numerous soluble proteins.[2] As a result, besides their role in coagulation and hemostasis, platelets are also involved in vasoconstriction, inflammation, immune response, angiogenesis and tissue regeneration and consequently, they participate in numerous physiologic signaling mechanisms and are related to multiple pathologies.[3–5]

The therapeutic use of platelet concentrates was first described by Whitman in 1997,[6] although blood-derived fibrin glues were already used 30 years earlier to seal wounds and stimulate their healing.[7] In 1998, platelet concentrates started to be known as platelet-rich plasma (PRP), generally defined as a volume of autologous plasma containing a higher platelet count than peripheral blood (150,000–350,000 platelets/μl).[8] Thereafter

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The Efficacy of Platelet-Rich Plasma on Tendon and Ligament Healing: A Systematic Review and Meta-Analysis with Bias Assessment

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Abstract

Background: There has been a surge in high level studies investigating platelet rich plasma (PRP) for tendon and ligament injuries. A number of meta-analysis have been published, but few studies have focused exclusively on tendon and ligament pathology.

Purpose: To perform a meta-analysis assessing the ability of PRP to reduce pain in patients with tendon and ligament injuries.

Study Design: Systematic review and meta-analysis

Methods: This study followed the PRISMA (Preferred Reporting Items and Systematic Reviews and Meta-Analyses) guidelines. A comprehensive search of the literature was carried out in April 2017 using electronic databases PubMed, MEDLINE, and the Cochrane Library. Only Level I studies were included. Platelet and leukocyte count, injection volume, kit used, participant age/gender, comparator, and activating agent used were recorded. The short-term and long-term efficacy of PRP was assessed using the visual analog scale (VAS), which measures pain intensity. Pathology subgroups (rotator cuff, tendinopathy, ACL, and lateral epicondylitis) were evaluated. Funnel plots and Egger's test were used to screen for publication bias and sensitivity analysis was performed to evaluate the impact of potential outliers by removing studies one at a time.

Results: Thirty-seven articles were included in this review, 21 (1031 participants) of which could be included in the quantitative analysis. The majority of studies published investigated rotator cuff (38.1%) or lateral epicondylitis (38.1%). 17 studies (844 participants) reported short-term VAS data and 14 studies (771 participants) reported long-term VAS data. Overall, long-term follow-up results showed significantly less pain in the PRP group compared to control (WMD: −0.84; 95% CI: −1.23, −0.44; $p<0.01$). Patients treated for rotator cuff injury (WMD: −0.53; 95% CI: −0.98, −0.09; $p=0.02$) and lateral epicondylitis (WMD: −1.39; 95% CI: −2.49, −0.29; $p=0.01$) both reported significantly less pain in the long-term. Substantial heterogeneity was reported at baseline (I^2: 72.0%, $p<0.01$), short term follow-up (I^2: 72.5%, $p<0.01$), long term follow-up (I^2: 76.1%, $p<0.01$), and overall (I^2: 75.8%, $p<0.01$). The funnel plot appeared to be asymmetric, with some missingness at the lower right portion of the plot suggesting possible publication bias.

Conclusion: This review shows that PRP may reduce the pain associated with lateral epicondylitis and rotator cuff pathology.

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Special Issue: "Orthobiologics: role of platelet-rich plasma in orthopaedic clinical practice"
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REVIEW ARTICLE OPEN ACCESS

An evidence-based evaluation on the use of platelet rich plasma in orthopedics – a review of the literature

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Abstract – Within orthopedics, the use of platelet-rich plasma (PRP) has been rapidly increasing in popularity, however, its true effectiveness has yet to be fully established. Several studies find that injecting PRP to the site of injury does not provide any significant benefit with respect to clinical outcomes; however, many others report the contrary. Due to the conflicting evidence and multiple meta-analyses conducted on the topic, a literature review of high-quality evidence on the use of PRP for common orthopaedic conditions was performed. Thus far, the evidence appears to suggest that PRP may provide some benefit in patients who present with knee osteoarthritis or lateral epicondylitis. On the other hand, evidence appears to be inconsistent or shows a minimal benefit for PRP usage in rotator cuff repair, patellar and Achilles tendinopathies, hamstring injuries, anterior cruciate ligament (ACL) repair, and medial epicondylitis. There is limited confidence in the conclusions from the published meta-analyses due to issues with statistical pooling, and limited subgroup analyses exploring the substantial heterogeneity across studies. Evidence-based clinicians considering the use of PRP in their patients with musculoskeletal injuries should be weary that the literature appears to be inconsistent and thus far, inconclusive.

Key words: Platelet rich plasma, Orthobiologics, Evidence-based medicine, Review.

Platelet-rich plasma in orthopedics

Within orthopedics, the use of platelet-rich plasma (PRP) has been increasing in popularity. United States estimates alone suggest that approximately 86,000 athletes are treated with PRP annually [1]. Even though its popularity is rising, its true effectiveness has yet to be fully established. Several studies find that injecting PRP to the site of injury does not add any significant benefit to clinical outcomes; however, many others report the contrary. This becomes even more of a concern since the cost of treatment can be relatively high. Peerbooms et al. (2010) reported that the cost for a single PRP injection is approximately $840.00 USD whereas a simple corticosteroid injection is around $300.00 USD [2]. With the conflicting evidence and high cost of PRP treatment, it is imperative that a more definitive answer regarding its efficacy is found. Given the continued uncertainty of PRP with regard to its efficacy at improving various clinical outcomes in a broad spectrum of orthopedic conditions, we undertook this review to help clinicians better understand the basics behind PRP and the clinical evidence surrounding it.

What is platelet-rich plasma?

The platelets contained within autologous blood play an important role in healing since they secrete several growth factors to the site of injury [3]. Briefly, among other roles, these platelets serve to promote mitogenesis of healing capable cells and angiogenesis in the tissue [4]. Autologous blood, which contains such platelets in higher than normal concentrations, is commonly referred to as platelet-rich plasma (PRP). For instance, the normal platelet count in healthy individuals is around $1.5–4.5 \times 10^5/\mu L$; however, to be considered PRP, the platelet should be 4–5 times above this amount [5]. This relatively recent biotechnology has been reported to enhance the healing process since an increased number of platelets results in an increased number of secreted growth factors, thereby theoretically improving the healing process [4, 6]. Some of the growth factors in PRP include: platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), and epithelial growth factor (EGF) [1, 3, 6]. Thus, unlike recombinant technology which is synthetic, PRP takes advantage of the naturally occurring proteins in the healing process. In addition to these factors, PRP contains adhesion molecules which

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Radiofrequency Ablation of Renal Tumors

Question: Should radiofrequency ablation of renal tumors be moved to a covered line?

Question source: Alison Little, CCO medical director

Issue: Conventional treatment of renal cancer is total or partial nephrectomy (open or laparoscopic). For some smaller tumors, cryoablation or radiofrequency ablation may be selected. Radiofrequency ablation (RFA) is one of several less invasive approaches that have been investigated for the treatment of kidney cancer. In RFA, an electric current from a radiofrequency (RF) generator delivers energy into the tumor, via an electrode. Tissue impedance leads to heat generation, production of lethal temperatures, and ablation of tissue. RFA has been used most often for adults with small kidney tumors. Indications include comorbidities that preclude surgery, a single kidney, and multifocal renal cell carcinoma.

Radiofrequency ablation of renal tumors (CPT 50592) is on line 662/GN173 and has not been reviewed in 15+ years.

Current Prioritized List status

CPT Code	**Code Description**	**Current Placement**
50240	Nephrectomy, partial	21 VESICOURETERAL REFLUX 49 CONGENITAL HYDRONEPHROSIS 86 CONGENITAL ANOMALIES OF GENITOURINARY SYSTEM 214 CANCER OF KIDNEY AND OTHER URINARY ORGANS 271 CANCER OF BLADDER AND URETER
50250	Ablation, open, 1 or more renal mass lesion(s), cryosurgical, including intraoperative ultrasound guidance and monitoring, if performed	86,214,271
50542	Laparoscopy, surgical; ablation of renal mass lesion(s), including intraoperative ultrasound guidance and monitoring, when performed	47 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS 86,214,271 511 BENIGN NEOPLASM OF KIDNEY AND OTHER URINARY ORGANS
50543	Laparoscopy, surgical; partial nephrectomy	47,86,214,271,511
50592	Ablation, 1 or more renal tumor(s), percutaneous, unilateral, radiofrequency	662
50593	Ablation, renal tumor(s), unilateral, percutaneous, cryotherapy	ANCILLARY PROCEDURES

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
50592	Radiofrequency ablation, 1 or more renal tumor(s)	Insufficient evidence of effectiveness	December 2005

