Health Evidence Review Commission's Value-based Benefits Subcommittee

May 17, 2018

8:00 AM - 1:00 PM

Clackamas Community College
Wilsonville Training Center, Room 111-112
29373 SW Town Center Loop E, Wilsonville, Oregon, 97070

Section 1.0

Call to Order

AGENDA
VALUE-BASED BENEFITS SUBCOMMITTEE
May 17, 2018
8:00am - 1:00pm
Clackamas Community College
29373 SW Town Center Loop E,
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
A working lunch will be served at approximately 12:00 PM
All times are approximate

I. Call to Order, Roll Call, Approval of Minutes – Kevin Olson **8:00 AM**

II. Staff report – Ariel Smits, Cat Livingston, Darren Coffman **8:05 AM**
A. Errata
B. Other staff report

III. Straightforward/Consent agenda – Ariel Smits **8:10 AM**
A. Consent table
B. Straightforward guideline note changes
C. Special consult only Lines May 2018 corrections
D. Surgical interventions of deforming foot conditions corrections May 2018

IV. Taskforce reports **8:15 AM**
A. Chronic Pain Taskforce interim report
    A. New Statement of Intent for treatment of chronic pain
    B. Revisions to the opioid guideline

V. New Codes **8:30 AM**
A. HCPCS "C" code review
    A. Blue light cystoscopy
    B. Eustacian tube inflation
    C. Balloon continence devices

VI. New discussion items **9:00 AM**
A. Coverage of developmental diagnoses
B. Dermatochalasis and blepharoplasty
C. Hypoglossal nerve stimulation for OSA
D. Incisional hernias
E. Robotic assisted surgery
F. Dermatology topics
    A. Severe inflammatory skin disease guideline
    B. PUVA and UVB and other light therapy

VII. 2020 Biennial Review **10:00 AM**

A. Severe Acne – Dr. Julie Dhossche
B. Burn line vital site definition and possible burn line reorganization

VIII. Coverage guidances **11:00 AM**

A. Gene Expression Profiling for Breast Cancer
B. Prostatic Urethral Lift for Treatment of Benign Prostatic Hypertrophy

IX. New Discussion Items **12:30 PM**

A. Chiropractic manipulation for non-axial indications—Dr. Trevor Douglass

X. Public comment **12:55 PM**

XI. Adjournment – Kevin Olson **1:00 PM**

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on March 8, 2018

For specific coding recommendations and guideline wording, please see the text of the 3/8/2018 VbBS minutes.

RECOMMENDED CODE MOVEMENT (effective 10/1/2018 unless otherwise noted)

- Delete the procedure codes for yttrium 90 administration from all lines on the Prioritized List and add to the noncovered line 500 for hepatocellular carcinoma and colorectal cancer metastatic to the liver and to line 660 for all other indications
- Add the procedure code for fractional exhaled nitric oxide testing to the covered asthma line
- Delete the inpatient and nursing facility procedure codes from the covered line for stereotyped movement resulting in self harm line
- Delete one inpatient procedure code and nursing facility procedure codes from the non-covered line for somatic disorders
- Add the procedure codes for treatment of corns and callouses to the covered preventive foot care line
- Make various coding clean up changes to the preventive foot care line
- Add a new procedure code for the Shingrix shingles vaccine to the preventive services line [effective April 1, 2018]
- Make various straightforward coding and guideline note changes to the Prioritized List

ITEMS CONSIDERED BUT NO RECOMMENDATIONS FOR CHANGES MADE

- Surgical treatment of deforming foot lesions was not added to the preventive foot care line
- PET scans for breast cancer staging was not added to the breast cancer line

RECOMMENDED GUIDELINE CHANGES (effective 10/1/2018 unless otherwise noted)

- Edit the newly adopted guideline for implantable cardiac defibrillators to match the updated National Coverage Determination from CMS
- Edit the guidelines associated with lines 500 and 660 with various entries for topics discussed
- Clarify the smoking and elective surgery guideline
- Delete the guideline note regarding primary and secondary progressive multiple sclerosis [effective April 1, 2018]
- Edit the prevention guideline reference to the ACIP vaccine schedule to include the Oregon specific vaccine schedule
- Modify the guideline note on the diagnosis of sleep apnea to encourage home sleep testing to be done preferentially over in-lab polysomnography in selected patients
- Modify the ancillary guideline on smoking cessation and elective surgical procedures to clarify intent

VALUE-BASED BENEFITS SUBCOMMITTEE
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
March 8, 2018
9:00 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; Mark Gibson; Holly Jo Hodges, MD; Vern Saboe, DC (via phone); Adrienne Irwin, PharmD.

Members Absent: Gary Allen, DMD; Susan Williams, MD.

Staff Present: Darren Coffman; Ariel Smits, MD, MPH; Cat Livingston, MD, MPH; Daphne Peck; Jason Gingerich.

Also Attending: K. Renae Wentz, MD, MPH, Mimi Luther and Dana Hargunani MD (Oregon Health Authority); David Barhoum, Christine Curry, PharmD, Paul Williams, and Shirley Quach (Genentech); Debby Ham, MD, Dan Bues, Beth Sayer, Pete Elson, and Steven McDen Castillo (Circassia).

- **Roll Call/Minutes Approval/Staff Report**

  The meeting was called to order at 9:10 a.m. and roll was called. Minutes from the January 18, 2018 VbBS meeting were reviewed. Hodges noted she was actually present for all votes but the minutes did not reflect this; staff will correct the minutes. The amended minutes were approved (Irwin abstained).

  Coffman gave an update on the HERC retreat. Smits reviewed the work of the Chronic Pain Taskforce and updated the group on the statement of intent for public health emergencies. Gingerich gave an update on legislative actions in the last session including new work assigned to HERC staff regarding extended stay centers.

- **Topic: Straightforward/Consent Agenda**

  Discussion: There was no discussion about the consent agenda items.

  Recommended Actions:
  1) Add 27006 (Tenotomy, abductors and/or extensor(s) of hip, open) and 27305 (Fasciotomy, iliotibial (tenotomy), open) to line 605 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR
  2) Add 38760 (Inguinofemoral lymphadenectomy, superficial, including Cloquet's node) and 38765 (Inguinofemoral lymphadenectomy, superficial, in continuity with pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes) to line 259 CANCER OF PENIS AND OTHER MALE GENITAL ORGANS
  3) Add N93.8 (Other specified abnormal uterine and vaginal bleeding) to line 420 MENSTRUAL BLEEDING DISORDERS
  4) Remove N93.8 from line 353 STRUCTURAL CAUSES OF AMENORRHEA
  5) Add line 401 CONDITIONS OF THE BACK AND SPINE to GN6 REHABILITATIVE AND HABILITATIVE THERAPIES

6) Modify GN32 as shown in Appendix A
7) Remove all L70 (Acne) ICD-10 codes from line 373 ACNE CONGLOBATA (SEVERE CYSTIC ACNE) other than L70.1 (Acne conglobata)
8) Add CPT 21235 (Graft; ear cartilage, autogenous, to nose or ear (includes obtaining graft)) to lines 311 HEARING LOSS - AGE 5 OR UNDER, 444 HEARING LOSS - OVER AGE OF FIVE, 473 CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM

MOTION: To approve the recommendations stated in the consent agenda. CARRIES 5-0.

- **Topic: Guideline for implantable cardiac defibrillators revisions**

Discussion: Smits reviewed the summary document. There was no discussion.

Recommended Actions:
1) Modify the guideline on implantable cardiac defibrillators adopted in January, 2018 as shown in Appendix A

MOTION: To approve the guideline note changes as presented. CARRIES 5-0.

- **Topic: Yttrium 90 for indications other than non-HCC and CRC metastatic to the liver**

Discussion: Smits reviewed the summary document. There was no discussion.

Recommended Actions:
1) Add HCPCS S2095 (Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres) to line 500/GN172
2) Modify the entry to GN172/line 500 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS as shown in Appendix A for yttrium-90 for treatment of primary hepatocellular carcinoma, or colorectal cancer metastatic to the liver
3) Remove CPT 79445 (Radiopharmaceutical therapy, by intra-arterial particulate administration) from all current lines on the Prioritized List
    a. Lines 129,130,160,161,162,165,195,204,214,238,242,262,265,274,279,291,292,299,319, 321, 333,346,376,439,465,533,600,611
4) Add an entry to GN173/line 660 for all non-HCC/CRC metastatic to the liver indications as experimental as shown in Appendix A

Note: Errors in the entries for S2095 in Guideline Note 172 and C2616 & S2095 in Guideline Note 173 in the meeting materials are shown corrected in Appendix A and will be confirmed at the HERC meeting in May.

MOTION: To approve the coding and guideline note changes as presented. CARRIES 5-0.

- **Topic: Diagnosis of sleep apnea**

  Discussion: Livingston reviewed the prior discussion about home sleep apnea testing. She clarified that concerns raised at the last meeting about cost-effectiveness of needing an additional night of home sleep testing were resolved, given additional information about the availability of auto-titrating CPAP.

  Livingston raised the question about the need for follow up of a negative home sleep test when clinical suspicion remained. Members discussed that there may not be that much difference in outcomes when treating this population, but if clinical suspicion is high enough, it was reasonable to do a follow up test. There were questions raised about being able to effectively define clinical suspicion. The group decided that by having most individuals do a home sleep study first, this would improve costs, and that following up negative home sleep study tests with in lab polysomnography when clinical suspicion remained was reasonable. Members suggested that home testing may increase access for some who otherwise may not be willing or able to have in-lab polysomnography. Overall, they agreed that there is value in ruling in a large population with a cheaper effective test.

  Recommended Actions:
  1) Modify the guideline note on the diagnosis of sleep apnea as shown in Appendix A.

  MOTION: To recommend the guideline note changes as presented. CARRIES 5-0.

- **Topic: Tobacco cessation and elective surgery guideline clarification**

  Discussion: Livingston reviewed the summary document. This guideline creates an administrative barrier to encourage optimization prior to elective surgery, and would be desirable by plastic surgeons and other surgeons trying to minimize harms. When the surgery would have no impact on the outcome of the cancer, it is appropriate to require tobacco cessation. Subcommittee members further wordsmithed the proposal to clarify intent. Similarly, further minor modifications were made to remove the reference to "reproductive procedures" and instead explicitly identify an exception for contraceptive procedures.

  Recommended Actions:
  1) Modify the guideline note further to clarify intent regarding contraceptive procedures and cancer-related procedures as shown in Appendix A.

  MOTION: To recommend the guideline note changes as amended. CARRIES 5-0.

- **Topic: Fractional exhaled nitric oxide (FeNO) for management of asthma**

  Discussion: Smits introduced the summary document. Olson noted that critical outcomes (e.g. hospitalizations, unplanned outpatient visits) did not have evidence of being affected with use of FeNO, but non-critical outcomes (e.g. oral steroid use) were. Irwin asked clarifying questions about how this test was coded in practice. Livingston raised questions about how this test was incorporated into existing asthma treatment algorithms. Olson noted that FeNO is a low cost test, but still could be costly if used by many patient at many visits. Wentz replied to that concern by

indicating that FFS or CCOs could limit use by putting in edits in the billing system to only allow a certain number of claims per year. Smits indicated that staff could look at claims and payments in the future to see if the test was a large cost-driver.

Public testimony was heard from Dan Bues and Dr. Debby Hamm from Circassia. Bues gave a market update, indicating that Regence BCBS has reviewed FeNO and now covers the test for diagnosis and management. Washington Medicaid removed PA for FeNO and now covers the test for diagnosis and management, as did Oklahoma Medicaid.

Hamm testified that the strength of evidence (SOE) in AHRQ was high for reducing exacerbation, defined in some cases as reduced ED visit or hospitalization. The AHRQ report showed reduced use of oral steroids with FeNO included in the management algorithm when data was pooled for adults and kids. The Cochrane review of pediatric data showed reduced use of oral steroids. Secondary outcomes had severe imprecision and low SOE in the AHRQ report. She noted that there is a clinical significant reduction in exacerbations – they are an important independent risk factor of having worse asthma outcomes. Hospitalization outcome had imprecise SOE, mainly because hospitalization is a rare event for asthma. The HERC quality of evidence statement takes into account harms, health equity and outcomes in specific subgroups. NICE and Cochrane both say that FeNO can be helpful in the management of specific groups of patients, such as patients still symptomatic with inhaled corticosteroid (ICS) therapy. The underling pathology of asthma is inflammation, which is what FeNO measures. The type of inflammation measured by FeNO occurs in only half of asthma patients. FeNO can help distinguish if the patient has the type of inflammation that ICS can help.

Hodges asked how the FeNO test would be used in the office for a known asthma patient. Hamm replied that the test is mostly used in a specialty setting. Certain patients won't need additional FeNO testing, but for other patients it might be helpful. ATS has an algorithm for FeNO use. If a patient has a high FeNO, and the FeNO score comes down with ICS, then you know the lower level is a reflection of good control and a higher level would indicate that a change in management is needed. Hodges asked how FeNO is different from peak flow. Hamm replied that peak flow measures another part of asthma and is used for different patients/indications. There are patients with normal peak flow but high FeNO scores; these patients do better on ICS that not on ICS even though the peak flow wouldn't indicate that. FeNO measures a biomarker to be used to monitor inflammation.

Olson asked a philosophic question as to whether the HERC should go against NICE and Cochrane, which is generally not our habit, but noted that the Circassia representatives had helped to explain why NICE and Cochrane made their decisions/conclusions. Gibson noted that the HERC has disagreed with NICE in the past. He felt that there was a strong enough signal in the evidence presented that it supported use of the FeNO test for management.

Olson wondered if the FeNO test is prone to misuse. Smits noted that OHA can monitor for misuse and re-examine if found to be highly used/a high cost driver in the future. Bues reported that FeNO use in Oregon is mainly in allergist and pulmonary offices, as well as a few pediatricians with a high number of asthmatics. 11-14 total devices are in use in Oregon currently. States that had PAs on FeNO have removed them due to low utilization. Providers are using it 3-4 times a year in the offices he works with. Utilization does not appear to be an issue on the commercial or Medicaid sides in his opinion. Wentz noted that when she practiced in an office with a FeNO machine and high numbers

of asthma kids, overuse was not an issue. The main issue in her office with kids with asthma was trying to get kids to come in and to take their medications. The clinical utility of FeNO was to find patients who were not compliant with medications.

Bues noted that currently 40 state Medicaid programs have approved FeNO testing for diagnosis and management; 2 other states are reviewing the test. Hamm noted that asthmatics are a vulnerable patient population, and FeNO helps give concrete data on their disease process which is helpful in uncovering lack of adherence with medications. AHRQ defined utilization as a high priority issue to determine how to use FeNO clinically. This AHRQ report should be out in the next year. All large asthma networks doing research on management are using FeNO to define disease subpopulations. Biologics are increasingly coming on the market for the treatment of asthma, and FeNO should be helpful in determining who should get these.

Recommended Actions:

1) Add fractional exhaled nitric oxide (FeNO; CPT 95012) to line 9 ASTHMA
2) Delete the diagnostic guideline approved at January meeting regarding FeNO

MOTION: To recommend the code and guideline note changes as presented. CARRIES 5-0.

- **Topic: Guideline note on immune modifying therapies for multiple sclerosis**

Discussion: Smits reviewed the summary document explaining the need to correct a technical error on the list. Guideline note 95 is outdated as it was create before a new treatment for progressive MS became available. David Barhume, Genentech, testified that he was there to give any needed information and answer questions, and that Genentech agreed with the staff recommendation to delete the guideline note. Gibson wanted to put into the record that he hopes there will be a time to review the evidence for these therapies in the future; Hodges agreed. Staff noted that the ability of the HERC to review evidence in prioritizing medications is a broader question and is scheduled to be brought back for discussion to HERC at their May meeting.

Recommended Actions:

1) Delete guideline note 95, effective April 1, 2018

MOTION: To recommend the guideline note change as presented. CARRIES 5-0.

- **Topic: Auricular acupuncture clarification**

Discussion: Smits reviewed the summary document. There was no discussion.

Recommended Actions:

1) Place S8930 (Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient) on line 660 and add an entry to Guideline Note 173 as shown in Appendix A

MOTION: To recommend the code and guideline note changes as presented. CARRIES 5-0.

- **Topic: Special consult only lines**

  Discussion: Smits reviewed the summary document. There was no discussion.

  Recommended Actions:
  1) Remove all inpatient and skilled nursing facility (SNF) CPT codes from line 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER, but leave ER visit codes
     a. 99217-99239 (hospital observation or inpatient care), 99304-99318 (SNF), 99324-99337 (domiciliary or rest home care), 99356-99357 (prolonged inpatient services)
  2) Remove any inpatient, SNF and ER codes from line 549 SOMATIC SYMPTOMS AND RELATED DISORDERS
     a. 99224 (Subsequent observation care, per day, for the evaluation and management of a patient…Typically, 15 minutes are spent at the bedside and on the patient's hospital floor or unit.) and 99324-99337 (domiciliary or rest home care)
  3) Change the treatment description for line 202 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS to "~~CONSULTATION/MEDICATION MANAGEMENT/BEHAVIORAL SUPPORT~~ MEDICAL THERAPY"

  MOTION: To recommend the code and treatment description changes as presented. CARRIES 5-0.

- **Topic: Surgical treatment of deforming foot lesions in high risk diabetic patients for prevention of ulcer**

  Discussion: Smits reviewed the summary document as well as recent phone meetings with local and national podiatry experts. Wentz expressed concern for the cost of treating foot ulcers; Smits noted that the expenditure for treatment of foot ulcer was high. However, the evidence does not give a number needed to treat for the prophylactic foot surgeries to prevent one foot ulcer. If the NNT is high, then the surgeries may not be cost effective; if the NNT is low, then it would be cost effective. Hodges noted that her CCO has lots of requests for these types of procedures. Wentz expressed concern that adding coverage of these procedures for a limited group of patients would result in a high PA review burden. Hodges replied that her CCO already PAs these procedures. Hodge's CCO approves these procedures in select cases in which there is a good argument that the procedure would be cost effective in that particular clinical situation and approves those by exception.

  There was concern for possible infection or other complications in use of these procedures to prevent ulcers, resulting in a possible cause of complications without definite benefit. The group was most interested in coverage of Achilles tendon lengthening, due to a higher level of evidence; however, Smits noted that the interest in covering this procedure by the podiatry experts was less than for other procedures.

  The decision was to not add coverage for prophylactic procedures to prevent foot ulcers but make other housekeeping changes to related lines. If this topic is brought back in the future, the group felt an orthopedic foot expert should be invited to give input.

Recommended Actions:

1) Add corn/callus treatment codes CPT codes 11055-11057 to line 165 PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS
2) Add CPT 28124 (Partial excision (craterization, saucerization, sequestrectomy, or diaphysectomy) bone (eg, osteomyelitis or bossing); phalanx of toe) to line 397 CHRONIC ULCER OF SKIN
3) Remove elective foot surgeries currently appearing on line 165 PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS
    a. CPT 28011 (Tenotomy, percutaneous, toe; multiple tendons)
    b. CPT 28100-28108 (Excision or curettage of bone cyst or benign tumor, bones of foot)
    c. CPT 28120-28124 (Partial excision (craterization, saucerization, sequestrectomy, or diaphysectomy) bone (eg, osteomyelitis or bossing, other foot bones)
4) Remove inpatient and ER CPT codes from line 165
    a. CPT 99218-99239, 99291-99292 (inpatient)
    b. CPT 99281-99285 (ER)
    c. CPT 99468-99480 (pediatric inpatient)

MOTION: To recommend the code changes as presented. CARRIES 5-0.

- **Topic: PET scan for staging of breast cancer**

Discussion: Smits reviewed the summary document. Olson reviewed PET imaging and its use in oncology. He is not aware of widespread use of PET in breast cancer patients. In his experience PET is used most in stage IV, where treatment is done with intent to prolong life. Bone scans can still be positive after cancer is treated because it reflects bone injury. PET will tell you if the bone metastases are active. The meta-analysis referenced convinces him to not cover in stage IV disease. He noted that PET scans involve a big dose of IV radiation and then the radiation of a CT scan. He feels coverage should be through exceptions. He also noted that lack of coverage for PET for breast cancer goes against standard of care for women with bone metastases and goes against a CMS NCD. He noted that the Commission may get provider and advocacy pushback.

Recommended Actions:

1) Add HCPCS G0252 (Pet imaging, full and partial-ring pet scanners only, for initial diagnosis of breast cancer and/or surgical planning for breast cancer (e.g., initial staging of axillary lymph nodes)) to line 660/GN173 with a new GN173 entry as shown in Appendix A

MOTION: To recommend the guideline note change as presented. CARRIES 5-0.

- **Topic: Vaccination issues**

Discussion: Smits reviewed the summary document. Mimi Luther from the Oregon Immunization Program spoke to the immunization table, and its role as a standing order for pharmacies and public health programs. Olson noted that the HERC generally refers to national guidelines, but noted that the Oregon specific table has more information and allows OHA to be congruent between programs.

Wentz raised the question about whether OHA can cover Shingrix if it is not covered currently by CMS. It was noted that some of the CCOs are already covering it. The group felt that coverage of Shingrix should be done as soon as feasible, and recommended that it be added to the April 1, 2018 Prioritized List if approved by HERC.

Luther brought up that there is another new vaccine, this one for hepatitis B in adults, which was just FDA approved and added to the ACIP vaccine schedule at their February meeting. The new vaccine is much more effective that the current vaccine, and is able to be administered in 2 doses over 28 days rather than 3 doses over 6 months. It was determined that the CPT code for this vaccine (CPT 90739) is already on Line 3 and no action is needed by HERC.

Recommended Actions:

1) Add CPT 90750 (Zoster vaccine recombinant, adjuvanted) to line 3 PREVENTION SERVICES WITH EVIDENCE OF EFFECTIVENESS, effective April 1, 2018
2) Modify GN106 as shown in Appendix A

MOTION: To recommend the code and guideline note changes as presented. CARRIES 5-0.

- **Public Comment:**

  No additional public comment was received.

- **Issues for next meeting:**

  There are no carry-over issues

- **Next meeting:**

  May 17, 2018 at Clackamas Community College Wilsonville Training Center, Wilsonville, Oregon, Rooms 111-112.

- **Adjournment:**

  The meeting adjourned at 12:40 PM.

Appendix A

Revised Guideline Notes

GUIDELINE NOTE 32, CATARACT

Line 296

Cataract extraction is included on this line for c~~C~~atarac~~t~~s causing symptomatic (i.e. causing the patient to seek medical attention) impairment of visual function not correctable with a tolerable change in glasses or contact lenses resulting in the patient's inability to function satisfactorily while performing activities of daily living (ADLs). Cataract removal must be likely to restore vision and allow the patient to resume activities of daily living. There are rare instances where cataract removal is medically necessary even if visual improvement is not the primary goal:

A) Hypermature cataract causing inflammation and glaucoma OR
B) To see the back of the eye to treat posterior segment conditions that could not be monitored due to the poor view and very dense lens opacity (i.e. diabetic retinopathy, glaucoma) OR
C) Significant anisometropia causing aniseikonia.

~~**GUIDELINE NOTE 95, IMMUNE MODIFYING THERAPIES FOR MULTIPLE SCLEROSIS**~~

~~*Line 252*~~

~~Once a diagnosis of primary progressive or secondary progressive multiple sclerosis is reached, immune modifying therapies are no longer covered.~~

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,619

Included on Line 3 are the following preventive services:

A) US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2016.
   1) http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
   2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.
B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   1) http://brightfutures.aap.org. Periodicity schedule available at http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule_FINAL.pdf.
   2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.
C) Health Resources **and Services Administration (HRSA) Women's Preventive Services - Required Health Plan Coverage Guidelines a**s retrieved from http://www.hrsa.gov/womensguidelines/ **on 1/1/2017.**
~~D)~~ Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP)~~:~~ ~~http://www.cdc.gov/vaccines/schedules/hcp/index.html~~ or approved for the Oregon Immunization Program: http://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/DMAPvactable.pdf

Appendix A

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 500

The following interventions are prioritized on Line 500 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration for use in treating primary hepatocellular carcinoma or colorectal cancer metastatic to the liver	Low cost-effectiveness compared to equally effective but less expensive standard chemotherapies; concern for possible harms compared to standard chemotherapy	January, 2018
C2616	Brachytherapy source, non-stranded, yttrium-90, per source, for use in treating primary liver cancer or metastatic cancer to the liver		
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres, for use in treating primary liver cancer or metastatic cancer to the liver		

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

Line 660

The following treatments are prioritized on Line 660, CONDITIONS FOR WHICH CERTAIN TREATMENTS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS, for the conditions listed here:

Procedure Code	Intervention Description	Rationale	Last Review
79445	Radiopharmaceutical therapy, by intra-arterial particulate administration for use in treating cancers other than primary hepatocellular carcinoma or colorectal cancer metastatic to the liver	No evidence of effectiveness	March, 2018

Appendix A

Procedure Code	Intervention Description	Rationale	Last Review
C2616 S2095	Brachytherapy source, non-stranded, yttrium-90, per source ~~for use in treating primary liver cancer or metastatic cancer to the liver~~, in treating cancers other than primary hepatocellular carcinoma or colorectal cancer metastatic to the liver Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres, in treating cancers other than primary hepatocellular carcinoma or colorectal cancer metastatic to the liver		
G0252	Pet imaging, full and partial-ring pet scanners only, for initial diagnosis of breast cancer and/or surgical planning for breast cancer (e.g., initial staging of axillary lymph nodes)	Not a recommended test for axillary staging	March, 2018
S8930	Electrical stimulation of auricular acupuncture points by proprietary electrical stimulation devices, such as P-Stim and E-pulse [note: auricular electroacupuncture provided by a licensed provider in a clinical setting is covered under CPT 97813-97814]	No evidence of effectiveness	January, 2013

GUIDELINE NOTE XXX, IMPLANTABLE CARDIAC DEFIBRILLATORS

Lines 98, 99,111,281,285

Implantable cardiac defibrillators are included on these lines for patients with one or more of the following:

1) Patients with a personal history of sustained ventricular tachyarrhythmia or cardiac arrest due to ventricular fibrillation. Patients must have demonstrated one of the following:

a) Documented episode of cardiac arrest due to ventricular fibrillation (VF), not due to a transient or reversible cause

~~b) Life threatening arrhythmias not due to transient or reversible cause~~

b) Documented sustained ventricular tachyarrhythmia (VT), either spontaneous or induced by an electrophysiology (EP) study, not associated with an acute myocardial infarction (MI) and not due to a transient or reversible cause

~~c) Documented familial or inherited conditions with a high risk of life-threatening VT, such as long QT syndrome or hypertrophic cardiomyopathy~~

~~2) Coronary artery disease with a documented prior MI, a measured left ventricular ejection fraction (LVEF) ≤ 0.35, and inducible, sustained VT or VF at EP study. (The MI must have occurred more than 40 days prior to defibrillator insertion. The EP test must be performed more than 4 weeks after the qualifying MI.)~~

2) ~~Documented prior MI and a measured LVEF ≤ 0.30. Patients must not have:~~ Patients with a prior myocardial infarction and a measured left ventricular ejection fraction (LVEF) ≤ 0.30. Patients must not have:

a) New York Heart Association (NYHC) classification IV heart failure; or

b) Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm; or

c) Had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary ~~angioplasty (PTCA)~~ intervention (PCI) with angioplasty and/or stenting, within past 3 months; or

d) Had ~~an acute MI~~ a myocardial infarction in the past 40 days; or

e) Clinical symptoms or findings that would make them a candidate for coronary revascularization~~; or~~

~~f) Any disease, other than cardiac disease (e.g., cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year.~~

3) ~~Ischemic dilated cardiomyopathy (IDCM), documented prior MI, NYHA Class II and III heart failure, and measured LVEF ≤ 35%;~~ Patients who have severe ischemic dilated cardiomyopathy but no personal history of sustained ventricular tachyarrhythmia or cardiac arrest due to ventricular fibrillation, and have New York Heart Association (NYHA) Class II or III heart failure, left ventricular ejection fraction (LVEF) ≤ 35%. Additionally, patients must not have:

a) Had a coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI) with angioplasty and/or stenting, within the past 3 months; or

b) Had a myocardial infarction within the past 40 days; or

c) Clinical symptoms and findings that would make them a candidate for coronar revascularization.

4) ~~Non-ischemic dilated cardiomyopathy (NIDCM) >9 months, NYHA Class II and III heart failure, and measured LVEF ≤ 35%;~~ Patients who have severe non-ischemic dilated cardiomyopathy but no personal history of sustained ventricular tachyarrhythmia or cardiac arrest due to ventricular fibrillation, and have New York Heart Association (NYHA) Class II or III heart failure, left ventricular ejection fraction (LVEF) ≤ 35%, been on optimal medical therapy (OMT) for at least 3 months. Additionally, patients must not have:

a) Had a coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI) with angioplasty and/or stenting, within the past 3 months; or

b) Had a myocardial infarction within the past 40 days; or

c) Clinical symptoms and findings that would make them a candidate for coronary revascularization.