Evidence

1) **NICE 2010**, percutaneous radiofrequency ablation for renal cell cancer
    a. Current evidence on the safety and efficacy of percutaneous radiofrequency ablation (RFA) for renal cancer in the short and medium term appears adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit, and provided that patients are followed up in the long term
    b. A meta-analysis of 47 studies (non-randomized comparative studies and case series) including a total of 1375 tumors treated by RFA (n = 775) or cryoablation (n = 600) reported local tumor progression (defined as radiographic or pathological evidence of residual disease after initial treatment, regardless of time to recurrence) in 13% (100/775) and 5% (31/600) of tumors respectively at a mean 19-month follow-up ($p < 0.001$). The meta-analysis reported progression to metastatic disease in 2% (19/775) of tumors treated by RFA and 1% (6/600) of tumors treated by cryoablation (p = not significant)
    c. In a non-randomized comparative study of 233 patients (260 tumors), residual or recurrent tumor on follow-up magnetic resonance imaging (MRI) was reported in 11% (9/81) of tumors treated by percutaneous RFA and 2% (3/ 179) of tumors treated by laparoscopic cryotherapy (1-year and 3-year median follow-up respectively).
    d. Adverse events:
        i. Hemorrhage was reported in 6% (5/85) of patients in a case series of 85 patients.
        ii. Hematoma requiring blood transfusion was reported in 1% (1/104) of patients in a case series and 1% (1/82) of RFA procedures in the non-randomized comparative study of 233 patients. Hematoma not requiring blood transfusion was reported in 5% (4/82) (3 perirenal requiring no treatment; 1 retroperitoneal) of RFA procedures in the non-randomized comparative study of 233 patients. Asymptomatic perirenal hematoma development was reported in 12% (4/34) (managed conservatively with no sequelae) of RFA procedures in the case series of 31 patients.
    e. The Specialist Advisers indicated that there was uncertainty about the procedure's efficacy in tumors 4 cm or greater in diameter.

Expert guidelines

1) NCCN Guideline Kidney Cancer Version 2.2022
    a. Thermal ablation (e.g. cryosurgery, radiofrequency ablation) is an option for the management of patients with clinical stage T1 renal lesions
        i. Thermal ablation is an option for masses <3 cm, but may also be an option for larger masses in select patients. Ablation in masses >3cm is associated with higher rates of local recurrence/persistence and complications
        ii. Biopsy of small lesions confirms a diagnosis of malignancy for surveillance, cryosurgery, and radiofrequency ablation strategies

2) American Urological Association 2017
    a. Physicians should consider thermal ablation **(TA)** as an alternate approach for the management of cT1a renal masses <3 cm in size. For patients who elect TA, a

percutaneous technique is preferred over a surgical approach whenever feasible to minimize morbidity. **(Conditional Recommendation; Evidence Level: Grade C)**

b. Both radiofrequency ablation and cryoablation are options for patients who elect thermal ablation. **(Conditional Recommendation; Evidence Level: Grade C)**
c. A renal mass biopsy should be performed prior to ablation to provide pathologic diagnosis and guide subsequent surveillance. **(Expert Opinion)**
d. Counseling about thermal ablation should include information regarding an increased likelihood of tumor persistence or local recurrence after primary thermal ablation relative to surgical extirpation, which may be addressed with repeat ablation if further intervention is elected. **(Strong Recommendation; Evidence Level: Grade B)**

Other payer policies

1) Aetna 2021

a. Aetna considers radiofrequency ablation (RFA) medically necessary for the following indications
    i. Renal cell carcinoma, up to 4-cm in size, in persons who meet the following criteria:
        1. High-risk surgical candidates; *or*
        2. Persons with renal insufficiency, as defined by a glomerular filtration rate of less than or equal to 60 ml/min/m^2; *or*
        3. Persons with a solitary kidney.

2) ConnecticCare (Connecticut Medicaid) 2020

a. Members with small undefined renal lesions (≤ 4 cm in diameter) that are suspected to be malignant, or with malignant potential, are eligible for coverage of either cryoablation or RFA by any modality (eg laparoscopically or percutaneously) when either of the following criteria is met:
    i. Medically or surgically inoperable tumor(s).
    ii. Poor candidacy for standard treatments (i.e., nephrectomy).

Radiofrequency Ablation of Renal Tumors

HERC staff summary

Treatment of small renal cell carcinomas (<3cm) by radiofrequency ablation or cryotherapy in patients who are poor surgical candidates is recommended by NCCN and the American Urological Association. A highly trusted evidence-based source (NICE) has found sufficient evidence of effectiveness in this population to recommend use. Only two other insurance policies were found, but both recommended coverage in limited circumstances.

HERC staff recommendations:

1) Add CPT 50592 (Ablation, 1 or more renal tumor(s), percutaneous, unilateral, radiofrequency) and 50593 (Ablation, renal tumor(s), unilateral, percutaneous, cryotherapy) to line 214 CANCER OF KIDNEY AND OTHER URINARY ORGANS
    a. Advise HSD to remove CPT 50593 from the Ancillary Procedures File
2) Delete CPT 50592 from line 662/GN173
3) Add a new guideline to line 214 as shown below

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
~~50592~~	~~Radiofrequency ablation, 1 or more renal tumor(s)~~	~~Insufficient evidence of effectiveness~~	~~December 2005~~

GUIDELINE NOTE XXX THERMAL ABLATION OF RENAL CELL CARCINOMA

Line 214

Thermal ablation (e.g. cryosurgery, radiofrequency ablation; CPT 50592, 50593) is included on this line only when:

1) The patient has biopsy confirmed stage T1 renal cell cancer of <3 cm size; AND
2) The patient either has a surgically inoperable tumor(s) or is a poor candidate for standard treatments (i.e., nephrectomy).

Percutaneous radiofrequency ablation for renal cancer

Interventional procedures guidance
Published: 28 July 2010
www.nice.org.uk/guidance/ipg353

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

This guidance replaces IPG91.

1 Guidance

This guidance replaces previous guidance on percutaneous radiofrequency ablation of renal cancer (interventional procedure guidance 91).

1.1 Current evidence on the safety and efficacy of percutaneous radiofrequency ablation (RFA) for renal cancer in the short and medium term appears adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit, and provided that patients are followed up in the long term.

1.2 Patient selection for percutaneous RFA for renal cancer should be carried out by a urological cancer multidisciplinary team.

1.3 NICE encourages data collection to provide information about the outcomes of this procedure in the long term. Further research should compare the long-term outcomes of RFA with those of other treatments for renal cancer.

2 The procedure

2.1 Indications and current treatments

2.1.1 There are few symptoms in the early stages of renal cancer. Typically, symptoms develop as the disease progresses. The first symptom is often blood in the urine; pain and flank mass are other classic symptoms.

2.1.2 Renal cancer may be diagnosed incidentally on imaging studies or patients may present with symptoms. Conventional treatment for renal cancer is total or partial nephrectomy (open or laparoscopic). One of a range of non-resectional ablative procedures such as cryoablation and RFA may be selected for some smaller tumours.

2.2 Outline of the procedure

2.2.1 Percutaneous RFA for renal cancer is carried out with the patient under either local anaesthesia and sedation or general anaesthesia. Hydrodisplacement may be used to displace the bowel away from the tumour. One or more

radiofrequency electrodes are inserted percutaneously into the tumour under imaging guidance. Radiofrequency energy is delivered via the electrode(s) to coagulate and destroy the tumour tissue in the target area. The procedure can be repeated if necessary.

Sections 2.3 and 2.4 describe efficacy and safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the overview.

2.3 Efficacy

2.3.1 A meta-analysis of 47 studies (non-randomised comparative studies and case series) including a total of 1375 tumours treated by RFA (n = 775) or cryoablation (n = 600) reported local tumour progression (defined as radiographic or pathological evidence of residual disease after initial treatment, regardless of time to recurrence) in 13% (100/775) and 5% (31/600) of tumours respectively at a mean 19-month follow-up ($p < 0.001$). The meta-analysis reported progression to metastatic disease in 2% (19/775) of tumours treated by RFA and 1% (6/600) of tumours treated by cryoablation (p = not significant).

2.3.2 In a non-randomised comparative study of 233 patients (260 tumours), residual or recurrent tumour on follow-up magnetic resonance imaging (MRI) was reported in 11% (9/81) of tumours treated by percutaneous RFA and 2% (3/179) of tumours treated by laparoscopic cryotherapy (1-year and 3-year median follow-up respectively).

2.3.3 A non-randomised comparative study of 264 patients (301 tumours) reported radiographic success (defined as no evidence of central or nodular enhancement after treatment) in 85% (62/73) of patients treated by percutaneous RFA and 90% (125/139) of patients treated by laparoscopic cryoablation at 6-month follow-up.

2.3.4 The case series of 151 patients reported a 3-year recurrence-free survival probability of 92% for all patients and 87% for the 84 patients with confirmed renal cell carcinoma. The case series of 31 patients reported disease-specific survival of 100%, recurrence-free survival of 89% and overall survival of 63% (all at 80 months).

2.3.5 The Specialist Advisers listed key efficacy outcomes as radiological confirmation of tumour devascularisation, imaging follow-up to confirm tumour involution at 2 and 5 years, and overall and disease-free survival. They indicated that there is uncertainty about the procedure's efficacy in tumours 4 cm or greater in diameter.