5) Patients with documented familial, or genetic disorders with a high risk of life-threatening tachyarrhytmias (sustained ventricular tachycardia or ventricular

fibrillation), to include, but not limited to, long QT syndrome or hypertrophic cardiomyopathy.

For these patients identified in #2-5, a formal shared decision making encounter must occur between the patient and a physician or qualified non-physician practitioner using an evidence-based decision tool on ICDs prior to initial ICD implantation. The shared decision making encounter may occur at a separate visit.

6) Patients with an existing ICD may receive an ICD replacement if it is required due to the end of battery life, elective replacement indicator (ERI) or device/lead malfunction.

All indications above in #1-6 must meet the following criteria:

~~i. Patients must not have irreversible brain damage from preexisting cerebral disease;~~

~~ii. MIs must be documented and defined according to the consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction~~

i. Patients must be clinically stable (e.g., not in shock, from any etiology);
ii. Left ventricular ejection fraction (LVEF) must be measured by echocardiography, radionuclide (nuclear medicine) imaging, or catheter angiography;
iii. Patients must not have:
    a) Significant, irreversible brain damage; or
    b) Any disease, other than cardiac disease (e.g., cancer, renal failure, liver failure) associated with a likelihood of survival less than 1 year; or
    c) Supraventricular tachycardia such as atrial fibrillation with a poorly controlled ventricular rate.

~~Indications 3 - 8 (primary prevention of sudden cardiac death) must also meet the following criteria:~~

~~a) Patients must be able to give informed consent;~~
~~b) Patients must not have:~~
- ~~Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;~~
- ~~Had a CABG or PTCA within the past 3 months;~~
- ~~Had an acute MI within the past 40 days;~~
- ~~Clinical symptoms or findings that would make them a candidate for coronary revascularization;~~
- ~~Any disease, other than cardiac disease (e.g., cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year;~~

~~c) Ejection fractions must be measured by angiography, radionuclide scanning, or echocardiography;~~

~~1) Patients with NIDCM >3 months, NYHA Class II or III heart failure, and measured LVEF ≤ 35%, only if the following additional criteria are also met:~~

~~a) Patients must be able to give informed consent;~~
~~b) Patients must not have:~~
~~a) Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;~~
~~b) Had a CABG or PTCA within the past 3 months;~~

~~c) Had an acute MI within the past 40 days;~~
~~d) Clinical symptoms or findings that would make them a candidate for coronary revascularization;~~
~~e) Irreversible brain damage from preexisting cerebral disease;~~
~~f) Any disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year;~~

~~c) Ejection fractions must be measured by angiography, radionuclide scanning, or echocardiography;~~

~~d) MIs must be documented and defined according to the consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction~~

Exceptions to waiting periods for patients that have had a coronary artery bypass graft (CABG), or percutaneous coronary intervention (PCI) with angioplasty and/or stenting, within the past 3 months, or had a myocardial infarction within the past 40 days:

i. Cardiac Pacemakers: Patients who meet all CMS coverage requirements for cardiac pacemakers and who meet the criteria in this national coverage determination for an ICD may receive the combined device in one procedure at the time the pacemaker is clinically indicated;
ii. Replacement of ICDs: Patients with an existing ICD may receive a ICD replacement if it is required due to the end of battery life, elective replacement indicator (ERI) or device/lead malfunction.

Other Indications:
For patients who are candidates for heart transplantation on the United Network for Organ Sharing (UNOS) transplant list awaiting a donor heart, coverage of ICDs, as with cardiac resynchronization therapy, as a bridge to transplant to prolong survival until a donor becomes available.

DIAGNOSTIC GUIDELINE D8, DIAGNOSTIC TESTING FOR OBSTRUCTIVE SLEEP APNEA (OSA) IN ADULTS

~~Type I PSG is covered when used to aid the diagnosis of OSA in patients who have clinical signs and symptoms indicative of OSA if performed attended in a sleep lab facility.~~

~~OHP clients should have access to least one of the alternatives listed below:~~

~~1) Type II or Type III sleep testing devices when used to aid the diagnosis of OSA in patients who have clinical signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.~~
~~2) Type IV sleep testing devices measuring three or more channels, one of which is airflow, when used to aid the diagnosis of OSA in patients who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.~~
~~3) Sleep testing devices measuring three or more channels that include actigraphy, oximetry, and peripheral arterial tone, when used to aid the diagnosis of OSA in patients who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.~~

~~CPAP titration should be performed as part of the diagnostic study, if possible.~~

Appendix A

In adults with clinical signs and symptoms consistent with obstructive sleep apnea (OSA), a home sleep study is the first-line diagnostic test for most patients, when available.

Polysomnography in a sleep lab is indicated as a first-line test for patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to a neuromuscular condition, awake hypoventilation or suspicion of sleep related hypoventilation, chronic opioid medication use, history of stroke or severe insomnia. If a patient has had an inconclusive *(or negative)* home sleep apnea test and a clinical suspicion for OSA remains, then attended polysomnography is included on this line. Split night diagnostic protocols are required when a diagnosis of OSA is confirmed in the first portion of the night.

For portable devices, Type II-III are included on this line. Type IV sleep testing devices must measure three or more channels, one of which is airflow, to be included on this line. Sleep testing devices that are not Type1-IV and measure three or more channels that include actigraphy, oximetry, and peripheral arterial tone, are included on this line.

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

~~**DIAGNOSTIC GUIDELINE DX, FRACTIONAL EXHALED NITRIC OXIDE**~~

~~Fractional exhaled nitric oxide (FeNO) is covered only for the initial diagnosis of asthma in patients 7 years of age and older. It is not included for the monitoring of asthma, selection of medications, or diagnosis of acute asthma exacerbations.~~

ANCILLARY GUIDELINE A4, SMOKING CESSATION AND ELECTIVE SURGICAL PROCEDURES

Smoking cessation is required prior to elective surgical procedures for active tobacco users. Cessation is required for at least 4 weeks prior to the procedure and requires objective evidence of abstinence from smoking prior to the procedure.

Elective surgical procedures in this guideline are defined as surgical procedures which are flexible in their scheduling because they do not pose an imminent threat nor require immediate attention within 1 month. ~~Reproductive (i.e. for contraceptive purposes), cancer-related and diagnostic procedures are excluded from this guideline.~~ Procedures for contraceptive/sterilization purposes, procedures targeted to active cancers (i.e. when a delay in the procedure could lead to cancer progression) and diagnostic procedures are not subject to the limitations in this guideline note.

The well-studied tests for confirmation of smoking cessation include cotinine levels and exhaled carbon monoxide testing. However, cotinine levels may be positive in nicotine replacement therapy (NRT) users, smokeless tobacco and e-cigarette users (which are not contraindications to elective surgery coverage). In patients using nicotine products aside from combustible cigarettes the following alternatives to urine cotinine to demonstrate smoking cessation may be considered:

- Exhaled carbon monoxide testing
- Anabasine or anatabine testing (NRT or vaping)

Appendix A

Certain procedures, such as lung volume reduction surgery, bariatric surgery, erectile dysfunction surgery, and spinal fusion have 6 month tobacco abstinence requirements. See Guideline Notes 8, 100, 112 and 159.

Section 2.0

Staff Report

Errata
May 2018

1) The line number referred to in GN167 was corrected:

GUIDELINE NOTE 167, CHOLECYSTECTOMY FOR CHOLECYSTITIS AND BILIARY COLIC

Lines 55,639

Cholecystectomy for cholecystitis and biliary colic are including on Line 55 when meeting the following criteria:

A) For cholecystitis, with either:
   1) The presence of right upper quadrant abdominal pain, mass, tenderness or a positive Murphy's sign, AND
   2) Evidence of inflammation (e.g. fever, elevated white blood cell count, elevated C reactive protein) OR
   3) Ultrasound findings characteristic of acute cholecystitis or non-visualization of the gall bladder on oral cholecystegram or HIDA scan, or gallbladder ejection fraction of < 35%.

B) For biliary colic (i.e. documented clinical encounter for right upper quadrant or epigastric pain with gallstones seen on imaging during each episode) without evidence of cholecystitis or other complications is included on line ~~59~~ 55 only when
   1) Recurrent (i.e. 2 or more episodes in a one year period) OR
   2) A single episode in a patient at high risk for complications with emergent cholecystitis (e.g. immunocompromised patients, morbidly obese patients, diabetic patients) OR
   3) When any of the following are present: elevated pancreatic enzymes, elevated liver enzymes or dilated common bile duct on ultrasound.

   Otherwise, biliary colic is included on Line 639.

2) CPT 58661 (Laparoscopy, surgical; with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)) was approved for addition to line 6 REPRODUCTIVE SERVICES by VBBS and HERC in November, 2017 but not added to the Prioritized List in error. 58661 is the laparoscopic equivalent to 58700 (Salpingectomy, complete or partial, unilateral or bilateral) which was also added to line 6 at that meeting.

3) Add CPT 97810-97814 (Acupuncture) to line 202 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS. Acupuncture is only intended to pair with post-stroke depression per the acupuncture guideline note, and this diagnosis is on line 202.
   a. From GUIDELINE NOTE 92, ACUPUNCTURE
      i. Line 202 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS Acupuncture is paired with the treatment of post-stroke depression only. Treatments may be billed to a maximum of 30 minutes face-to-face time and limited to 12 total sessions per year, with documentation of meaningful improvement; patients may have additional visits authorized beyond these limits if medically appropriate

Section 3.0

Consent Agenda-

Straightforward Items

Consent Agenda Issues—May, 2018

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
20910	Cartilage graft; costochondral	160 TRAUMATIC AMPUTATION OF ARM(S), HAND(S), THUMB(S), AND FINGER(S) (COMPLETE)(PARTIAL) WITH AND WITHOUT COMPLICATION 641 TMJ DISORDERS	This cartilage graft procedure can be used to reconstruct various areas of the body for a variety of conditions. HSD and HERC staff recommend that it be removed from its current lines () and placed on the Ancillary List	Remove 20910 from lines 160,641 Advise HSD to add 20910 to the Ancillary List
93285 93290-93291	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis… Interrogation device evaluation (in person) with analysis…	98 HEART FAILURE	These CPT codes were mistakenly added to line 98 in January, 2018 during the implantable cardiac defibrillator review. These codes should remain only on the Diagnostic Procedures File	Remove 93285, 93290 and 93291 from line 98
97810-97814	Acupuncture	204 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE	Acupuncture is only intended to pair with post-stroke depression per the acupuncture guideline note, and this diagnosis is on line 202. Line 204 is not listed in the acupuncture guideline	Remove 97810-97840 from line 204
11400-11446	Excision, benign lesion	541 FOREIGN BODY GRANULOMA OF MUSCLE, SKIN AND SUBCUTANEOUS TISSUE	There are no skin excision CPT codes on line 541. A CCO medical director requested that the series be added to pair with removal of foreign body granulomas	Add 11400-11446 to line 541

Straightforward Guideline Note Changes
May 2018

1) Add back the reference to the ACIP vaccination table to the preventive services guideline. GN 106 references both tables. The Oregon table is preferred; however, when the Oregon table is not yet updated for a new vaccine or other changes, the ACIP table should be available for reference.

GUIDELINE NOTE 106, PREVENTIVE SERVICES

Lines 3,619

Included on Line 3 are the following preventive services:

A) US Preventive Services Task Force (USPSTF) "A" and "B" Recommendations in effect and issued prior to January 1, 2016.
   1) http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/
   2) USPSTF "D" recommendations are not included on this line or any other line of the Prioritized List.

B) American Academy of Pediatrics (AAP) Bright Futures Guidelines:
   1) http://brightfutures.aap.org. Periodicity schedule available at http://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule_FINAL.pdf.
   2) Screening for lead levels is defined as blood lead level testing and is indicated for Medicaid populations at 12 and 24 months. In addition, blood lead level screening of any child between ages 24 and 72 months with no record of a previous blood lead screening test is indicated.

C) Health Resources **and Services Administration (HRSA) Women's Preventive Services - Required Health Plan Coverage Guidelines a**s retrieved from http://www.hrsa.gov/womensguidelines/ **on 1/1/2017.**

D) Immunizations as recommended by the Advisory Committee on Immunization Practices (ACIP): http://www.cdc.gov/vaccines/schedules/hcp/index.html or approved for the Oregon Immunization Program: http://public.health.oregon.gov/PreventionWellness/VaccinesImmunization/ImmunizationProviderResources/Documents/DMAPvactable.pdf

2) Modify the continuous glucose monitoring guideline to clarify that the guideline refers to personal monitoring devices (as opposed to those found in a clinical setting):

GUIDELINE NOTE 108, CONTINUOUS GLUCOSE MONITORING

Line 8

Real-time (personal) continuous glucose monitoring (CGM) is included on Line 8 for:

A) Adults with type 1 diabetes mellitus not on insulin pump management:
   1) Who have received or will receive diabetes education specific to the use of CGM AND
   2) Who have used the device for at least 50% of the time at their first follow-up visit AND
   3) Who have baseline HbA1c levels greater than or equal to 8.0%, frequent or severe hypoglycemia, or impaired awareness of hypoglycemia (including presence of these conditions prior to initiation of CGM).

B) Adults with type 1 diabetes on insulin pump management (including the CGM-enabled insulin pump):
   1) Who have received or will receive diabetes education specific to the use of CGM AND
   2) Who have used the device for at least 50% of the time at their first follow-up visit

C) Women with type 1 diabetes who are pregnant or who plan to become pregnant within six months without regard to HbA1c levels.
D) Children and adolescents under age 21 with type 1 diabetes:
   1) Who have received or will receive diabetes education specific to the use of CGM AND
   2) Who have used the device for at least 50% of the time at their first follow-up visit

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

Special "Consult Only" Lines

Issue: In March, 2018, VBBS/HERC approved changed to 3 lines designated as "consultation" lines. These lines were created to allow limited treatment for conditions which generally have no definitive long term therapies. Inpatient, SNF, and ER CPT codes were removed from these lines. On review, staff have found two additional CPT codes not proposed for removal in March which should be removed.

Line 202 CHRONIC ORGANIC MENTAL DISORDERS INCLUDING DEMENTIAS

No changes made

Line 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER

Remove all inpatient and SNF CPT codes but leave ER visit codes

Line 549 SOMATIC SYMPTOMS AND RELATED DISORDERS

Remove any inpatient, SNF and ER codes

HERC staff recommendations:

1) Remove from line 436 STEREOTYPED MOVEMENT DISORDER WITH SELF-INJURIOUS BEHAVIOR DUE TO NEURODEVELOPMENTAL DISORDER and line 549 SOMATIC SYMPTOMS AND RELATED DISORDERS
    a. CPT 99339-99340 Individual physician supervision of a patient (patient not present) in home, domiciliary or rest home (eg, assisted living facility) requiring complex and multidisciplinary care modalities involving regular physician development and/or revision of care plans, review of subsequent reports of patient status, review of related laboratory and other studies, communication (including telephone calls) for purposes of assessment or care decisions with health care professional(s), family member(s), surrogate decision maker(s) (eg, legal guardian) and/or key caregiver(s) involved in patient's care, integration of new information into the medical treatment plan and/or adjustment of medical therapy, within a calendar month

Surgical Treatment of Deforming Foot Lesions in
High Risk Patients for Prevention and Treatment of Ulcers
Corrections, May 2018

Issue: The high risk foot care line, 165 PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS, was reviewed at the March, 2018 VBBS/HERC meetings and various code clean ups and changes were made. Staff have identified several additional codes which need to be removed from this line.