2.4 Safety

2.4.1 Haemorrhage was reported in 6% (5/85) of patients in a case series of 85 patients. Life-threatening haematuria approximately 42 hours after RFA treatment which required transcatheter embolisation was described in a case report.

2.4.2 Haematoma requiring blood transfusion was reported in 1% (1/104) of patients in a case series and 1% (1/82) of RFA procedures in the non-randomised comparative study of 233 patients. Haematoma not requiring blood transfusion was reported in 5% (4/82) (3 perirenal requiring no treatment; 1 retroperitoneal) of RFA procedures in the non-randomised comparative study of 233 patients. Asymptomatic perirenal haematoma development was reported in 12% (4/34) (managed conservatively with no sequelae) of RFA procedures in the case series of 31 patients.

2.4.3 Ureteric stricture development was reported after 1% (1/120) of treatments and in 1% (1/85) and 2% (2/104) of patients in case series of 97, 85 and 104 patients respectively.

2.4.4 Urinoma (a collection of fluid resulting from a urine leak) was reported in 1 patient each in the case series of 97 and 85 patients. Ureteropelvic junction obstruction requiring nephrectomy was described in a case report.

2.4.5 Thermal injury to the duodenum requiring laparotomy was reported in 1 patient in the case series of 97 patients.

2.4.6 Renoduodenal fistula was diagnosed 5 days after the procedure in 1 patient in a case report. A computed tomography (CT) scan at 6 months showed that the tumour (a clear cell carcinoma) was growing again and an open nephrectomy was performed.

2.4.7 Neuromuscular complications after RFA treatment were reported in 3 of 48 patients in one series. One patient developed persistent laxity of flank muscles. The other 2 developed sensory loss and paraesthesia of the lateral abdominal wall (resolved after 3 months).

2.4.8 The Specialist Advisers stated that theoretical adverse events include bowel perforation, perirenal haematoma, pelvicalyceal injury, and pain due to intercostal nerve damage.

3 Further information

3.1 For related NICE guidance see our website.

Information for patients

NICE has produced information on this procedure for patients and carers ('Understanding NICE guidance'). It explains the nature of the procedure and the guidance issued by NICE, and has been written with patient consent in mind.

4 About this guidance

NICE interventional procedure guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS. It is for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland, and is endorsed by Healthcare Improvement Scotland for implementation by NHSScotland.

This guidance was developed using the NICE interventional procedure guidance process.

It updates and replaces NICE interventional procedure guidance 91.

We have produced a summary of this guidance for patients and carers. Information about the evidence it is based on is also available.

Changes since publication

3 January 2012: minor maintenance.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the available evidence. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

Accreditation

the future, such as moderate to severe hypertension, diabetes mellitus, recurrent urolithiasis, or morbid obesity. (Conditional Recommendation; Evidence Level: Grade C)

17. In patients who elect PN, physicians should prioritize preservation of renal function through efforts to optimize nephron mass preservation and avoidance of prolonged warm ischemia. (Expert Opinion)
18. For patients undergoing PN, negative surgical margins should be a priority. The extent of normal parenchyma removed should be determined by surgeon discretion taking into account the clinical situation, tumor characteristics including growth pattern, and interface with normal tissue. Tumor enucleation should be considered in patients with familial RCC, multifocal disease, or severe CKD to optimize parenchymal mass preservation. (Expert Opinion)

RADICAL NEPHRECTOMY (RN)

19. Physicians should consider RN for patients with a solid or Bosniak 3/4 complex cystic renal mass where increased oncologic potential is suggested by tumor size, RMB, and/or imaging characteristics and in whom active treatment is planned. (Conditional Recommendation; Evidence Level: Grade B) In this setting, RN is preferred if all of the following criteria are met: 1) high tumor complexity and PN would be challenging even in experienced hands; 2) no preexisting CKD or proteinuria; and 3) normal contralateral kidney and new baseline eGFR will likely be greater than 45 ml/min/1.73m^2. (Expert Opinion)

SURGICAL PRINCIPLES

20. For patients who are undergoing surgical excision of a renal mass with clinically concerning regional lymphadenopathy, physicians should perform a lymph node dissection for staging purposes. (Expert Opinion)
21. For patients who are undergoing surgical excision of a renal mass, physicians should perform adrenalectomy if imaging and/or intraoperative findings suggest metastasis or direct invasion of the adrenal gland. (Clinical Principle)
22. In patients undergoing surgical excision of a renal mass, a minimally invasive approach should be considered when it would not compromise oncologic, functional and perioperative outcomes. (Expert Opinion)
23. Pathologic evaluation of the adjacent renal parenchyma should be performed after PN or RN to assess for possible intrinsic renal disease, particularly for patients with CKD or risk factors for developing CKD. (Clinical Principle)

THERMAL ABLATION (TA)

24. Physicians should consider thermal ablation (TA) as an alternate approach for the management of cT1a renal masses <3 cm in size. For patients who elect TA, a percutaneous technique is preferred over a surgical approach whenever feasible to minimize morbidity. (Conditional Recommendation; Evidence Level: Grade C)
25. Both radiofrequency ablation and cryoablation are options for patients who elect thermal ablation. (Conditional Recommendation; Evidence Level: Grade C)
26. A renal mass biopsy should be performed prior to ablation to provide pathologic diagnosis and guide subsequent surveillance. (Expert Opinion)
27. Counseling about thermal ablation should include information regarding an increased likelihood of tumor persistence or local recurrence after primary thermal ablation relative to surgical extirpation, which may be addressed with repeat ablation if further intervention is elected. (Strong Recommendation; Evidence Level: Grade B)

ACTIVE SURVEILLANCE (AS)

28. For patients with small solid or Bosniak 3/4 complex cystic renal masses, especially those <2cm, AS is an option for initial management. (Conditional Recommendation; Evidence Level: Grade C)
29. For patients with a solid or Bosniak 3/4 complex cystic renal mass, physicians should prioritize active surveillance/expectant management when the anticipated risk of intervention or competing risks of death outweigh the potential oncologic benefits of active treatment. (Clinical Principle)

Pelvic Congestion Syndrome

Question: Should the diagnosis and treatment of pelvic congestion syndrome be moved to the covered region of the Prioritized List?

Question source: Carl Stevens, CCO medical director

Issue: Pelvic congestion syndrome is a chronic pelvic pain syndrome of variable location and intensity, which is associated with dyspareunia and postcoital pain and aggravated by standing. The underlying etiology is thought to be related to varices of the ovarian veins, leading to pelvic vascular congestion. Because there are many etiologies of chronic pelvic pain, the pelvic congestion syndrome is often a diagnosis of exclusion, with the identification of varices using a variety of imaging methods, such as magnetic resonance imaging, computed tomography, or contrast venography. However, the syndrome is still not well-defined, and it is unclear whether pelvic congestion syndrome causes chronic pelvic pain. Although venous reflux is common, not all women with this condition experience chronic pelvic pain and, conversely, chronic pelvic pain is reported by women without pelvic congestion syndrome.

Initial treatment of pelvic congestion syndrome includes psychotherapy and medical therapy (e.g., nonsteroidal anti-inflammatory drugs) and hormonal therapy. For patients who fail initial therapy, surgical ligation of the ovarian vein may be considered. Embolization therapy and/or sclerotherapy of the ovarian and internal iliac veins has been proposed as an alternative to surgical ovarian vein ligation.

CareOregon has been receiving requests for pelvic vein embolization for pelvic congestion syndrome and would like HERC guidance on treatments for this condition.

Current Prioritized List status

CPT code	**Code description**	**Current Placement**
37241	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; venous, other than hemorrhage (eg, congenital or acquired venous malformations, venous and capillary hemangiomas, varices, varicoceles)	**327** FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION **547** SUBLINGUAL, SCROTAL, AND PELVIC VARICES **627** BENIGN NEOPLASMS OF SKIN AND OTHER SOFT TISSUES
ICD-10 Code		
I86.2	Pelvic varices	**547** SUBLINGUAL, SCROTAL, AND PELVIC VARICES
N94.89	Other specified conditions associated with female genital organs and menstrual cycle [includes pelvic congestion syndrome as a subdiagnosis]	**531** CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA
R10.2	Pelvic and perineal pain	**531**

Pelvic Congestion Syndrome

Evidence

1) **Champaneria 2014**, Health Technology Assessment, he relationship between pelvic vein incompetence and chronic pelvic pain in women: systematic reviews of diagnosis and treatment effectiveness. https://www.journalslibrary.nihr.ac.uk/hta/hta20050/#/full-report
    a. Accuracy review N=12 studies (10 ultrasound, 2 MRI vs conventional venography
        i. There was no single, clearly defined criterion for a diagnosis that was reported in the all of studies included in the review.
        ii. The proportion of women found to have pelvic vein incompetence (PVI) who reported chronic pelvic pain (CPP) ranged considerably, from 39% to 91%.
    b. Effusiveness review N=22 studies (1 poor quality RCT of 1208 women, 21 case series)
        i. approximately one-third of patients clearly had bilateral embolisation, with metal coil placement being the dominant technique. Early substantial relief from pain symptoms was observed in approximately 75% of women, a figure which generally increased over time and was sustained. Where pain was measured on a visual analogue scale, statistically significant reductions following treatment were observed in all studies. Reintervention rates were generally low. Where measured, embolisation reduced the diameter of dilated veins to a significant degree, with minimal residual reflux. There were few data on the impact on menstruation, ovarian reserve or fertility, but no concerns were noted. Transient pain was a common occurrence following foam embolisation, while there was a < 2% risk of coil migration
    a. Conclusions: The data supporting the diagnosis and treatment of PCS are limited and of variable methodological quality. There is some evidence to tentatively support a causative association, but it cannot be categorically stated that PVI is the cause of CPP in women with no other pathology. Embolisation appears to provide symptomatic relief in the majority of women and is safe. However, the majority of included studies of embolism were relatively small case series and only the randomized controlled trial was considered at risk of potential biases.