HERC staff recommendations:

1) Remove additional elective foot surgeries currently appearing on line 165 PREVENTIVE FOOT CARE IN HIGH RISK PATIENTS
    a. CPT 28200-29202 Repair, tendon, flexor, foot
    b. CPT 28208-28210 Repair, tendon, extensor, foot
2) Remove inpatient CPT codes from line 165
    a. CPT 99184 Initiation of selective head or total body hypothermia in the critically ill neonate, includes appropriate patient selection by review of clinical, imaging and laboratory data, confirmation of esophageal temperature probe location, evaluation of amplitude EEG,
    b. CPT 99217 Observation care discharge day management
    c. CPT 99356-99357 Prolonged service in the inpatient or observation setting
    d. CPT 99358-99359 Prolonged evaluation and management service before and/or after direct patient care
    e. CPT 99360 Standby service, requiring prolonged attendance

Section 4.0

Interim CPTF Report To HERC

Chronic Pain Taskforce
Interim Report to the Health Evidence Review Commission

Issue 1

The Chronic Pain Taskforce has met four times, and has worked on a two stage proposal for the HERC to improve the treatment of patients with chronic pain conditions. As a first step, the CPTF is requesting consideration of the addition of a statement of intent to the Prioritized List, effective October 1, 2018 if possible. The Taskforce is continuing to work on the creation of a new line with a guideline for chronic pain conditions. This new line and guideline work is ongoing, and the Taskforce expects to present this work to the HERC in the fall of 2017, for possible adoption as part of the biennial review process for implementation in January, 2020.

The statement of intent below has been reviewed by the CPTF at several meetings, and was approved at their April, 2018 meeting. The Taskforce feels that this SOI is a good step towards their goal of standardizing and improving treatment of chronic pain patients. The SOI will also raise awareness in the provider community about what is good care of patients with chronic pain.

This SOI was circulated among the CCO medical directors, who requested that wording about "covered" conditions be added to clarify that this SOI does not guarantee any new coverage or services. Several CPTF members objected to this addition. HERC staff are including this possible stakeholder edit in blue in the SOI shown below as a point of discussion for the VBBS meeting.

CPTF recommendation:

1) Adopt the following new statement of intent, effective October 1, 2018

STATEMENT OF INTENT XXX TREATMENT OF CHRONIC PAIN

It is the intent of the Commission that covered [stakeholder proposed edit] chronic pain conditions be treated in a multidisciplinary fashion, with a focus on active therapies, improving function, and demedicalizing the condition. Care should include education on sleep, nutrition, stress reduction, mood, exercise, and knowledge of pain. All providers seeing chronic pain patients should be trained in pain science (e.g. a contemporary understanding of the central and peripheral nervous system in chronic pain), motivational interviewing, culturally sensitive care, and trauma-informed care. Care should be provided as outlined in the Oregon Pain Management Commission pain management module: http://www.oregon.gov/oha/HPA/CSI-PMC/Pages/module.aspx.

Issue 2

The Chronic Pain Taskforce also gave interim recommendations for changes to the opioid guideline, to correct out-of-date portions, specifically the taper portion. These changes were approved via an email discussion. The Taskforce does not agree with the tapering off of opioids for all patients, but voted non-unanimously to include the proposed edits as an interim solution to the dating problem in the guideline. The Taskforce plans further revisions to this guideline as part of their continuing deliberations. In the meantime, the Taskforce desires that the change outlined below be adopted for October 1, 2018.

The opioid taper paragraph was written with the intent that all opioid patients with back and neck conditions would be tapered off opioids by January 1, 2018. Due to step-wise implementation of tapers and other barriers encountered, all OHP back and neck pain patients have not been tapered off opioids to date. Additionally, new OHP patients who are receiving long-term opioids for back and neck

conditions have come on the plan. These groups of patients need to have guidance on their tapers off these medications.

CPTF recommendation:

1) Adopt the following revisions to GN60, effective October 1, 2018

GUIDELINE NOTE 60, OPIOIDS FOR CONDITIONS OF THE BACK AND SPINE

Lines 346,361,401,527

Opioid medications are only included on these lines under the following criteria:

For acute injury, acute flare of chronic pain, or after surgery:

1) During the first 6 weeks opioid treatment is included on these lines ONLY:
   a) When each prescription is limited to 7 days of treatment, AND
   b) For short acting opioids only, AND
   c) When one or more alternative first line pharmacologic therapies such as NSAIDs, acetaminophen, and muscle relaxers have been tried and found not effective or are contraindicated, AND
   d) When prescribed with a plan to keep active (home or prescribed exercise regime) and with consideration of additional therapies such as spinal manipulation, physical therapy, yoga, or acupuncture, AND
   e) There is documented verification that the patient is not high risk for opioid misuse or abuse.
2) Treatment with opioids after 6 weeks, up to 90 days after the initial injury/flare/surgery is included on these lines ONLY:
   a) With documented evidence of improvement of function of at least thirty percent as compared to baseline based on a validated tools (e.g. Oswestry, Neck Disability Index, SF-MPQ, and MSPQ).
   b) When prescribed in conjunction with therapies such as spinal manipulation, physical therapy, yoga, or acupuncture.
   c) With verification that the patient is not high risk for opioid misuse or abuse. Such verification may involve
      i) Documented verification from the state's prescription monitoring program database that the controlled substance history is consistent with the prescribing record
      ii) Use of a validated screening instrument to verify the absence of a current substance use disorder (excluding nicotine) or a history of prior opioid misuse or abuse
      iii) Administration of a baseline urine drug test to verify the absence of illicit drugs and non-prescribed opioids.
   d) Each prescription must be limited to 7 days of treatment and for short acting opioids only
3) Chronic opioid treatment (>90 days) after the initial injury/flare/surgery is not included on these lines except for the taper process described below.

Transitional coverage for patients on long-term opioid therapy ~~as of July 1, 2016~~:

For patients ~~on covered chronic~~ receiving long-term opioid therapy ~~as of July 1, 2016, opioid medication is included on these lines only from July 1, 2016 to December 31, 2016. During the period from January 1, 2017 to December 31, 2017~~, continued coverage of opioid medications requires an individual treatment plan ~~developed by January 1, 2017~~ which includes a taper with an end to opioid therapy no later than ~~January 1, 2018~~ one year after the start of the taper. Taper plans must include nonpharmacological treatment strategies for managing the patient's pain based on Guideline Note 56 NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE. If a patient has

developed dependence and/or addiction related to their opioids, treatment is ~~available~~ included on Line 4 SUBSTANCE USE DISORDER**.**

Section 5.0

New Codes

HCPCS "C" Code Review

Issue: In the past, HERC staff was under the impression that "C" codes did not require review due to the fact that these codes are bundled into outpatient DRG-type payments. However, it has come to our attention that these codes do require review. While some of these codes are indeed bundled into outpatient DRG payments, others pay individually.

On review, many of these codes appear to be for DME materials such as catheters or for drugs. Some code for devices, like vascular stents, that can be used for a wide variety of diagnoses. These codes should continue to be ancillary. Other codes are used for materials only utilized on a few lines, such as cardiac pacemakers. These codes could easily be placed on lines, and appropriate lines are recommended by staff. There are also codes that are used for procedures. Such codes need evidence reviews. Some reviews had previously been done, and codes were recommended for placement where indicated in those reviews. Three reviews were conducted as part of the current review and are presented separately.

HERC staff recommendations:

1) Code placement recommendations as presented in the Excel spreadsheet
2) GN173 entry edits below for codes as noted in spreadsheet

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

The following Interventions are prioritized on Line 660 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
19294 C9726	Intraoperative radiation therapy (IORT) concurrent with partial Mastectomy Placement and removal (if performed) of applicator into breast for intraoperative radiation therapy, add-on to primary breast procedure	Unproven treatment	November, 2017
22867-22870 C1821	Insertion of interlaminar/ interspinous process stabilization/ distraction device, without fusion, including image guidance when performed, with open decompression, lumbar Interspinous process distraction device (implantable)	Insufficient evidence of effectiveness	November, 2016
C9733	Non-ophthalmic fluorescent vascular angiography	Unproved therapy	December, 2012
52441-52442 C9739-9740	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant Cystourethroscopy, with insertion of transprostatic implant	No evidence of effectiveness	March, 2015 Coverage Guidance

Procedure Code	Intervention Description	Rationale	Last Review
C9747	Ablation of prostate, transrectal, high intensity focused ultrasound (hifu), including imaging guidance	No evidence of effectiveness	March, 2015 Coverage Guidance