Expert Guideline

1) **ACOG 2020**, Practice Bulletin 218 Chronic Pelvic Pain
    a. Pelvic congestion syndrome is a proposed etiology of chronic pelvic pain related to pelvic venous insufficiency. Although venous congestion appears to be associated with chronic pelvic pain, evidence is insufficient to conclude that there is a cause-and-effect relationship. In addition, there is no consensus on the definition of this condition, and diagnostic criteria are variable. Further research is needed to establish greater consistency in diagnosis and homogeneity in treatment studies.

Other payer policies

1) **Aetna 2021**: Aetna considers embolization (e.g., using metallic coils or foam/gel sclerotherapy) of gonadal veins or ovarian veins, with or without the internal iliac veins, medically necessary for the treatment of pelvic congestion syndrome (PCS) when both of the following criteria are met:
    a. The member has had a definitive diagnostic venography, computed tomography (CT) or magnetic resonance imaging (MRI); *and*
    b. The member has failed a trial of appropriate pharmacotherapy (e.g., analgesics, hormonal therapy).

2) **United Healthcare 2021**: Embolization of the Ovarian Vein or Internal Iliac Vein is unproven and not medically necessary for treating Pelvic Congestion Syndrome due to insufficient evidence of efficacy
3) **Wellmark BCBS 2021**: Endovascular occlusion of the ovarian vein and internal iliac veins is considered investigational as a treatment of pelvic congestion syndrome because the evidence is insufficient to determine the effects of the technology on net health outcomes.

Pelvic Congestion Syndrome

HERC staff summary

Pelvic congestion syndrome is a poorly defined entity with no standardized diagnostic criteria. Pelvic vein embolization for treatment of pelvic congestion syndrome appears promising, but the evidence base to date is very small and at high risk of bias. Most private insurers do not cover treatment for pelvic congestion syndrome. ACOG notes there are no agreed upon diagnostic or treatment criteria.

HERC staff recommendations:

1) Add a new guideline note to line 531 CHRONIC PELVIC INFLAMMATORY DISEASE, PELVIC PAIN SYNDROME, DYSPAREUNIA as shown below

GUIDELINE NOTE XXX PELVIC CONGESTION SYNDROME

Line 531

Pelvic congestion syndrome is included on this line using ICD-10-CM N94.89. This condition does not pair with any vein embolization procedures due to lack of evidence of effectiveness.

Cyanoacrylate ablation Therapy for Varicose Veins

Question: Should cyanoacrylate ablation therapy be paired as a treatment for varicose veins?

Question source: Max Kaiser, CCO medical director

Issue: Cyanoacrylate glue occlusion (CPT 36482-36483) for varicose veins aims to close the veins by adherence then fibrosis of the lumen, without the need for tumescent anesthesia and with reduced need for postoperative compression therapy. The procedure is done using local anesthesia. An introducer sheath is inserted into the distal great saphenous vein and, using ultrasound guidance, a delivery catheter is advanced into position before the saphenofemoral junction. The proximal vein is compressed, and medical glue is delivered in measured doses through the tip of the catheter to seal the vein.

This procedure was reviewed as a new CPT code in November 2017. At that time, evidence review found three case series of 50, 62, and 180 patients were identified from 2016 and 2017 that indicated that vein ablation with cyanoacrylate was feasible. A NICE review of treatment of varicose veins from 2013 was reviewed and found to only recommend endothermal ablation or ultrasound-guided foam sclerotherapy. Based on the lack of evidence on this technology, it was placed on line 662/GN173.

Dr. Kaiser is requesting a re-review of this technology. He states: "After having performed the procedure for a few years, our local surgeons feel it is a superior procedure to radio frequency ablation (covered per GN 68) in terms of patient comfort, possibly lower cost as it's lower RVUs, and has a similar or improved efficacy/side effect profile."

Current Prioritized List status:
ICD-10-CM I82.xxx (Varicose veins, with pain/with other complications/with ulcer/asymptomatic/etc.) are on lines 379 CHRONIC ULCER OF SKIN; VARICOSE VEINS WITH MAJOR COMPLICATIONS and 639 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION

ICD-10-CM I87.xxx (Postthrombotic syndrome) is on line 519 POSTTHROMBOTIC SYNDROME

Currently covered endovenous treatments for varicose veins:

CPT 36465-36466: Injection of non-compounded foam sclerosant
CPT 36470-36471: Injection of sclerosant
CPT 36473-36479: Endovenous ablation therapy of incompetent vein (includes radiofrequency ablation, endovenous laser ablation)

GUIDELINE NOTE 68, TREATMENT OF CHRONIC LOWER EXTREMITY VENOUS DISEASE

Lines 379,519,639

Medical treatment of chronic lower extremity venous disease with major complications (skin ulceration, recurrent cellulitis or clinically significant bleeding) is included on Line 379, including medical compression garments.

Surgical treatment of chronic lower extremity venous disease is only included on Line 379 when

A) The patient has had an adequate 3-month trial of conservative therapy and failed; AND
B) Ultrasound findings of severe axial venous reflux (>1 second in the greater or small saphenous vein or accessory saphenous vein; AND

C) The patient has one of the following:
   1) Non-healing skin ulceration in the area of the varicose vein(s), OR
   2) Recurrent episodes of cellulitis associated with chronic venous disease OR
   3) Clinically significant bleeding from varicose vein(s).

Otherwise, these diagnoses are included on Lines 519 and 639.

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
36482-36483	Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate)	Unproven treatment	November, 2017

Evidence

1) **NICE 2020**, Cyanoacrylate glue occlusion for varicose veins
    a. 14 included papers
        i. N=2 systematic reviews (1,645 patients in 15 studies; 918 patients in 7 studies)
        ii. N=3 randomized controlled trials (222, 456 and 339 patients)
            1. Comparisons were other endovenous ablation techniques
        iii. N=3 non-randomized comparative studies (310, 244, and 573 patients 0
            1. Comparisons were other endovenous ablation techniques
        iv. N=4 case series (573, 538, 160, 50 patients)
        v. N=2 case reports
    b. Saphenous vein occlusion rates of at least 95% at 6 months after the cyanoacrylate closure (CAC) procedure were reported in 2 systematic reviews. Also, 9 studies described occlusion rates, which were more than 97% at 1 month post-procedure, more than 96% at 6 months, more than 94% at 12 months, and more than 92% at 24 months and was 95% at 36 months. Although there was a trend of better occlusion rates in CAC than in radiofrequency ablation (RFA), endovenous laser ablation (EVLA), and/or mechanochemical ablation (MOCA), these differences were not statistically significant at 6 months after the procedure
    c. Before and after the CAC procedure, a statistically significant reduction (improvement) in VCSS was reported in 9 studies
        i. VCSS is the Venous Clinical Severity Score, a measure of symptoms caused by varicose veins
    d. A statistically significant or clinically relevant reduction in the AVVQ scores posttreatment was reported in 2 systematic reviews. A statistically significant reduction after the CAC procedure at different follow-up intervals was reported in 7 studies
        i. AVVQ is the Aberdeen Varicose Vein Questionnaire which looks at pain, limitations on daily activity, and other quality of life measures
    e. Adverse events included hives, allergic contact dermatitis
        i. Small proportions (1% to 7%) of patients, who developed phlebitis after the CAC procedure, were reported in 8 studies. Phlebitis happened statistically significantly less in CAC patients (2% [3/150]) compared with EVLA patients (8% [15/189], p=0.015) in the non-randomized comparative study of 339 patients
        ii. In the systematic review and meta-analysis of 15 studies (n=1645), thrombophlebitis was reported in 6 CAC studies ranging from less than 1% to 18%, and deep venous thrombosis was described in 4 CAC studies ranging from 0 to 4%1 . In the non-randomized comparative study of 244 patients, thrombophlebitis happened in 2% (2/116) of patients in the CAC group compared with 3% (4/128) in the RFA group (p=0.685)
    f. Conclusion: Evidence on the safety and efficacy of cyanoacrylate glue occlusion for varicose veins is adequate to support the use of this procedure

Other payer policies:

1) Aetna 2021 does not cover cyanoacrylate vein ablation
2) Cigna 2021 does not cover cyanoacrylate vein ablation
3) Wellmark BCBS 2021 does not cover cyanoacrylate vein ablation

Cyanoacrylate ablation Therapy for Varicose Veins

HERC staff summary

Cyanoacrylate vein ablation appears to be at least as effective at occluding varicose veins, reducing pain and increasing quality of life from varicose veins as currently covered endovenous treatments according to one trusted source (NICE). No private payer surveyed is covering cyanoacrylate vein ablation.