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C2617	Stent, non-coronary, temporary, without delivery system	Ancillary procedures	Ancillary procedures	DME Stents can be used for many purposes, including repair of aneurysms, treatment of peripheral vascular disease, hemodialysis, etc.	No separate payment	
C2618	Probe/needle, cryoablation	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C2619	Pacemaker, dual chamber, non rate-responsive (implantable)	Ancillary procedures	69 Acute and subacute ischemic heart disease, myocardial infarction 111 Congenital heart block; other obstructive anomalies of heart 189 Chronic ischemic heart disease 281 Life-threatening cardiac arrhythmias 285 Complications of a procedure always requiring treatment 347 Cardiac arrhythmias	contain pacemaker insertion codes	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C2620	Pacemaker, single chamber, non rate-responsive (implantable)	Ancillary procedures	69, 111, 189, 281, 285, 347	contain pacemaker insertion codes	No separate payment	
C2621	Pacemaker, other than single or dual chamber (implantable)	Ancillary procedures	69, 111, 189, 281, 285, 347	contain pacemaker insertion codes	No separate payment	
C2622	Prosthesis, penile, non-inflatable	Ancillary procedures	521 SEXUAL DYSFUNCTION	contain implantation CPT codes	No separate payment	
C2623	Catheter, transluminal angioplasty, drug-coated, non-laser	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C2624	Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components		Ancillary procedures	DME	No separate payment	
C2625	Stent, non-coronary, temporary, with delivery system	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C2626	Infusion pump, non-programmable, temporary (implantable)	Ancillary procedures	Ancillary procedures	DME Can be used for many conditions	No separate payment	
C2627	Catheter, suprapubic/cystoscopic	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C2628	Catheter, occlusion	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C2629	Introducer/sheath, other than guiding, other than intracardiac electrophysiological, laser	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C2630	Catheter, electrophysiology, diagnostic/ablation, other than 3d or vector mapping, cool-tip	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C2631	Repair device, urinary, incontinence, without sling graft	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C2634	Brachytherapy source, non-stranded, high activity, iodine-125, greater than 1.01 mci (nist), per source	Ancillary procedures	Ancillary procedures	Drug		
C2635	Brachytherapy source, non-stranded, high activity, palladium-103, greater than 2.2 mci (nist), per source	Ancillary procedures	Ancillary procedures	Drug		
C2636	Brachytherapy linear source, non-stranded, palladium-103, per 1 mm	Ancillary procedures	Ancillary procedures	Drug		
C2637	Brachytherapy source, non-stranded, ytterbium-169, per source	Ancillary procedures	Ancillary procedures	Drug		
C2638	Brachytherapy source, stranded, iodine-125, per source	Ancillary procedures	Ancillary procedures	Drug		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C2639	Brachytherapy source, non-stranded, iodine-125, per source	Ancillary procedures	Ancillary procedures	Drug		
C2640	Brachytherapy source, stranded, palladium-103, per source	Ancillary procedures	Ancillary procedures	Drug		
C2641	Brachytherapy source, non-stranded, palladium-103, per source	Ancillary procedures	Ancillary procedures	Drug		
C2642	Brachytherapy source, stranded, cesium-131, per source	Ancillary procedures	Ancillary procedures	Drug		
C2643	Brachytherapy source, non-stranded, cesium-131, per source	Ancillary procedures	Ancillary procedures	Drug		
C2644	Brachytherapy source, cesium-131 chloride solution, per millicurie		Ancillary procedures	Drug		
C2645	Brachytherapy planar source, palladium-103, per square millimeter	Ancillary procedures	Ancillary procedures	Drug		
C2698	Brachytherapy source, stranded, not otherwise specified, per source	Ancillary procedures	Ancillary procedures	Drug		
C2699	Brachytherapy source, non-stranded, not otherwise specified, per source	Ancillary procedures	Ancillary procedures	Drug		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area	Ancillary procedures	57 Burn, full thickness greater than 10% of body surface 72 Burn, partial thickness greater than 30% of body surface or with vital site; full thickness, less than 10% of body surface 181 Conditions involving exposure to natural elements (e.g., lightning strike, heatstroke) 197 Burn, partial thickness without vital site requiring grafting, up to 30% of body surface 379 Chronic ulcer of skin	CPT codes for skin substitutes on these lines		
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)	Ancillary procedures	57,72,181,197,379	CPT codes for skin substitutes on these lines	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children	Ancillary procedures	57,72,181,197,379	CPT codes for skin substitutes on these lines		
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)	Ancillary procedures	57,72,181,197,379	CPT codes for skin substitutes on these lines	No separate payment	
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area	Ancillary procedures	57,72,181,197,379	CPT codes for skin substitutes on these lines		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1713	Anchor/screw for opposing bone-to-bone or soft tissue-to-bone (implantable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1714	Catheter, transluminal atherectomy, directional	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1715	Brachytherapy needle	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1716	Brachytherapy source, non-stranded, gold-198, per source	Ancillary procedures	Ancillary procedures	DME		
C1717	Brachytherapy source, non-stranded, high dose rate iridium-192, per source	Ancillary procedures	Ancillary procedures	DME		
C1719	Brachytherapy source, non-stranded, non-high dose rate iridium-192, per source	Ancillary procedures	Ancillary procedures	DME		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1721	Cardioverter-defibrillator, dual chamber (implantable)	Ancillary procedures	69 Acute and subacute ischemic heart disease, myocardial infarction 98 Heart failure 99 Cardiomyopathy 111 Congenital heart block; other obstructive anomalies of heart 189 Chronic ischemic heart disease 281 Life-threatening cardiac arrhythmias 347 Cardiac arrhythmias	CPT codes for defibrillator insertion on these lines	No separate payment	
C1722	Cardioverter-defibrillator, single chamber (implantable)	Ancillary procedures	39,98,99,111,189,281,347	CPT codes for defibrillator insertion on these lines	No separate payment	
C1724	Catheter, transluminal atherectomy, rotational	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1725	Catheter, transluminal angioplasty, non-laser (may include guidance, infusion/perfusion capability)	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1726	Catheter, balloon dilatation, non-vascular	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1727	Catheter, balloon tissue dissector, non-vascular (insertable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1728	Catheter, brachytherapy seed administration	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1729	Catheter, drainage	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1730	Catheter, electrophysiology, diagnostic, other than 3d mapping (19 or fewer electrodes)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1731	Catheter, electrophysiology, diagnostic, other than 3d mapping (20 or more electrodes)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1732	Catheter, electrophysiology, diagnostic/ablation, 3d or vector mapping	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1733	Catheter, electrophysiology, diagnostic/ablation, other than 3d or vector mapping, other than cool-tip	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1749	Endoscope, retrograde imaging/illumination colonoscope device (implantable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1750	Catheter, hemodialysis/peritoneal, long-term	Ancillary procedures	59 End stage renal disease 339 CHRONIC KIDNEY DISEASE		No separate payment	
C1751	Catheter, infusion, inserted peripherally, centrally or midline (other than hemodialysis)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1752	Catheter, hemodialysis/peritoneal, short-term	Ancillary procedures	59 End stage renal disease 103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS 127 Acute kidney injury 148 ACQUIRED HEMOLYTIC ANEMIAS 222 Disorders of fluid, electrolyte, and acid-base balance 339 Chronic kidney disease	Contain CPT codes for hemodialysis	No separate payment	
C1753	Catheter, intravascular ultrasound	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1754	Catheter, intradiscal	Ancillary procedures	476 CLOSED DISLOCATIONS/FRACTURES OF NON-CERVICAL VERTEBRAL COLUMN WITHOUT NEUROLOGIC INJURY OR STRUCTURAL INSTABILITY	Contains CPT codes for percutaneous intradiscal electrothermal annuloplasty	No separate payment	
C1755	Catheter, intraspinal	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1756	Catheter, pacing, transesophageal	Ancillary procedures	Ancillary procedures	No change-CPR is Ancillary	No separate payment	
C1757	Catheter, thrombectomy/embolectomy	Ancillary procedures	Ancillary procedures	Procedures using this DME on multiple lines	No separate payment	
C1758	Catheter, ureteral	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1759	Catheter, intracardiac echocardiography	Ancillary procedures	Ancillary procedures	DME for a diagnostic procedure	No separate payment	
C1760	Closure device, vascular (implantable/insertable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1762	Connective tissue, human (includes fascia lata)	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1763	Connective tissue, non-human (includes synthetic)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1764	Event recorder, cardiac (implantable)	Diagnostic procedures	Diagnostic procedures	CPT 33282 (Implantation of patient-activated cardiac event recorder) is diagnostic	No separate payment	
C1765	Adhesion barrier	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1766	Introducer/sheath, guiding, intracardiac electrophysiological, steerable, other than peel-away	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1767	Generator, neurostimulator (implantable), non-rechargeable	Ancillary procedures	174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 250 Parkinson's disease 292 Neurological dysfunction in posture and movement caused by chronic conditions 346 Conditions of the back and spine with urgent surgical indications 361 Scoliosis 440 Trigeminal and other nerve disorders 527 Conditions of the back and spine without urgent surgical indications 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT	Contain insertion codes for various neurostimulators Alternative: Ancillary as DME Note: spine neurostimulators currently under review as a coverage guidance	No separate payment	
C1768	Graft, vascular	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1769	Guide wire	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1770	Imaging coil, magnetic resonance (insertable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1771	Repair device, urinary, incontinence, with sling graft	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1772	Infusion pump, programmable (implantable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1773	Retrieval device, insertable (used to retrieve fractured medical devices)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1776	Joint device (implantable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1777	Lead, cardioverter-defibrillator, endocardial single coil (implantable)	Ancillary procedures	39,98,99,111,189,281,347	CPT codes for defibrillator insertion on these lines	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1778	Lead, neurostimulator (implantable)	Ancillary procedures	174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS 250 Parkinson's disease 292 Neurological dysfunction in posture and movement caused by chronic conditions 346 Conditions of the back and spine with urgent surgical indications 361 Scoliosis 440 Trigeminal and other nerve disorders 527 Conditions of the back and spine without urgent surgical indications 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT	Contain insertion codes for various neurostimulators Alternative: Ancillary as DME Note: spine neurostimulators currently under review as a coverage guidance	No separate payment	
C1779	Lead, pacemaker, transvenous vdd single pass	Ancillary procedures	69, 111, 189, 281, 285, 347	contain pacemaker insertion codes	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1780	Lens, intraocular (new technology)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1781	Mesh (implantable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1782	Morcellator	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1783	Ocular implant, aqueous drainage assist device	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1784	Ocular device, intraoperative, detached retina	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1785	Pacemaker, dual chamber, rate-responsive (implantable)	Ancillary procedures	69,111,189,281,285,300	contains other pacemaker codes	No separate payment	
C1786	Pacemaker, single chamber, rate-responsive (implantable)	Ancillary procedures	69,111,189,281,285,300	contains other pacemaker codes	No separate payment	
C1787	Patient programmer, neurostimulator	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1788	Port, indwelling (implantable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1789	Prosthesis, breast (implantable)	Ancillary procedures	191 Cancer of breast; at high risk of breast cancer 312 Gender dysphoria/transexualism 634 Galactorrhea, mastodynia, atrophy, benign neoplasms and unspecified disorders of the breast		No separate payment	
C1813	Prosthesis, penile, inflatable	Ancillary procedures	521 SEXUAL DYSFUNCTION		No separate payment	
C1814	Retinal tamponade device, silicone oil	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1815	Prosthesis, urinary sphincter (implantable)	Ancillary procedures	71 Neurological dysfunction in breathing, eating, swallowing, bowel, or bladder control caused by chronic conditions; attention to ostomies 87 Congenital anomalies of genitourinary system 327 Functional and mechanical disorders of the genitourinary system including bladder outlet obstruction	Contain CPT 53445 (Insertion of inflatable urethral/bladder neck sphincter, including placement of pump, reservoir, and cuff)	No separate payment	
C1816	Receiver and/or transmitter, neurostimulator (implantable)	Ancillary procedures	174, 250, 292, 346, 361, 440, 527, 660	Contain insertion codes for various neurostimulators Alternative: Ancillary as DME Note: spine neurostimulators currently under review as a coverage guidance	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1817	Septal defect implant system, intracardiac	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1818	Integrated keratoprosthesis	Ancillary procedures	296 CATARACT	Pair with CPT 65770 (Keratoprosthesis)	No separate payment	
C1819	Surgical tissue localization and excision device (implantable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system	Ancillary procedures	174, 250, 292, 346, 361, 440, 527, 660	Contain insertion codes for various neurostimulators Alternative: Ancillary as DME Note: spine neurostimulators currently under review as a coverage guidance	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1821	Interspinous process distraction device (implantable)	Ancillary procedures	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	Pair with CPT 22870 (Insertion of interlaminar/interspinous process stabilization/distraction device) which is on line 660 Note: add to entry for CPT 22870 in GN173	No separate payment	
C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system	Ancillary procedures	174, 250, 292, 346, 361, 440, 527, 660	Contain insertion codes for various neurostimulators Alternative: Ancillary as DME Note: spine neurostimulators currently under review as a coverage guidance	No separate payment	
C1830	Powered bone marrow biopsy needle	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1840	Lens, intraocular (telescopic)	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1841	Retinal prosthesis, includes all internal and external components	Ancillary procedures	Ancillary procedures	DME		
C1874	Stent, coated/covered, with delivery system	Ancillary procedures	Ancillary procedures	DME. Stents can be used in many areas, including repair of aneurysms, treatment of peripheral vascular disease, hemodialysis, etc.	No separate payment	
C1875	Stent, coated/covered, without delivery system	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1876	Stent, non-coated/non-covered, with delivery system	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1877	Stent, non-coated/non-covered, without delivery system	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1878	Material for vocal cord medialization, synthetic (implantable)	Ancillary procedures	66 Laryngeal stenosis or paralysis with airway complications 516 Paralysis of vocal cords or larynx	CPT 31591 (Laryngoplasty, medialization, unilateral)	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1880	Vena cava filter	Ancillary procedures	1 Pregnancy 79 Phlebitis and thrombophlebitis, deep 214 Acute pulmonary heart disease and pulmonary emboli 280 Budd-Chiari syndrome, and other venous embolism and thrombosis	CPT 37191 Insertion of intravascular vena cava filter	No separate payment	
C1881	Dialysis access system (implantable)	Ancillary procedures	59 End stage renal disease 103 POISONING BY INGESTION, INJECTION, AND NON-MEDICINAL AGENTS 127 Acute kidney injury 148 ACQUIRED HEMOLYTIC ANEMIAS 222 Disorders of fluid, electrolyte, and acid-base balance 339 Chronic kidney disease	Contain CPT codes for hemodialysis	No separate payment	
C1882	Cardioverter-defibrillator, other than single or dual chamber (implantable)	Ancillary procedures	39,98,99,111,189,281,347	CPT codes for defibrillator insertion on these lines	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1883	Adapter/extension, pacing lead or neurostimulator lead (implantable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1884	Embolization protective system	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1885	Catheter, transluminal angioplasty, laser	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1886	Catheter, extravascular tissue ablation, any modality (insertable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1887	Catheter, guiding (may include infusion/perfusion capability)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1888	Catheter, ablation, non-cardiac, endovascular (implantable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1889	Implantable/insertable device for device intensive procedure, not otherwise classified	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1891	Infusion pump, non-programmable, permanent (implantable)	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1892	Introducer/sheath, guiding, intracardiac electrophysiological, fixed-curve, peel-away	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1893	Introducer/sheath, guiding, intracardiac electrophysiological, fixed-curve, other than peel-away	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1894	Introducer/sheath, other than guiding, other than intracardiac electrophysiological, non-laser	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C1895	Lead, cardioverter-defibrillator, endocardial dual coil (implantable)	Ancillary procedures	39,98,99,111,189,281,347	CPT codes for defibrillator insertion on these lines	No separate payment	
C1896	Lead, cardioverter-defibrillator, other than endocardial single or dual coil (implantable)	Ancillary procedures	39,98,99,111,189,281,347	CPT codes for defibrillator insertion on these lines	No separate payment	
C1897	Lead, neurostimulator test kit (implantable)	Ancillary procedures	174, 250, 292, 346, 361, 440, 527, 660	Contain insertion codes for various neurostimulators Alternative: Ancillary as DME Note: spine neurostimulators currently under review as a coverage guidance	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C1898	Lead, pacemaker, other than transvenous vdd single pass	Ancillary procedures	69,111,189,281,285,300	contains other pacemaker codes	No separate payment	
C1899	Lead, pacemaker/cardioverter-defibrillator combination (implantable)	Ancillary procedures	39,98,99,111,189,281,347	CPT codes for defibrillator insertion on these lines	No separate payment	
C1900	Lead, left ventricular coronary venous system	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C2613	Lung biopsy plug with delivery system	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C2614	Probe, percutaneous lumbar discectomy	Ancillary procedures	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	CPT 62287 (Decompression procedure, percutaneous, of nucleus pulposus of intervertebral disc, any method utilizing needle based technique to remove disc material under fluoroscopic imaging or other form of indirect visualization, with discography and/or epidural injection(s) at the treated level(s), when performed, single or multiple levels, lumbar) is on line 660 Add C2614 to GN173 entry with CPT 62287	No separate payment	
C2615	Sealant, pulmonary, liquid	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C2616	Brachytherapy source, non-stranded, yttrium-90, per source	Ancillary procedures	500	Previous reviewed and placed on line 500		
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)	Ancillary procedures	57 Burn, full thickness greater than 10% of body surface 72 Burn, partial thickness greater than 30% of body surface or with vital site; full thickness, less than 10% of body surface 181 Conditions involving exposure to natural elements (e.g., lightning strike, heatstroke) 197 Burn, partial thickness without vital site requiring grafting, up to 30% of body surface 379 Chronic ulcer of skin	CPT 15277 and 15278 (Application of skin substitute graft) are on lines 57,72,181,197,379	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children	Ancillary procedures	57,72,181,197,379	CPT 15277 and 15278 (Application of skin substitute graft) are on lines 57,72,181,197,379		
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)	Ancillary procedures	57,72,181,197,379	CPT 15277 and 15278 (Application of skin substitute graft) are on lines 57,72,181,197,379	No separate payment	
C8900	Magnetic resonance angiography with contrast, abdomen	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C8901	Magnetic resonance angiography without contrast, abdomen	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8902	Magnetic resonance angiography without contrast followed by with contrast, abdomen	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8903	Magnetic resonance imaging with contrast, breast; unilateral	Ancillary procedures	Diagnostic Procedures File	Use govered by DIAGNOSTIC GUIDELINE D6, BREAST CANCER SCREENING IN ABOVE-AVERAGE RISK WOMEN		
C8904	Magnetic resonance imaging without contrast, breast; unilateral	Ancillary procedures	Diagnostic Procedures File	See above		
C8905	Magnetic resonance imaging without contrast followed by with contrast, breast; unilateral	Ancillary procedures	Diagnostic Procedures File	See above		
C8906	Magnetic resonance imaging with contrast, breast; bilateral	Ancillary procedures	Diagnostic Procedures File	See above		
C8907	Magnetic resonance imaging without contrast, breast; bilateral	Ancillary procedures	Diagnostic Procedures File	See above		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C8908	Magnetic resonance imaging without contrast followed by with contrast, breast; bilateral	Ancillary procedures	Diagnostic Procedures File	See above		
C8909	Magnetic resonance angiography with contrast, chest (excluding myocardium)	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8910	Magnetic resonance angiography without contrast, chest (excluding myocardium)	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8911	Magnetic resonance angiography without contrast followed by with contrast, chest (excluding myocardium)	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8912	Magnetic resonance angiography with contrast, lower extremity	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8913	Magnetic resonance angiography without contrast, lower extremity	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8914	Magnetic resonance angiography without contrast followed by with contrast, lower extremity	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8918	Magnetic resonance angiography with contrast, pelvis	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C8919	Magnetic resonance angiography without contrast, pelvis	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8920	Magnetic resonance angiography without contrast followed by with contrast, pelvis	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8921	Transthoracic echocardiography with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; complete	Ancillary procedures	Diagnostic Procedures File	CPT 93306 and similar ECHO codes are Diagnostic Procedures File		
C8922	Transthoracic echocardiography with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; follow-up or limited study	Ancillary procedures	Diagnostic Procedures File			
C8923	Transthoracic echocardiography with contrast, or without contrast followed by with contrast, real-time with image documentation (2d), includes m-mode recording, when performed, complete, without spectral or color doppler echocardiography	Ancillary procedures	Diagnostic Procedures File			

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C8924	Transthoracic echocardiography with contrast, or without contrast followed by with contrast, real-time with image documentation (2d), includes m-mode recording, when performed, follow-up or limited study	Ancillary procedures	Diagnostic Procedures File			
C8925	Transesophageal echocardiography (tee) with contrast, or without contrast followed by with contrast, real time with image documentation (2d) (with or without m-mode recording); including probe placement, image acquisition, interpretation and report	Ancillary procedures	Diagnostic Procedures File			
C8926	Transesophageal echocardiography (tee) with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; including probe placement, image acquisition, interpretation and report	Ancillary procedures	Diagnostic Procedures File			

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C8927	Transesophageal echocardiography (tee) with contrast, or without contrast followed by with contrast, for monitoring purposes, including probe placement, real time 2-dimensional image acquisition and interpretation leading to ongoing (continuous) assessment of (dynamically changing) cardiac pumping function and to therapeutic measures on an immediate time basis	Ancillary procedures	Diagnostic Procedures File			
C8928	Transthoracic echocardiography with contrast, or without contrast followed by with contrast, real-time with image documentation (2d), includes m-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report	Ancillary procedures	Diagnostic Procedures File	Other stress ECHOs (eg. 93350) are Diagnostic Procedures File		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C8929	Transthoracic echocardiography with contrast, or without contrast followed by with contrast, real-time with image documentation (2d), includes m-mode recording, when performed, complete, with spectral doppler echocardiography, and with color flow doppler echocardiography	Ancillary procedures	Diagnostic Procedures File			
C8930	Transthoracic echocardiography, with contrast, or without contrast followed by with contrast, real-time with image documentation (2d), includes m-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report; including performance of continuous electrocardiographic monitoring, with physician supervision	Ancillary procedures	Diagnostic Procedures File			

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C8931	Magnetic resonance angiography with contrast, spinal canal and contents	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8932	Magnetic resonance angiography without contrast, spinal canal and contents	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8933	Magnetic resonance angiography without contrast followed by with contrast, spinal canal and contents	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8934	Magnetic resonance angiography with contrast, upper extremity	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8935	Magnetic resonance angiography without contrast, upper extremity	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8936	Magnetic resonance angiography without contrast followed by with contrast, upper extremity	Ancillary procedures	Diagnostic Procedures File	Other MRAs with CPT codes are DPF		
C8957	Intravenous infusion for therapy/diagnosis; initiation of prolonged infusion (more than 8 hours), requiring use of portable or implantable pump	Ancillary procedures	Ancillary procedures	DME		
C9014	Injection, cerliponase alfa, 1 mg	New (added) Codes	Ancillary procedures	Drug		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9015	Injection, c-1 esterase inhibitor (human), haegarda, 10 units	New (added) Codes	Ancillary procedures	Drug		
C9016	Injection, triptorelin extended release, 3.75 mg	New (added) Codes	Ancillary procedures	Drug		
C9024	Injection, liposomal, 1 mg daunorubicin and 2.27 mg cytarabine	New (added) Codes	Ancillary procedures	Drug		
C9028	Injection, inotuzumab ozogamicin, 0.1 mg	New (added) Codes	Ancillary procedures	Drug		
C9029	Injection, guselkumab, 1 mg	New (added) Codes	Ancillary procedures	Drug		
C9113	Injection, pantoprazole sodium, per vial	Ancillary procedures	Ancillary procedures	Drug	No separate payment	
C9132	Prothrombin complex concentrate (human), kcentra, per i.u. of factor ix activity	Ancillary procedures	Ancillary procedures	Drug		
C9248	Injection, clevidipine butyrate, 1 mg	Ancillary procedures	Ancillary procedures	Drug	No separate payment	
C9250	Human plasma fibrin sealant, vapor-heated, solvent-detergent (artiss), 2 ml	Ancillary procedures	Ancillary procedures	Drug		
C9254	Injection, lacosamide, 1 mg	Ancillary procedures	Ancillary procedures	Drug	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9257	Injection, bevacizumab, 0.25 mg	Ancillary procedures	Ancillary procedures	Drug		
C9275	Injection, hexaminolevulinate hydrochloride, 100 mg, per study dose	Ancillary procedures	Ancillary procedures	Drug	No separate payment	
C9285	Lidocaine 70 mg/tetracaine 70 mg, per patch	Ancillary procedures	Ancillary procedures	Drug	No separate payment	
C9290	Injection, bupivacaine liposome, 1 mg	Ancillary procedures	Ancillary procedures	Drug	No separate payment	
C9293	Injection, glucarpidase, 10 units	Ancillary procedures	Ancillary procedures	Drug		
C9352	Microporous collagen implantable tube (neuragen nerve guide), per centimeter length	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C9353	Microporous collagen implantable slit tube (neurawrap nerve protector), per centimeter length	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C9354	Acellular pericardial tissue matrix of non-human origin (veritas), per square centimeter	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C9355	Collagen nerve cuff (neuromatrix), per 0.5 centimeter length	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9356	Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (tenoglide tendon protector sheet), per square centimeter	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C9358	Dermal substitute, native, non-denatured collagen, fetal bovine origin (surgimend collagen matrix), per 0.5 square centimeters	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C9359	Porous purified collagen matrix bone void filler (integra mozaik osteoconductive scaffold putty, integra os osteoconductive scaffold putty), per 0.5 cc	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C9360	Dermal substitute, native, non-denatured collagen, neonatal bovine origin (surgimend collagen matrix), per 0.5 square centimeters	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C9361	Collagen matrix nerve wrap (neuromend collagen nerve wrap), per 0.5 centimeter length	Ancillary procedures	Ancillary procedures	DME	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9362	Porous purified collagen matrix bone void filler (integra mozaik osteoconductive scaffold strip), per 0.5 cc	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C9363	Skin substitute, integra meshed bilayer wound matrix, per square centimeter	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C9364	Porcine implant, permacol, per square centimeter	Ancillary procedures	Ancillary procedures	DME	No separate payment	
C9399	Unclassified drugs or biologicals	Ancillary procedures	Ancillary procedures	Drug		
C9447	Injection, phenylephrine and ketorolac, 4 ml vial		Ancillary procedures	Drug	No separate payment	
C9460	Injection, cangrelor, 1 mg	Ancillary procedures	Ancillary procedures	Drug		
C9482	Injection, sotalol hydrochloride, 1 mg	Ancillary procedures	Ancillary procedures	Drug		
C9488	Injection, conivaptan hydrochloride, 1 mg	New (added) Codes	Ancillary procedures	Drug		
C9492	Injection, durvalumab, 10 mg	New (added) Codes	Ancillary procedures	Drug		
C9493	Injection, edaravone, 1 mg	New (added) Codes	Ancillary procedures	Drug		
C9497	Loxapine, inhalation powder, 10 mg	Ancillary procedures	Ancillary procedures	Drug		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9600	Percutaneous transcatheter placement of drug eluting intracoronary stent(s), with coronary angioplasty when performed; single major coronary artery or branch	Ancillary procedures	45 Coronary artery anomaly 69 Acute and subacute ischemic heart disease, myocardial infarction 98 Heart failure 189 Chronic ischemic heart disease 285 Complications of a procedure always requiring treatment	Similar CPT codes (eg 92928 Percutaneous transcatheter placement of intracoronary stent(s)) are on 45,69,98,189,285 Reviewed in 2012 as part of new 2013 HCPCS codes an placement was for the equivalents of lines 45, 69, 98, 189. Line 285 would match non-drug eluding stents. The meeting notes recommend that HTAS review this technology		Not allowed in ASC

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9601	Percutaneous transcatheter placement of drug-eluting intracoronary stent(s), with coronary angioplasty when performed; each additional branch of a major coronary artery (list separately in addition to code for primary procedure)	Ancillary procedures	45,69,98,189,285	See above		Not allowed in ASC
C9602	Percutaneous transluminal coronary atherectomy, with drug eluting intracoronary stent, with coronary angioplasty when performed; single major coronary artery or branch	Ancillary procedures	45,69,98,189,285	See above		Not allowed in ASC
C9603	Percutaneous transluminal coronary atherectomy, with drug-eluting intracoronary stent, with coronary angioplasty when performed; each additional branch of a major coronary artery (list separately in addition to code for primary procedure)	Ancillary procedures	45,69,98,189,285	See above		Not allowed in ASC

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9604	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of drug-eluting intracoronary stent, atherectomy and angioplasty, including distal protection when performed; single vessel	Ancillary procedures	45,69,98,189,285	See above		Not allowed in ASC
C9605	Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of drug-eluting intracoronary stent, atherectomy and angioplasty, including distal protection when performed; each additional branch subtended by the bypass graft (list separately in addition to code for primary procedure)	Ancillary procedures	45,69,98,189,285	See above		Not allowed in ASC

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9606	Percutaneous transluminal revascularization of acute total/subtotal occlusion during acute myocardial infarction, coronary artery or coronary artery bypass graft, any combination of drug-eluting intracoronary stent, atherectomy and angioplasty, including aspiration thrombectomy when performed, single vessel	Ancillary procedures	45,69,98,189,285	See above		Not allowed in ASC
C9607	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of drug-eluting intracoronary stent, atherectomy and angioplasty; single vessel	Ancillary procedures	45,69,98,189,285	See above		Not allowed in ASC

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9608	Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of drug-eluting intracoronary stent, atherectomy and angioplasty; each additional coronary artery, coronary artery branch, or bypass graft (list separately in addition to code for primary procedure)	Ancillary procedures	45,69,98,189,285	See above		Not allowed in ASC
C9725	Placement of endorectal intracavitary applicator for high intensity brachytherapy	Ancillary procedures	All radiation therapy lines	Brachytherapy CPT codes on all radiation therapy lines		
C9726	Placement and removal (if performed) of applicator into breast for intraoperative radiation therapy, add-on to primary breast procedure	Ancillary procedures	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	CPT 19294 (Intraoperative radiation therapy (IORT) concurrent with partial mastectomy) is on line 600 Need to add to GN173 entry	No separate payment	

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9727	Insertion of implants into the soft palate; minimum of three implants	Ancillary procedures	64 Congenital anomalies of upper alimentary tract, excluding tongue 287 Cancer of oral cavity, pharynx, nose and larynx 300 Cleft palate and/or cleft lip 321 Dermatologic hemangiomas, complicated 625 Benign neoplasms of skin and other soft tissues	Palate procedure codes are on these lines		
C9728	Placement of interstitial device(s) for radiation therapy/surgery guidance (e.g., fiducial markers, dosimeter), for other than the following sites (any approach): abdomen, pelvis, prostate, retroperitoneum, thorax, single or multiple	Ancillary procedures	Ancillary procedures			

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9733	Non-ophthalmic fluorescent vascular angiography	Excluded File (travel vaccines etc.)	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	Reviewed in 2012 as part of the 2013 HCPCS codes. Recommendation was Excluded file. See GN173 entry		
C9734	Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (mr) guidance	Ancillary procedures		Reviewed as part of coverage guidance on alterntives to TURP in March, 2015 and recommended to add to the Ancillary Procedures File.		
C9738	Adjunctive blue light cystoscopy with fluorescent imaging agent (list separately in addition to code for primary procedure)	New (added) Codes	Diagnostic Procedures File	See separate review document	No separate payment	
C9739	Cystourethroscopy, with insertion of transprostatic implant; 1 to 3 implants	Excluded File (travel vaccines etc.)	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	Reviewed as part of coverage guidance on alterntives to TURP in March, 2015 and recommended to add to the Excluded List. Add to GN173 entry		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9740	Cystourethroscopy, with insertion of transprostatic implant; 4 or more implants	Excluded File (travel vaccines etc.)	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	See above		
C9741	Right heart catheterization with implantation of wireless pressure sensor in the pulmonary artery, including any type of measurement, angiography, imaging supervision, interpretation, and report	Diagnostic procedures		Reviewed as new code in November, 2014		
C9744	Ultrasound, abdominal, with contrast	Ancillary procedures	Diagnostic Procedure File			
C9745	Nasal endoscopy, surgical; balloon dilation of eustachian tube	New (added) Codes	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	See separate review document		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9746	Transperineal implantation of permanent adjustable balloon continence device, with cystourethroscopy, when performed and/or fluoroscopy, when performed	New (added) Codes	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	See separate review document		
C9747	Ablation of prostate, transrectal, high intensity focused ultrasound (hifu), including imaging guidance	New (added) Codes	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	Reviewed as part of coverage guidance on alterntives to TURP in March, 2015 and recommended to not cover. No code available for placement at that time. Noted to be non-covered in GN145 Add to GN173 entry		

HCPCS code	Code description	Current Placement	Recommended Placement	Notes	OPPS Indicator*	ASC Indicator**
C9748	Transurethral destruction of prostate tissue; by radiofrequency water vapor (steam) thermal therapy	New (added) Codes	327 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION	To match CPT 53852 (Transurethral destruction of prostate tissue; by radiofrequency thermotherapy), which was reviewed as part of the alternatives to TURP in March, 2015		
C9898	Radiolabeled product provided during a hospital inpatient stay	Ancillary procedures	Ancillary procedures	Drug		
C9899	Implanted prosthetic device, payable only for inpatients who do not have inpatient coverage	Ancillary procedures	Ancillary procedures	DME		

2018 HCPCS "C" Code Review
Blue Light Cystoscopy

Question: where should blue light cystoscopy with fluorescent imaging agent be placed on the Prioritized List/other lists?

Question source: 2018 HCPCS "C" code review

Issue: Traditionally, white light (or standard) cystoscopy, typically performed by urologists, has been the gold standard for diagnosing bladder cancer. Enhanced bladder cancer diagnostics, such as narrow band imaging or blue light cystoscopy, increase tumor detection in nonmuscle invasive bladder cancer over white light cystoscopy alone, thus enabling more precise tumor removal by the urologist. Flat lesions such as CIS or low-graded tumors are often missed under standard white light cystoscopy. A new technique termed "blue light" cystoscopy has been introduced to improve the visibility of tumors by using a photosensitizing agent and fluorescent light in the photodynamic diagnosis of NMIBC. In fluorescent cystoscopy, the photosensitizing agent such as 5-aminolevulenic acid (5-ALA) or hexaminolevulinate (HAL), a derivative of 5-ALA, are first instilled into the bladder. The drug then incorporates into the urothelial cytoplasm where abnormal cells appear red and normal cells appear blue green upon illumination with fluorescent light. Thus, "blue light" or fluorescent cystoscopy may help the detection of tumors more accurately and may reduce the risk of recurrence and progression compared to white light cystoscopy.