HERC staff recommendations:

1) Add CPT 36482-36483 (Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate)) to lines 379 CHRONIC ULCER OF SKIN; VARICOSE VEINS WITH MAJOR COMPLICATIONS and 639 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR OTHER MAJOR COMPLICATION
2) Delete CPT 36482-36483 from line 662 and the GN173 entry

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS

Line 662

The following Interventions are prioritized on Line 662 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Procedure Code	Intervention Description	Rationale	Last Review
~~36482-36483~~	~~Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate)~~	~~Unproven treatment~~	~~November, 2017~~

Cyanoacrylate glue occlusion for varicose veins

Interventional procedures guidance
Published: 4 March 2020
www.nice.org.uk/guidance/ipg670

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

This guidance replaces IPG526.

1 Recommendations

1.1 Evidence on the safety and efficacy of cyanoacrylate glue occlusion for varicose veins is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit. Find out what standard arrangements mean on the NICE interventional procedures guidance page.

1.2 The procedure should only be done by clinicians with appropriate training in this procedure and experience in the use of venous ultrasound.

2 The condition, current treatments and procedure

The condition

2.1 Varicose veins are a sign of underlying venous insufficiency. Primary valvular incompetence is the most common underlying cause of varicose veins. The saphenous veins are the most frequently affected vessels. Most people with varicose veins have no symptoms, but venous insufficiency may cause fatigue, heaviness, aching, throbbing, itching and cramps in the legs. Chronic venous insufficiency can lead to skin discoloration, inflammatory dermatitis and ulceration.

Current treatments

2.2 NICE's guideline describes the diagnosis and management of varicose veins. Interventional treatment options include endothermal ablation (such as radiofrequency ablation and endovenous laser ablation therapy), foam sclerotherapy, mechanochemical ablation and surgery (usually stripping and ligation of the great and small saphenous veins, and phlebectomies).

The procedure

2.3 Cyanoacrylate glue occlusion for varicose veins aims to close the veins by adherence then fibrosis of the lumen, without the need for tumescent anaesthesia and with reduced need for postoperative compression therapy.

2.4 The procedure is done using local anaesthesia. An introducer sheath is inserted into the distal great saphenous vein and, using ultrasound guidance, a delivery catheter is advanced into position before the saphenofemoral junction. The proximal vein is compressed, and medical glue is delivered in measured doses through the tip of the catheter to seal the vein.

2.5 This is repeated at different positions as the catheter is withdrawn, using ultrasound imaging to monitor the procedure. The procedure may also be done in a similar way for the small saphenous vein.

3 Committee considerations

The evidence

3.1 NICE did a rapid review of the published literature on the efficacy and safety of this procedure. This comprised a comprehensive literature search and detailed review of the evidence from 14 sources, which was discussed by the committee. The evidence included 2 systematic reviews, 3 randomised controlled trials, 3 non-randomised comparative studies, 4 case series and 2 case reports. It is presented in table 2 of the interventional procedures overview. Other relevant literature is in the appendix of the overview.

3.2 The specialist advisers and the committee considered the key efficacy outcomes to be: saphenous vein occlusion rate, recanalisation, symptom relief and quality of life.

3.3 The specialist advisers and the committee considered the key safety outcomes to be: hypersensitivity, granuloma formation, thromboembolism, and nerve injury or paraesthesia.

3.4 Three commentaries from patients who have had this procedure were discussed by the committee.

Committee comments

3.5 The committee was informed that the incidence of hypersensitivity reactions was reported to be about 7% and granuloma formation was rare.

3.6 The committee was informed that there are different products available for this procedure.

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Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

Accreditation

Breast Reconstruction After Lumpectomy

Question: Is breast reconstruction after lumpectomy a covered service on the Prioritized List?

Question source: Kristin Garrett, CCO medical director

Issue: The Women's Health and Cancer Rights Act requires insurance to cover breast reconstruction including surgery on the contralateral breast after "mastectomy." Currently, GN79 BREAST RECONSTRUCTION states that "breast reconstruction is only covered after mastectomy". Dr. Garrett is requesting clarification of coverage of reconstruction after lumpectomy for breast cancer. Lumpectomy is a surgery where only a portion of the breast is removed, and it is becoming increasingly common for certain stages of breast cancer. Lumpectomy is generally less morbid than mastectomy, and requires fewer follow up procedures. The CPT codes used for lumpectomy list the procedure as "mastectomy, partial."

In some cases, lumpectomy removes only a small portion of breast tissue and no reconstruction is desired. In other cases, lumpectomy can remove a considerable portion of breast tissue, leaving a significant disproportion between breasts. Most private insurance payers will cover breast reconstruction or contralateral breast reduction or similar surgeries after lumpectomy.

There is concern that coverage for reconstruction only after mastectomy might incentivize patients on OHP to opt for mastectomy when a lumpectomy would be a reasonable treatment approach. Mastectomy is a much more morbid procedure, and generally the reconstruction afterwards involves multiple steps and procedures.

From CMS
https://www.cms.gov/CCIIO/Programs-and-Initiatives/Other-Insurance-Protections/whcra_factsheet (accessed October 19, 2021)

> The Women's Health and Cancer Rights Act of 1998 (WHCRA) is a federal law that provides protections to patients who choose to have breast reconstruction in connection with a mastectomy.
>
> If WHCRA applies to you and you are receiving benefits in connection with a mastectomy and you elect breast reconstruction, coverage must be provided for:
>
> - All stages of reconstruction of the breast on which the mastectomy has been performed;
> - Surgery and reconstruction of the other breast to produce a symmetrical appearance; and
> - Prostheses and treatment of physical complications of all stages of the mastectomy, including lymphedema.
>
> This law applies to two different types of coverage:
>
> 1. Group health plans (provided by an employer or union);
> 2. Individual health insurance policies (not based on employment).

Breast Reconstruction After Lumpectomy

Current Prioritized List status

CPT 19301-19302 (Mastectomy, partial (eg, lumpectomy, tylectomy, quadrantectomy, segmentectomy) are on line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER

GUIDELINE NOTE 79, BREAST RECONSTRUCTION

Line 191

Breast reconstruction is only covered after mastectomy as a treatment for breast cancer or as prophylactic treatment for the prevention of breast cancer in a woman who qualifies under Guideline Note 3, and must be completed within 5 years of initial mastectomy.

Breast reconstruction may include contralateral reduction mammoplasty (CPT 19318) or contralateral mastopexy (CPT 19316). Mastopexy is only to be covered when contralateral reduction mammaplasty is inappropriate for breast reconstruction and mastopexy will accomplish the desired reconstruction result.

Expert guidelines

1) **NCCN Breast Cancer** treatment guideline, version 8.2021
    a. After lumpectomy, prior to radiation therapy
        i. No reconstruction required if ration of tumor to breast volume is small and minimal cosmetic deformity with result, OR
        ii. Consider oncoplastic reduction or mastopexy and simultaneous or delayed contralateral matching procedure, OR
        iii. Consider bilateral breast reduction if symptoms warrant, or
        iv. Local tissue rearrangement, regional flap
    b. After lumpectomy and radiation therapy
        i. Delayed fat grafting
        ii. Delayed flap for correction of contour defects
        iii. Contralateral reduction/mastopexy for symmetry

Other payer policies

1) Aetna 2021
    - Aetna considers reconstructive breast surgery medically necessary after a medically necessary mastectomy or a medically necessary lumpectomy that results in a significant deformity (i.e., mastectomy or lumpectomy for treatment of or prophylaxis for breast cancer and mastectomy or lumpectomy performed for chronic, severe fibrocystic breast disease, also known as cystic mastitis, unresponsive to medical therapy).
2) Cigna 2021
    - Breast reconstruction following mastectomy or lumpectomy is considered medically necessary for EITHER of the following:
        - breast reconstruction procedures performed on the diseased/affected breast (i.e., breast on which the mastectomy/lumpectomy was performed),
        - breast reconstruction procedures performed on the nondiseased/unaffected/contralateral breast, in order to produce a symmetrical appearance

3) Anthem BCBS 2021
    - The Women's Health and Cancer Rights Act of 1998 (WHCRA) mandated that reconstructive breast surgery for women and men who have undergone mastectomy be covered by their benefits for those who have opted to have breast reconstruction. In individuals who have undergone a medically necessary lumpectomy, surgery to create a more normal anatomy is considered reconstructive.
4) MODA 2020
    - Reconstructive breast surgery is performed following a mastectomy, lumpectomy or prophylactic mastectomy for high-risk patients to re-establish symmetry between the two breasts.