CMS adopted a new HCPCS code for blue light cystoscopy for 2018.

Similar codes:
CPT 52204 (Cystourethroscopy, with biopsy(s)) is on the Diagnostic Procedures File

Evidence:
CADTH 2017, rapid review of blue light cystoscopy:
https://www.cadth.ca/sites/default/files/pdf/htis/2017/RC0848_Blue%20Light%20Cystoscopy_Final.pdf

1) N=2 studies
    a. One systematic review of high quality
    b. One systematic review of moderate quality
2) Meta-analysis:
    a. For the detection and resection of non-muscle invasive bladder cancer (NMIBC) with transurethral resection of the bladder tumor (TURBT), fluorescent cystoscopy was associated with a statistically significantly reduced risk of bladder cancer recurrence compared with white light cystoscopy at short-term (evidence from 10 RCTs) and long-term follow-up (evidence from 12 RCTs). The strength of evidence was low due to risk of performance or publication bias.
    b. A pooled analysis of all trials using 5-ALA or HAL showed no difference between fluorescent cystoscopy compared with white light cystoscopy in the risk of progression to muscle invasive bladder cancer. Subgroup analysis showed that the risk of progression was statistically significantly lower in trials using HAL, but not in trials using 5-ALA. The strength of the evidence was moderate. The other SR also found that HAL-guided TURBT was associated with statistically significant reduction in the risk of progression compared to white light guided TURBT.

   c. There was no difference in mortality between fluorescent cystoscopy and white light cystoscopy in trials using 5-ALA or HAL. The strength of the evidence was low due to imprecision and sparse data.
   d. Data on harms were sparse.

3) Conclusions and Implications for Decision or Policy Making
   a. Low to moderate quality evidence from recent SRs has suggested that TURBT guided by fluorescent or "blue light" cystoscopy using HAL as photosensitizing agent in the detection and resection of NMIBC was associated with a decreased risk of bladder cancer recurrence and a decreased risk of progression to muscle invasive bladder cancer compared to white light cystoscopy. The effects of fluorescent cystoscopy on mortality were inconclusive due to sparse data.

HERC staff summary

Blue light cystoscopy has low to moderate evidence of increasing detection and reducing progression and recurrence of non-muscle invasive bladder cancer compared to traditional white light cystoscopy.

HERC staff recommendation:

1) Add HCPCS C9738 (Adjunctive blue light cystoscopy with fluorescent imaging agent) to the Diagnostic Procedures File

2018 HCPCS "C" Code Review
Transnasal Balloon Dilation of the Eustachian Tube

Question: Should transnasal balloon dilation of the Eustachian tube be paired with various ear diagnoses on the Prioritized List?

Question source: Primary Health CCO

Issue: A new HCPCS code for transnasal balloon dilation of the Eustachian tube (C9745) was introduced with the 2018 new codes, but not reviewed as part of the HERC code review in fall 2017. In the past, HERC staff was under the impression that "C" codes did not require review; however, it has come to our attention that these codes do require review. Primary Health CCO received a request for pairing this procedure with Eustachain tube dysfunction (ICD-10 H69.81), conductive hearing loss (ICD-10 H90.11), and tinnitus (ICD-10 H93.11) and requested HERC review of the procedure.

Eustachian tubes are small tubes that run between the middle ear and the pharynx. They are responsible for equalizing ear pressure and draining fluid from the middle ear. Blocked eustachian tubes can cause pain, hearing difficulties, and a feeling of fullness in the ears. Such a phenomenon is referred to as eustachian tube dysfunction (ETD). Conventional medical treatment includes nasal steroids, decongestants, or antihistamines. Balloon dilation involves the inflation of a balloon in the cartilaginous part of the Eustachian tube to cause local dilation and was first described in 2010.

Current Prioritized List status

1) ICD-10 H69.8 (Eustachain tube dysfunction) is on line 652 SENSORY ORGAN CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY

Evidence

1) **Huisman 2018**, systematic review of eustachian tube dilation: https://onlinelibrary.wiley.com/doi/pdf/10.1002/lary.26800
    a. N=15 studies, all case series
        i. Total patients: 1,155
    b. All articles showed short-term improvement of original symptoms; some showed further improvement over time. Follow-up ranged from just after therapy to 50 months. Relatively mild and self-limiting complications were described in 36 patients.
    c. Conclusion: All current studies suggest that balloon dilation of the Eustachian tube can be a helpful treatment in patients with Eustachian tube dysfunction. However, placebo controlled trials are still warranted.
2) **Hwang 2016**, systematic review of eustachian tube dilation
    a. N=9 studies (474 patients)
    b. Ability to perform a Valsalva manoeuvre improved from 20 to 177 out of 245 ears following eustachian tube balloon dilation and, where data were reported in terms of patient numbers, from 15 to 189 out of 210 patients. Tympanograms were classified as type A in 7 out of 141 ears pre-operatively and in 86 out of 141 ears post-operatively.
    c. Conclusion: Prospective case series can confirm the safety of eustachian tube balloon dilation. As a potential solution for chronic eustachian tube dysfunction, further investigations are warranted to establish a higher level of evidence of efficacy.

2018 HCPCS "C" Code Review
Transnasal Balloon Dilation of the Eustachian Tube

HERC staff summary:
Eustachian tube dilation appears to be a promising but unproved treatment for Eustachian tube dysfunction.

HERC staff recommendation:
1) Add Eustachian tube dilation (HCPCS C9745) to GN173/line 660

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

The following Interventions are prioritized on Line 660 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
C9745	Nasal endoscopy, surgical; balloon dilation of eustachian tube	Insufficient evidence of effectiveness	May, 2018

The Journal of Laryngology & Otology (2016), ***130*** (Suppl. S4), *S2–S6*.

doi:10.1017/S0022215116008252

REVIEW ARTICLE

Balloon dilation for eustachian tube dysfunction: systematic review

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Abstract

Background: Eustachian tube dysfunction is a disorder for which there are limited medical and surgical treatments. Recently, eustachian tube balloon dilation has been proposed as a potential solution.

Method: A systematic literature review was performed. Abstracts were selected for relevance, and pooled data analysis and qualitative analysis was conducted.

Results: Nine prospective studies, describing 713 eustachian tube balloon dilations in 474 patients (aged 18–86 years), were identified. Follow-up duration ranged from 1.5 to 18 months. Ability to perform a Valsalva manoeuvre improved from 20 to 177 out of 245 ears following eustachian tube balloon dilation and, where data were reported in terms of patient numbers, from 15 to 189 out of 210 patients. Tympanograms were classified as type A in 7 out of 141 ears pre-operatively and in 86 out of 141 ears post-operatively.

Conclusion: Prospective case series can confirm the safety of eustachian tube balloon dilation. As a potential solution for chronic eustachian tube dysfunction, further investigations are warranted to establish a higher level of evidence of efficacy.

Key words: Auditory Tube; Balloon; Dilation; Eustachian Tube

Introduction

Eustachian tube dysfunction is a physiological disorder of the eustachian tube that results in inadequate middle-ear ventilation, causing aural fullness and tinnitus. In addition, complications such as serous otitis media, tympanic membrane retraction and cholesteatoma can occur.[1] Eustachian tube dysfunction affects around 1 per cent of adults.[2,3]

Current treatment modalities for eustachian tube dysfunction, which include pharmacological agents, mechanical devices and nasal surgery, can be ineffective.[1,2] Treatment may entail multiple insertions of ventilation tubes in patients with chronic eustachian tube dysfunction, leading to complications such as tympanosclerosis, chronic perforation and cholesteatoma.[4]

Recently, eustachian tube balloon dilation has been researched in prospective cohort studies and is currently used 'off-label' as a potential treatment for chronic eustachian tube dysfunction.[5,6] It aims to improve eustachian tube compliance and middle-ear ventilation. Its proposed mechanisms include mechanical dilation of the cartilaginous eustachian tube and initiation of histopathological changes to the mucosa that can alter the inflammatory process.[7]

However, eustachian tube balloon dilation is a new procedure, and the operative technique needs to be verified for its efficacy and complications. This paper systematically reviews the available evidence on eustachian tube balloon dilation for treating chronic eustachian tube dysfunction.

Materials and methods

Criteria for study eligibility

Studies were eligible for inclusion in data analysis if they were prospective (cohort or randomised), aimed to assess the effectiveness of eustachian tube balloon dilation in adults, and included outcomes of ability to perform Valsalva or Toynbee's manoeuvre and/or tympanometry results. Retrospective studies, studies that did not include one of the two aforementioned outcomes, cadaveric studies and technical studies were excluded from data analysis but included in the discussion. Published conference abstracts and case reports were excluded from this review.

Literature search and study selection

Two authors (SH and JW) independently searched Medline, PubMed and Embase databases for relevant

Accepted for publication 19 April 2016

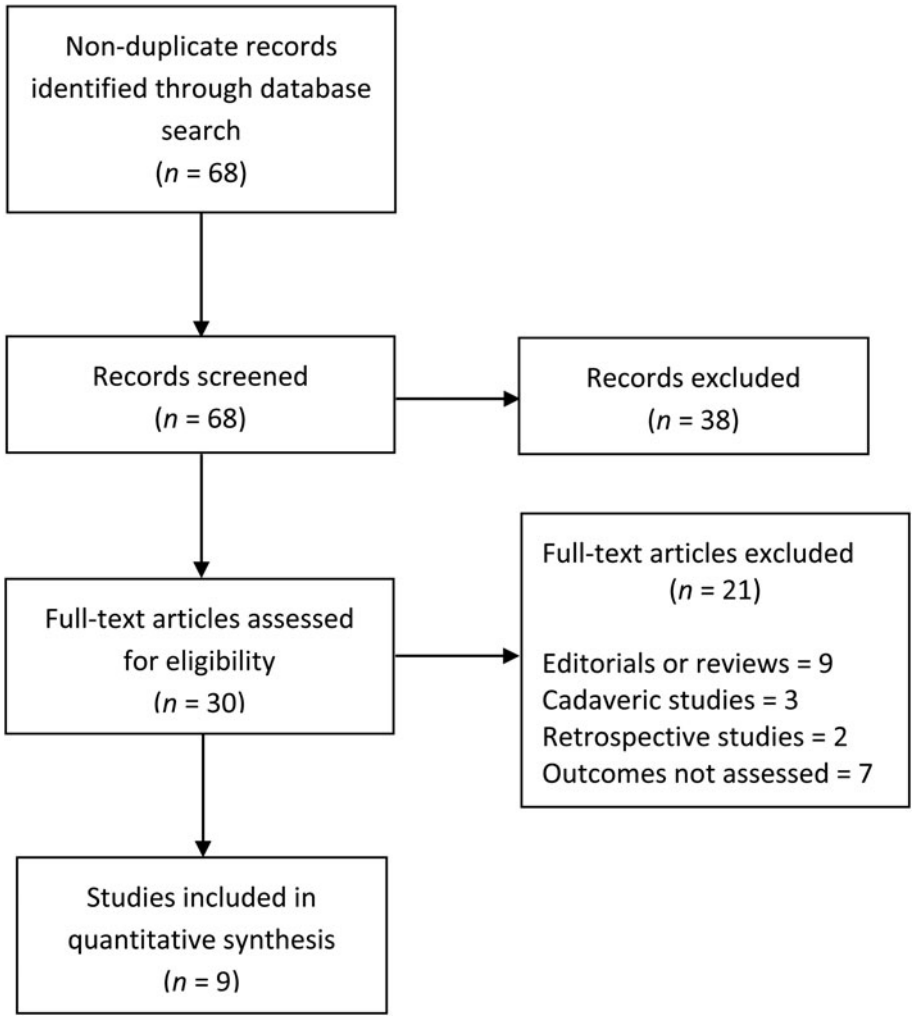

FIG. 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') flow diagram of search method.

papers published from 1950 to October 2015. No restrictions were made on language. The keywords 'eustachian tube', 'auditory tube', 'dilation', 'dilatation' and 'balloon' were used. This search was supplemented by using the 'related article' function. The search was repeated on Google Scholar to locate additional abstracts. A manual search of references of eligible manuscripts was also performed.

Studies that were eligible for inclusion in the systematic review were assessed independently and any disagreements were resolved by discussion between the two aforementioned authors. Figure 1 demonstrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') flow diagram.

Data extraction and statistical analysis

Data extraction was performed independently by two authors (SH and JW). Pooled data analysis was performed.

Results

Nine prospective studies,[4,6,8–14] describing 713 eustachian tube balloon dilations in 474 patients (aged 18–86 years), were identified. Follow-up duration ranged from 1.5 to 18 months. The included studies are summarised in Tables I and II.

Indications

The indication for eustachian tube balloon dilation in all studies was chronic eustachian tube dysfunction. The method of diagnosis varied between the studies, but all included clinical history and otoscopy, with six studies using tympanometry and two studies using tubomanometry.

Techniques

Two main balloon dilation techniques were described in the literature, with five studies[6,8,11,13,14] reporting the use of the Bielefeld technique (developed in Germany) and four studies[4,9,10,12] using the Acclarent balloon technique (developed in North America). Both techniques were performed under general anaesthetic, with pre-operative topical decongestant applied to nasal mucosa and the eustachian tube orifice.