Expert input

Danielle Bertoni and John Vetto, breast surgeons: both felt that reconstruction after lumpectomy was standard of care.

Breast Reconstruction After Lumpectomy

HERC staff summary

Due to concern that WHCRA requires coverage for reconstruction after partial mastectomy (lumpectomy) and a desire to not create an incentive to elect a mastectomy when a lumpectomy is sufficient treatment, HERC staff recommend amending GN79 to clarify that breast reconstruction after lumpectomy is a covered service.

HERC staff recommendation:

1) Modify Guideline Note 79 as shown below

GUIDELINE NOTE 79, BREAST RECONSTRUCTION

Line 191

Breast reconstruction is only covered after mastectomy, or lumpectomy that results in a significant deformity or asymmetry, as a treatment for breast cancer or as prophylactic treatment for the prevention of breast cancer in a woman who qualifies under Guideline Note 3, and must be completed within 5 years of initial mastectomy.

Breast reconstruction may include contralateral reduction mammoplasty (CPT 19318) or contralateral mastopexy (CPT 19316). Mastopexy is only to be covered when contralateral reduction mammaplasty is inappropriate for breast reconstruction and mastopexy will accomplish the desired reconstruction result.

Breast MRI

Question: How best can the coverage of breast MRI be clarified on the Prioritized List

Question source: several CCO medical directors

Issue: There are currently 3 guidelines that relate to breast MRI on the Prioritized List, and the CCO medical directors frequently have questions about how they relate to one another. They have previously requested clarification of these guidelines, but even those clarifications are not sufficient for the CCO PA process. There have also been questions about the lack of Prioritized List coverage for MRI after breast cancer diagnosis, which has generally become standard of care.

From Max Kaiser, CCO medical director

> The main impetus are cases where member's meet for breast MRI screening, but haven't had the screening, and are now was diagnosed with a new breast cancer. As the member met for screening, the surgeon uses that as reasoning to request screening of the uninvolved breast so they could treat any identified breast cancer at the same time and image the involved breast for other occult lesions. That scenario may warrant clarification with the NCCN caveat that false-positives are common and should be confirmed with tissue sampling. We had also talked about aligning D6 and D26 to indicated when after the member's original treatment an MRI is covered for future screening. Currently it's covered annually. Does this mean 1 year after treatment or would it also be covered, as with the mammogram, 6 months after radiotherapy if treated with breast conserving therapy? I also get fairly regular requests for a breast MRI in a newly diagnosed member that I approve by exception as they align with NCCN, such as poorly defined disease on mammogram/ultrasound or multifocal/multicentric

Current Prioritized List status:

DIAGNOSTIC GUIDELINE D6, BREAST CANCER SCREENING IN ABOVE-AVERAGE RISK WOMEN

Annual screening mammography and annual screening MRI are covered only for women at above-average risk of breast cancer. This coverage, beginning at 30 years of age, includes women who have one or more of the following:

- Greater than 20% lifetime risk of breast cancer
- BRCA1 or BRCA2 gene mutation, or who have not been tested for BRCA but have a first-degree relative who is a BRCA carrier
- A personal history or a first-degree relative diagnosed with Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome, or Li-Fraumeni syndrome
- Other germline gene mutations known to confer a greater than 20% lifetime risk of breast cancer

For women with a history of high dose chest radiation (≥ 20 Gray) before the age of 30, annual screening MRI and annual screening mammography are covered beginning 8 years after radiation exposure or at age 25, whichever is later.

For women with both a personal history and a family history of breast cancer which give a greater than 20% lifetime risk of breast cancer, annual mammography, annual breast MRI and annual breast ultrasound are covered.

For women with increased breast density, supplemental screening with breast ultrasound, MRI, or digital breast tomosynthesis is not covered.

Breast PET-CT scanning and breast-specific gamma imaging are not covered for breast cancer screening.

For surveillance for a treated breast cancer, see Guideline Note 26 BREAST CANCER SURVEILLANCE.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

DIAGNOSTIC GUIDELINE D9, MRI FOR BREAST CANCER DIAGNOSIS
In women with recently diagnosed breast cancer, preoperative or contralateral MRI of the breast is not a covered service.

GUIDELINE NOTE 26, BREAST CANCER SURVEILLANCE
Line 191
History and physical exam is indicated every 3 to 6 months for the first three years after primary therapy, then every 6-12 months for the next 2 years, then annually thereafter.

Mammography is indicated annually, and patients treated with breast-conserving therapy, initial mammogram of the affected breast should be 6 months after completion of radiotherapy.

No other surveillance testing is indicated.

For ongoing screening for a new breast cancer, see Guideline Note 2006 BREAST CANCER SCREENING IN ABOVE-AVERAGE RISK WOMEN.

Expert guidelines

1) **NCCN Breast Cancer** treatment guideline, version 8.2021
    a. Clinical indications and applications for breast MRI
        i. May be used for staging evaluation to define extent of cancer or presence of multifocal or multicentric cancer in the ipsilateral breast, or as screening of the contralateral breast cancer at time of initial diagnosis (category 2B). there are no high-level data to demonstrate that the use of MRI to facilitate local therapy decision-making improves local recurrence or survival
        ii. May be helpful for breast cancer evaluation before and after preoperative systemic therapy to define extent of disease, response to treatment, and potential for breast-conserving therapy
        iii. May be useful in identifying otherwise clinically occult disease in patients presenting with axillary nodal metastases (cT0, CN+), with Paget disease, or with invasive lobular carcinoma poorly (or inadequately) defined on mammography, ultrasound or physical examination
        iv. False-positive findings on breast MRI are common. Surgical decisions should not be based solely on the MRI findings. Additional tissue sampling of areas of concern identified by breast MRI is recommended
        v. The utility of MRI in follow-up screening of patients with prior breast cancer is undefined. It should generally be considered only in those whose lifetime risk of a second primary breast cancer is >20% based on models largely dependent on

family history, such as those with the risk associated with inherited susceptibility to breast cancer.

b. Specific clinical situations:
    i. DCIS: breast MRI has not been shown to increase likelihood of negative margins or decrease conversion to mastectomy. Data to support improved long-term outcomes is lacking
    ii. Non-metastatic (M0) invasive breast cancer and higher stage invasive breast cancer: breast MRI is optional, may be useful for characterizing axillary and/or internal mammary nodal disease. MRI findings tend to overestimate extent of disease resulting increase in frequency of mastectomies. Two prospective randomized studies have examined the utility of pre-operative MRI in determining disease extent, and neither demonstrated improvement in rates of post-lumpectomy re-excision. One systematic review found MRI staging altered surgical treatment in 7.8-33.3% of women; however, no differences in local recurrent or survival has been demonstrated.

2) **NCCN Breast Cancer screening and diagnosis**, version 1.2021
    a. Recommend annual MRI screening:
        i. For individuals with a genetic mutation, or a first-degree relative of gene mutation carrier
        ii. For individuals who received thoracic radiation therapy between the ages of 10 and 30 years
            1. Begin 8 years after radiation therapy but not prior to age 25 years
        iii. For individuals with a lifetime risk of ≥ 20% as defined by models that are largely dependent on family history
            1. To begin 10 years prior to when the youngest family member was diagnosed with breast cancer, not prior to age 25 years or age 40 years (whichever comes first)
3) **American Society of Breast Surgeons 2017**: consensus guideline on diagnostic and screening MRI of the breast
    a. The ASBrS does not recommend routine diagnostic MRI in newly diagnosed breast cancer patients except as part of a scientific study.
    b. The ASBrS supports the use of MRI in the following situations:
        i. To search for occult breast cancer in patients with Paget's disease of the nipple or in patients with axillary node metastasis when clinical examination and conventional breast imaging fail to detect a primary breast cancer. MRI identifies an ipsilateral cancer focus in 60-70% of patients who present with axillary nodal metastases and no cancer identified on clinical examination, mammography, or ultrasound.
        ii. For determining the extent of cancer or presence of multi-focal or multi-centric tumor or the presence of contralateral cancer, in patients with a proven breast cancer and associated clinical or conventional indeterminate imaging findings suspicious for malignancy. This may include patients with invasive lobular carcinoma or extremely dense breast tissue (limiting mammographic sensitivity), or when there are significant discrepancies in the estimated tumor size as measured on clinical exam, mammogram, and ultrasound. The American College of Radiology Appropriateness Criteria and a recent meta-analysis by Houssami et al conclude there are no proven criteria for any patient sub-

population that benefits the most from routine MRI based on specific patient, tumor, or mammographic characteristics.

iii. To aid the assessment for eligibility and response to neoadjuvant endocrine therapy or chemotherapy before, during, or after treatment. MRI can help identify those patients who are candidates for breast conservation, and assist in determining the extent of resection40,41. After neoadjuvant chemotherapy (NAC), MRI has a sensitivity of 92% to detect residual disease and a specificity of 60% for pathologic complete response (pCR), based on a meta-analysis of studies including 2050 patients reported by Marinovich et al in 2013. Compared to mammography, MRI was better in assessing response to NAC, but a negative MRI did not always exclude residual microscopic disease. In two updated metaanalyses (2016 and 2017) assessing pCR, Gu et al and Sheikhbahaei et al reported pooled sensitivities and specificities of 64%/88% and 92%/55% respectively. MRI is not mandatory in patients undergoing neoadjuvant systemic therapy.

iv. For the further evaluation of suspicious clinical or imaging findings that remain indeterminate after complete mammographic and sonographic evaluations. If lesions meet the criteria for biopsy by clinical examination or conventional imaging, then it may be preferable to perform minimally invasive needle biopsy, targeted by mammogram or US, rather than obtain an MRI.

v. For evaluation of suspected breast implant rupture, especially in patients with silicone implants, if the MRI findings will aid the decision-making for implant removal or aid the diagnostic evaluation of indeterminate clinical or conventional imaging findings in patients with implants. The MRI protocol for detection of silicone leak is different from the protocol for detection of breast cancer. Thus, it is important to clearly define the purpose of the breast MRI if the concern is a silicone leak.

<u>Expert input</u>:

Steve Kornfeld, breast surgeon:

Dr. Kornfeld recommended against including coverage for first degree relatives of mutation carriers, as confirmation testing is readily available and inexpensive. The relative has a 50% chance of having the mutation. If she does not carry it, then she is normal risk and should be screened with mammograms.

Dr. Kornfeld also felt that preoperative breast MRI is standard of care for women, specifically if breast conservation (lumpectomy) is being considered over mastectomy. The rationale is to look for multifocal tumors. This is listed in NCCN as an option (2B recommendation).

Danielle Bertoni, breast surgeon:

I think there is one major group missing which is patients who have a genetic mutation or are at high risk for genetic mutation and are planning breast conservation. If we have a patient who is newly diagnosed with breast cancer and meets criteria for genetic testing or has extensive family history of breast cancer and is planning breast conservation, then we may need to follow them for screening going forward with breast MRI. If this is the case, then we would want the breast MRI prior to going to surgery for their cancer treatment. We would not want to wait until

they are due for MRI screening in 6 months and then find a new lesion in the same or contralateral breast that we could have and should have addressed at diagnosis. This is more of a concern in patients who also have dense breast tissue and are more likely to have things missed by conventional imaging. IF they know they want breast conservation regardless of genetic testing results, we often go to surgery prior to results coming back. In many cases, even if results are negative, they are still high risk based on family history and we would want to screen them with MRI going forward, again especially with dense breast tissue. Ultimately, if someone meets the high risk criteria and has cancer, they should be approved for an MRI at diagnosis.

The other time we have had difficulty getting them approved is if someone has a breast MRI and it has a birads 3 finding. They are recommended for 6 month follow up and it is getting denied.

Winnie Henderson, breast surgeon

Our practice follows the ASBrS recommendations [see above]

Breast MRI

HERC staff summary

The current three guidelines regarding breast cancer screening modalities continue to be confusing to CCOs and difficult to administer. There are generally few barriers to mammography or breast ultrasound; therefore, staff feel that the guidelines should be simplified and only outline when breast MRI is covered.

NCCN addresses coverage of MRI only for two situations: 1) screening for breast cancer in high-risk women, and 2) peri-operative MRI. In terms of perioperative MRI, the current NCCN guidelines give a "may" recommendation, and note that no differences have been found in the rate of re-excision, conversion to mastectomy from planned lumpectomy, local recurrence or survival with pre-operative MRI. The breast surgeons consulted on this topic argue that preoperative breast MRI is standard of care, particularly in women pursuing breast conserving therapy (lumpectomy).

Expert guidelines address coverage of breast MRI in two additional situations: 1) evaluation of suspicious lesions when other imaging is equivocal and 2) evaluation of possible breast implant rupture.

HERC staff recommendations:

1) Delete Diagnostic Guideline D9 and Guideline Note 26
2) Replace current Diagnostic Guideline D6 with the guideline shown below:
    a. Includes NCCN recommended screening for high-risk women [current coverage]
    b. Includes perioperative coverage only for women who would otherwise qualify for high risk MRI screening, based on expert input [clarification of current coverage]
    c. Includes expert guideline recommendations regarding evaluation of possible breast cancer in equivocal cases and for evaluation of possible implant rupture [new coverage]

DIAGNOSTIC GUIDELINE D6 BREAST MRI

Breast MRI is covered in the following circumstances:

1) Annual breast MRI screening for high-risk patients:
    a. For individuals with a genetic mutation known to confer a greater than 20% lifetime risk of breast cancer (e.g. BRCA1, BRCA2, Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome, or Li-Fraumeni syndrome), beginning 10 years prior to when the youngest family member was diagnosed with breast cancer (but not prior to age 25 years) or age 40 years (whichever comes first)
    b. For individuals who received high dose chest radiation (≥ 20 Gray) between the ages of 10 and 30 years beginning 8 years after radiation exposure or at age 25, whichever is later
    c. For individuals with a lifetime risk of ≥ 20% as defined by models that are largely dependent on family history, beginning 10 years prior to when the youngest family member was diagnosed with breast cancer (but not prior to age 25 years) or age 40 years (whichever comes first)
2) Evaluation of possible breast cancer:
    a. To search for occult breast cancer in patients with Paget's disease of the nipple or in patients with axillary node metastasis when clinical examination and conventional breast imaging fail to detect a primary breast cancer.

   b. For the further evaluation of suspicious clinical or imaging findings that remain indeterminate after complete mammographic and sonographic evaluations in lesions that do not meet criteria for breast biopsy
3) Preoperative breast MRI
   a. ONLY covered for patients with recently diagnosed breast cancer who qualify for MRI screening based on the high-risk criteria above.
4) Evaluation of suspected breast implant rupture
   a. Breast MRI is covered for evaluation of suspected breast implant rupture, if the MRI findings will aid the decision-making for implant removal or aid the diagnostic evaluation of indeterminate clinical or conventional imaging findings in patients with implants.

Breast MRI is NOT covered for breast cancer screening in women with increased breast density.

Breast PET-CT scanning and breast-specific gamma imaging are not covered for breast cancer screening.

The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx

~~**DIAGNOSTIC GUIDELINE D6, BREAST CANCER SCREENING IN ABOVE-AVERAGE RISK WOMEN**~~

~~Annual screening mammography and annual screening MRI are covered only for women at above-average risk of breast cancer. This coverage, beginning at 30 years of age, includes women who have one or more of the following:~~

- ~~Greater than 20% lifetime risk of breast cancer~~
- ~~BRCA1 or BRCA2 gene mutation, or who have not been tested for BRCA but have a first-degree relative who is a BRCA carrier~~
- ~~A personal history or a first-degree relative diagnosed with Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome, or Li-Fraumeni syndrome~~
- ~~Other germline gene mutations known to confer a greater than 20% lifetime risk of breast cancer~~

~~For women with a history of high dose chest radiation (≥ 20 Gray) before the age of 30, annual screening MRI and annual screening mammography are covered beginning 8 years after radiation exposure or at age 25, whichever is later.~~

~~For women with both a personal history and a family history of breast cancer which give a greater than 20% lifetime risk of breast cancer, annual mammography, annual breast MRI and annual breast ultrasound are covered.~~

~~For women with increased breast density, supplemental screening with breast ultrasound, MRI, or digital breast tomosynthesis is not covered.~~

~~Breast PET-CT scanning and breast-specific gamma imaging are not covered for breast cancer screening.~~

~~For surveillance for a treated breast cancer, see Guideline Note 26 BREAST CANCER SURVEILLANCE.~~

~~The development of this guideline note was informed by a HERC coverage guidance. See https://www.oregon.gov/oha/HPA/DSI-HERC/Pages/Evidence-based-Reports.aspx~~

~~**DIAGNOSTIC GUIDELINE D9, MRI FOR BREAST CANCER DIAGNOSIS**~~

~~In women with recently diagnosed breast cancer, preoperative or contralateral MRI of the breast is not a covered service.~~

~~**GUIDELINE NOTE 26, BREAST CANCER SURVEILLANCE**~~

~~*Line 191*~~

~~History and physical exam is indicated every 3 to 6 months for the first three years after primary therapy, then every 6-12 months for the next 2 years, then annually thereafter.~~

~~Mammography is indicated annually, and patients treated with breast-conserving therapy, initial mammogram of the affected breast should be 6 months after completion of radiotherapy.~~

~~No other surveillance testing is indicated.~~

~~For ongoing screening for a new breast cancer, see Guideline Note 2006 BREAST CANCER SCREENING IN ABOVE-AVERAGE RISK WOMEN.~~

Clarification of Childhood Growth and Development as a Comorbid Condition

Question: Should Statement of Intent 4 be modified to include growth and development in children as a called out "co-morbid" condition?

Question source: HERC staff

Issue: STATEMENT OF INTENT 4 ROLE OF THE PRIORITIZED LIST IN COVERAGE outlines when treatment of an unfunded condition might be considered for coverage because the condition exacerbates a funded condition (OAR 141-410-3820 (10)). For example, treatment of allergic rhinitis (unfunded condition) is covered if it is making asthma (funded) difficult to control.

Similarly, health services which would address challenges related to childhood growth, development, and ability to participate in school based on individual circumstances are often considered in the same fashion, but these do not necessarily have specific diagnoses on the Prioritized List. Clarifying the intent of the Commission regarding such services is important in order to align expectations for CCO decision-making and reporting purposes.

Schools are required to provide services necessary to allow children to participate in school, and a limited portion of these services can be billed to fee-for-service to Medicaid (not CCOs). The proposed changes would not affect these obligations (or the limits to the Medicaid billing) that are required to be provided by schools to eligible children per the federal Individuals with Disabilities Act (IDEA) and outlined in the students Individualized Education Plan (IEP). These changes will create a mechanism for Medicaid to cover additional services not provided as a part of an IEP to be provided in the community if they would improve a child's ability to grow, develop or participate in school (see Appendix A for specific rules on school responsibilities).

Feedback from CCO medical directors indicates a need for clarity regarding this; some medical directors indicated they are already making coverage exceptions for these sorts of situations; others have expressed concerns that this could open a pathway to coverage for services the Commission intends to be below the funding line, resulting in cost increases.

Context: Services in the unfunded region of the List appear there for several reasons and require different kinds of considerations. As a baseline, even services in the funded region of the List should be covered only when medically necessary and appropriate for the individual member[1], and can be denied if it is determined that they are not the least costly alternative.

Examples of services in the unfunded region of the List include:

- Services determined by the Commission to be not as important as other higher-priority items based on their low impact on health, such as ear tubes for children with chronic otitis media, treatments for mild to moderate acne, seasonal allergies, mild psoriasis and routine circumcision or circumcision for phimosis without a funded condition.
    - Some of these services are arguably "medically necessary" according to some providers. Others would typically be denied as not medically necessary by commercial insurance plans.
- Services with insufficient evidence of effectiveness, evidence of harm, or harms which outweigh the benefits

[1] See OHA Definition of Medical Necessity and medical appropriateness - OAR 410-120-0000(145-146)

    - Examples include prolotherapy, cranial electrical stimulation, allogenic islet cell transplant from pancreas, functional MRI, whirlpools for wound healing and sensory integration therapy. Many of these would be denied as not medically necessary by many other health plans.
- Services which are effective and have an important impact on health but which have more cost-effective alternatives. Often these appear on Guideline Note 172. Examples relevant for children include photo-screening and mechanical chest wall oscillation (the latter is currently under review by EbGS).
    - Some of these services are arguably "medically necessary" according to some providers. Others would typically be denied as not medically necessary by commercial insurance plans.
- Experimental services.

In addition, current OHA Health Services Division (HSD) rules (OAR 141-410-3820(13)[2]) require a medical director's determination of medical necessity and appropriateness for unpaired services where the HERC has not considered the pairing within the past five years.

In recent months, based on stakeholder feedback during the 1115(a) waiver renewal process, staff have brought recommendations to reconsider prioritization for several services for children. Based on the number of services reprioritized already, staff will continue to review and work toward identifying additional services which may warrant reprioritization.

<u>HERC staff recommendation</u>:

1) Modify SOI4 as shown below
    a. Adds clarity for coverage of services which affect childhood growth, development, or ability to participate in school
    b. Corrects OAR reference to updated rule number

[2] (13) Ad hoc coverage determinations.

(a) When a member requests a hearing pertaining to a funded condition and a funded or unfunded treatment that does not pair on the HERC Prioritized List of Health Services, and the treatment is not included in guideline note 172 or 173 of the prioritized list, before the hearing the Division shall determine if the requested treatment is appropriate and necessary for the member.

(b) For treatments determined to be appropriate and necessary under (a) in this section, the Division determines whether the HERC has considered the funded condition/treatment pair for inclusion on the Prioritized List within the last five years. If the HERC has not considered the pair for inclusion within the last five years, the Division shall make an ad hoc coverage determination in consultation with the HERC.

(c) For treatments determined to not be appropriate and necessary under (a) in this section the hearing process shall proceed.

STATEMENT OF INTENT 4: ROLE OF THE PRIORITIZED LIST IN COVERAGE

The Commission makes its prioritization decisions based on the best available published evidence about treatments for each condition. The Prioritized List prioritizes health services according to their importance for the population served and the legislature determines where to place the funding line on the Prioritized List.

The Commission recognizes that a condition and treatment pairing above the funding line does not necessarily mean that the service will be covered by the Oregon Health Plan (OHP). There may be other restrictions that apply, such as the service not being medically necessary or appropriate for an individual member. Likewise, the absence of a treatment and condition pairing above the funding line is not meant to be an absolute exclusion from coverage. Coverage may still be authorized under applicable federal and state laws, and Oregon's Medicaid State Plan and Waiver for an individual member. For example, OAR 410-141-~~0480~~ 3820 (Oregon Health Plan Benefit Package of Covered Services) includes services such as, but not limited to, the following:

- Diagnostic services, subject to the List's diagnostic guideline notes when applicable;
- Ancillary services (such as hospitalization, durable medical equipment, certain medications and anesthesia) provided for conditions appearing above the funding line, subject to the List's ancillary guideline notes when applicable; and
- Services paired with (or ancillary to) an unfunded condition -which is causing or exacerbating a funded condition, the treatments for the funded condition are not working or contraindicated, and treatment of the unfunded condition would improve the outcome of treating the funded condition (the "Comorbidity Rule" OAR 410-141-~~0480(8)(a through b))~~3820 (10))
- Services paired with (or ancillary to) an unfunded condition (or otherwise not consistent with the funded region of the List) which, based on the child's individual circumstances, adversely affects the child's ability to grow, develop, or participate in school only when providing the unfunded service would improve the child's ability to grow, develop or participate in school.

In addition, Oregon's 1115(a) Waiver includes coverage for services such as, but not limited to:

- Services on unfunded lines for children from birth through age 1
- Services provided for a condition appearing in the funded region of the List in conjunction with federal requirements for Early and Periodic Screening, Diagnosis and Treatment (EPSDT) and Oregon's waiver

As a result, the Prioritized List must be used in conjunction with applicable OHP provisions found in federal and state laws, the State Plan and Waiver in coverage determination.

Appendix A

410-141-3565
Managed Care Entity Billing

(8) Payment by the MCE to participating providers for capitated or coordinated care services is a matter between the MCE and the participating provider:

(h) MCEs may not delay or deny payments for occupational therapy, physical therapy, speech therapy, nurse services, etc., when a child is receiving such services as school-based health services (SBHS) through either an Individual Educational Plan (IEP) or an Individualized Family Service Plan (IFSP). These services are supplemental to other health plan covered therapy services and are not considered duplicative services. Individuals with Disabilities Education Act (IDEA) mandated school sponsored SBHS will not apply toward the member's therapy allowances. SBHS Medicaid covered IDEA services are provided to eligible children in their education program settings by public education enrolled providers billing MMIS for these services to Medicaid through the Authority for reimbursement under Federal Financial Participation (FFP) as part of cost sharing on a fee-for-service basis;

Comments from Linda Williams, OHA (HSD)

Jason [Gingerich] and I discussed services to allow a child to "participate in school" as the responsibility of the school district for health related services provided to eligible children with disabilities as required by the Individuals with Disabilities Act (IDEA).

School Districts and Education Service Districts can and do provide services provided by or under the supervision of medically qualified staff within the scope of practice of their license for services provided to eligible children for: OT, PT, SLP, Audiologist, LCSW, Psychologists, Psychiatrist, nurse services provided by or under the supervision of NP or RN.

The above services are defined as related services under the IDEA and provided pursuant to a child's Individualized Family Service Plan (IFSP) for:

- Early Intervention infants and toddler birth to 3yrs.
- Early Childhood Special Education (ECSE) 3 & 4 years; and

For children/students Kindergarten through grade 12 for children/students age 5 to 21 yrs. pursuant to the eligible child/student's Individualized Education Program (IEP).

School district are also required to provide services as an accommodation for a child/student with a disability eligible under Section 504 of the Rehabilitation Act of 1973 pursuant to a 504 plan

Clarification of Childhood Growth and Development as a Comorbid Condition

Medicaid is first payer before education for IDEA services as required by section 1903(c) of the Social Security Act to ensure children with disabilities have access to and benefit from their Free and Appropriate Public Education (FAPE) required by federal regulations see 34CFR300.154

The important thing to remember regarding services above described is:

A child/student with a disability eligible under the IDEA or eligible under The Rehabilitation Act of 1973, Section 504, required by schools to provide are provided in support of a child's education.

Schools are not clinics charged with responsibilities of providing "medical services" to address overall healthcare needs that are the responsibility of MCO CCO primary care providers