In the Bielefeld technique, a Storz micro-endoscope is used to visualise the insertion of a purpose-built

TABLE I
PAPERS EVALUATING EUSTACHIAN TUBE BALLOON DILATION

Authors	Year	Pt age (mean (range); years)	Number of cases	Technique	Mean follow-up time (months)
Ockermann *et al.*[6]	2010	44.1 (21–81)	13 ETBDs in 8 pts	Bielefeld catheter	2
Poe *et al.*[10]	2011	51.8 (33–76)	11 ETBDs in 11 pts	Acclarent catheter	7 (median)
Catalano *et al.*[4]	2012	45 (18–73)	100 ETBDs in 70 pts	Acclarent catheter	7
McCoul & Anand[9]	2012	55.1 (NR)	35 ETBDs in 22 pts	Acclarent catheter	10 (median)
Jurkiewicz *et al.*[8]	2013	45.8 (23–61)	7 ETBDs in 4 pts	Bielefeld catheter	1.5
Schroder *et al.*[11]	2013	54 (18–86)	135 ETBDs in 78 pts	Bielefeld catheter	12
Tisch *et al.*[13]	2013	46 (18–74)	320 ETBDs in 210 pts	Bielefeld catheter	3
Wanscher & Svane-Knudsen[14]	2014	45 (20–74)	50 ETBDs in 34 pts	Bielefeld catheter	2
Silvola *et al.*[12]	2014	48 (15–38)	41 ETBDs in 37 pts	Acclarent catheter	18

Pt = patient; ETBD = eustachian tube balloon dilation; NR = not reported

TABLE II
RESULTS OF EUSTACHIAN TUBE BALLOON DILATION

Authors	Ability to perform Valsalva (*n*)		Type A tympanometry (*n*)	
	Pre-op	Post-op	Pre-op	Post-op
Ockermann *et al.*[6]	0/13	12/13	N/A	N/A
Poe *et al.*[10]	0/11	11/11	0/11	4/11
Catalano *et al.*[4]	N/A	N/A	0/28	25/28
McCoul & Anand[9]	N/A	N/A	0/35	34/35
Jurkiewicz *et al.*[8]	1/7	6/7	0/7	6/7
Schroder *et al.*[11]	16/135	86/135	N/A	N/A
Tisch *et al.*[13]	15/210*	189/210*	N/A	N/A
Wanscher & Svane-Knudsen[14]	3/38	29/38	0/44	12/44
Silvola *et al.*[12]	0/41	33/41	1/17	23/29

*Results reported as numbers of patients not individual eustachian tubes. Pre-op = pre-operative; post-op = post-operative; N/A = not applicable

Bielefeld balloon catheter into the eustachian tube. The balloon is inflated to a pressure of 10 bars for 2 minutes, with the aim of inflating the balloon to a size of 3×20 mm.

In the Acclarent balloon technique, a 30- or a 45-degree, 4 mm Hopkins rod is used to visualise the insertion of an angled 70-degree catheter into the eustachian tube. Balloon sizes, pressures and duration of inflation vary between the papers that use this technique. These include a 5×16 mm balloon inflated to 8 atm for 30 seconds,[4] a 5×24 mm or 7×24 mm balloon (adjusted for individual patients) inflated to 10 atm for 2 minutes,[9] or a 7×16 mm balloon inflated to 12 atm for 1 minute.[10,12]

Valsalva

The ability to perform a Valsalva or Toynbee's manoeuvre pre- and post-eustachian tube balloon dilation was reported in seven studies. This improved from 20 (8 per cent) to 177 (72 per cent) out of 245 ears following eustachian tube balloon dilation,[6,8,10–12,14] and, where data were reported in terms of patient numbers, from 15 (7 per cent) to 189 (90 per cent) out of 210 patients.[13]

Tympanometry

Tympanometry results were reported in six studies.[8–12,14] Tympanograms were classified as type A in 7 out of 141 ears (5 per cent) pre-operatively, and this improved to 86 out of 141 ears (61 per cent) post-operatively. Twelve of these classifications (9 per cent) were because of grommets being removed and/or tympanic membrane perforations healing.

Tubomanometry

Tubomanometry was performed pre-operatively in two studies,[6,11] but no post-operative data were provided. Tubomanometry was mainly used as an adjunct to aid in the diagnosis of eustachian tube dysfunction.

Quality of life

One study[9] used the 7-item Eustachian Tube Dysfunction Questionnaire and the 22-item Sino-Nasal Outcome Test (SNOT-22) to evaluate improvement in symptoms and quality of life pre- and post-eustachian tube balloon dilation.

There were statistically significant improvements in both measures: the 7-item Eustachian Tube Dysfunction Questionnaire pre-operative mean score of 4.5 decreased to 2.8 at 6 months ($p < 0.001$), and the SNOT-22 pre-operative mean score decreased from 51.4 to 30 at 6 months ($p = 0.001$).

Complications

All studies documented complications. Four studies[6,8,9,12] reported no eustachian tube balloon dilation related complications and one study[11] reported only minor epistaxis. More serious complications included two cases of self-resolving subcutaneous emphysema in two separate studies.[4,13]

Complications associated with a learning curve were described by Wanscher and Svane-Knudsen,[14] who reported 3 cases of acute otitis media in the first 20 eustachian tube balloon dilations, which decreased to 1 out of 30 after 5 days of post-operative prophylactic oral antibiotics.

Poe *et al.*[10] reported 5 cases of minor mucosal lacerations in 11 eustachian tube balloon dilations

and 1 case of C6–C7 contralateral radiculopathy, the latter of which was thought to be caused by operative positioning.

There were no reported cases of carotid artery injury or patulous eustachian tube in any of the papers reviewed.

Discussion

The eustachian tube in adults is approximately 37.5 mm long, and consists of bony and cartilaginous portions, extending from the middle-ear cleft to the nasopharynx.[15] It has several physiological functions, which include pressure equalisation, drainage of the middle ear and protection from the nasopharyngeal environment.[15]

Poor or inadequate eustachian tube function causes eustachian tube dysfunction, which is a physiological disorder that may be temporary and spontaneously resolving.[1] Chronic eustachian tube dysfunction occurs when the dysfunction lasts for over three months; it is a poorly defined clinical entity, with variable diagnostic criteria based on clinical history, otoscopy and tympanogram results.[2] It can be a difficult pathology to manage, with debilitating symptoms affecting quality of life; current conventional treatments may not be effective.

A recent health technology assessment found that there was minimal evidence of effectiveness for current medical and surgical interventions, including nasal decongestants, topical and systematic corticosteroids, antihistamines, mechanical devices, and nasal surgery.[2] It identified only one study with a low risk of bias, a randomised, controlled trial, which found no improvement in eustachian tube dysfunction symptoms after six weeks of nasal steroids.[16]

In cases of chronic eustachian tube dysfunction refractory to conventional treatment, multiple insertions of ventilation tubes may be required. This can cause persistent perforation requiring dry ear precautions and/or myringoplasty. As a potential solution for this, eustachian tube balloon dilation (proposed as a treatment for chronic eustachian tube dysfunction) aims to ventilate and drain the middle ear by improving the physiological function of the eustachian tube.[6,10]

The initial papers by Ockermann *et al*. in 2010[5,6] and Poe *et al*. in 2011[10,17] focused on establishing the safety of eustachian tube balloon dilation by performing both cadaveric and clinical studies. The cadaveric studies revealed no evidence of fractures to the cartilaginous or bony lumen, and no damage to the internal carotid artery. Only minor mucosal lacerations at the eustachian tube orifice were noted.[5,17]

Since then, numerous prospective cohort studies have examined the role of eustachian tube balloon dilation. Pooled data analysis in this review revealed that the ability to perform a Valsalva improved from 8 per cent pre-eustachian tube balloon dilation to 72 per cent post-eustachian tube balloon dilation, while the rate of type A tympanograms increased from 5 to 61 per cent. Further statistical analysis is inappropriate because of the heterogeneity of the inclusion criteria, techniques and outcome measures in the papers included in this review.

The mechanisms by which eustachian tube balloon dilation improves eustachian tube function is an area of ongoing research, but appear to include both anatomical dilation of the cartilaginous eustachian tube and the initiation of histopathological changes.[7] A recent study examining the histopathological changes associated with eustachian tube balloon dilation found that the balloon had a crushing effect on inflammatory cells within the eustachian tube mucosa while sparing the basal layer, rapidly replacing the inflamed mucosa with a fibrous scar.[7]

One major concern of eustachian tube balloon dilation is the theoretical risk of injury to a dehiscent carotid artery running adjacent to the bony eustachian tube;[18] hence, computed tomography (CT) of the petrous temporal bones was routinely performed as a part of the pre-operative investigations. Abdel-Aziz *et al*.[18] conducted a retrospective analysis of petrous temporal bone CT scans of 285 patients who underwent eustachian tube balloon dilation. The authors found that 24 eustachian tube balloon dilations were performed in 17 patients with carotid canal dehiscence, with no complications or technical difficulties. This suggests that routine petrous temporal bone CT is not indicated before eustachian tube balloon dilation.

Another area of concern for eustachian tube balloon dilation is its use in the paediatric population, where middle-ear disease is more prevalent[19] because of a shorter, more horizontal eustachian tube, with a lumen that is less than half the size of an adult eustachian tube.[15] Currently, there are 2 retrospective case series that describe eustachian tube balloon dilations in 33 children aged 5–14 years (mean, 9 years),[19] and in 66 children aged 4–14 years (mean, 8 years),[20] with no reported complications and an improvement in middle-ear symptoms.

Despite the aforementioned results of this review, Bluestone[21] suggested, in 2014, that the efficacy of eustachian tube balloon dilation remains unverified. This is because the majority of studies have small numbers of patients, limited follow up, a weak definition of 'cure' and do not evaluate the direct effect of eustachian tube balloon dilation on eustachian tube function. This suggests that a more rigorous clinical trial is required.

Any future clinical trial on eustachian tube balloon dilation would require strict inclusion criteria and should use commonly accepted outcome measurements. The authors of this paper believe that the appropriate outcome measures should include: clinical measures of otoscopy and the ability to perform a Valsalva manoeuvre; objective measures of tympanometry, audiometry and/or tubomanometry; and patient-reported measures acquired using a verified questionnaire such as the seven-item Eustachian Tube Dysfunction Questionnaire.[22]

Our evaluation of the evidence for eustachian tube balloon dilation is limited by the quality of the papers

included, as the highest level of evidence available is prospective case series. Three papers[6,8,10] had less than 20 patients, and only 2 papers[11,12] had an average follow-up period longer than 12 months. Also, there were significant variations in terms of the assessment of patients, indications for eustachian tube balloon dilation and assessment of outcomes.

The diagnosis, investigations and indications for eustachian tube balloon dilation were not standard across the papers. This standardisation is in part limited by the subjective clinical nature by which chronic eustachian tube dysfunction is diagnosed. Although all studies reviewed used clinical history, otoscopy and tympanometry to diagnose chronic eustachian tube dysfunction, the indications for eustachian tube balloon dilation differed. In some papers, eustachian tube dysfunction refractory to conventional treatment was required, while in others a diagnosis of chronic eustachian tube dysfunction was sufficient. In future evaluations of eustachian tube balloon dilation, diagnostic criteria that include objective measurements of tympanometry and the seven-item Eustachian Tube Dysfunction Questionnaire should be used.

In addition, the technique of eustachian tube balloon dilation differed across the nine papers, with the two main techniques being those described in the Results section. In both techniques, the target for balloon dilation is the 8–12 mm segment that acts as a valve within the cartilaginous eustachian tube, as this is where the physiological deficiency in chronic eustachian tube dysfunction is thought to originate.[17] Hence, care is taken to not push the balloon catheter past the cartilaginous and bony isthmus, or to use a balloon size that is too large for the patient.

However, this has meant that a variety of balloon sizes and pressures have been employed, especially among those who use the Acclarent balloon catheters. No 'best' way to perform eustachian tube balloon dilation has yet been established; at the current early stages of evaluating its efficacy, the heterogeneity of techniques confounds the ability to draw conclusions.

Overall, this review found that eustachian tube balloon dilation is a procedure with a low rate of complications and may be considered for refractory chronic eustachian tube dysfunction in adults. More rigorous studies with standardised indications, techniques and outcomes are required to provide a higher level of evidence before its mainstream use. Nevertheless, the current data suggest a potential benefit of this procedure for a condition that can be difficult to manage.

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Dr S Y Hwang takes responsibility for the integrity of the content of the paper
Competing interests: None declared

2018 HCPCS "C" Code Review
Balloon Continence Devices

Question: Where should balloon continence devices for treatment of urinary incontinence in women be placed on the Prioritized List?

Question source: HCPCS "C" Code review

Issue: HCPCS C9746 (Transperineal implantation of permanent adjustable balloon continence device, with cystourethroscopy, when performed and/or fluoroscopy, when performed) codes for a procedure in which balloons are inserted around the urethra to increase urethral resistance and providing support to the bladder neck. These devices are designed to help with urinary stress incontinence. This devices is available commercially as the ProACT Therapy System.

The procedure (per NICE 2017): With the patient under local, regional or general anaesthesia, an incision is made in the perineum. Specially designed introducers are used to insert 2 small silicone balloons. Under radiological guidance the balloons are positioned on either side of the urethra, close to the bladder neck. The balloons are filled with a mixture of water and radiocontrast medium to enable the positioning to be confirmed. Each balloon is then attached to a subcutaneous port sited in the labia major. These ports can be used to add or remove fluid to the balloon postoperatively, thereby achieving the best balance between voiding and leakage.

Evidence

1) **NICE 2017**
    a. Current evidence on the safety and efficacy of extraurethral (noncircumferential) retropubic adjustable compression devices for stress urinary incontinence in women is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.
    b. In a systematic review of 8 studies, the mean number of pads used per day reduced from a range of 4.1 to 5.4 at baseline to a range of 1.1 to 1.2 at 2-year follow-up.
        i. All included studies were case series (N=41-162 patients)
    c. Complications:
        i. Intraoperative urethral or bladder perforation was reported in 3% to 17% of patients in a systematic review of 8 studies.
        ii. Urethral erosion was reported in 2% to 15% of patients and cutaneous erosion of the port was reported in 3% to 8% of patients, during the first year of follow-up, in the systematic review of 8 studies.
        iii. Balloon migration during the first year was reported in 7% to 18% of patients in the same study and balloon dysfunction during the first year was reported in 0.6% to 6% of patients.
        iv. Device infection during the first year was reported in 0.6% to 9% of patients in the systematic review of 8 studies. Urinary tract infection was reported in 2% of patients in a case series of 162 patients.
        v. Dysuria or acute urinary retention was reported in 2% to 7% of patients in the systematic review of 8 studies. De novo urgency during the first year of follow-up was reported in 11% of patients in 1 study included in the systematic review of 8 studies.
        vi. The device was explanted in 18% (28/153) of patients during the first year of follow-up in the case series of 162 patients. Reasons for explantation included

NICE guidance

Extraurethral (non-circumferential) retropubic adjustable compression devices for stress urinary incontinence in women

Interventional procedures guidance
Published: 22 March 2017
nice.org.uk/guidance/ipg576

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 IPG133.

1 Recommendations

1.1 Current evidence on the safety and efficacy of extraurethral (non-circumferential) retropubic adjustable compression devices for stress urinary incontinence in women is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

1.2 Clinicians wishing to insert extraurethral retropubic adjustable compression devices for stress urinary incontinence in women should:

- Inform the clinical governance leads in their trusts.
- Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, use of NICE's information for the public is recommended.
- Audit and review clinical outcomes of all patients having extraurethral retropubic adjustable compression devices for stress urinary incontinence (see section 7.3).

1.3 All adverse events involving any medical devices used in this procedure should be reported to the Medicines and Healthcare products Regulatory Agency.

1.4 Further research into this procedure should include detailed safety outcomes, long-term results and patient-reported outcome measures. NICE may update the guidance on publication of further evidence.

2 Indications and current treatments

2.1 Stress urinary incontinence is the involuntary leakage of urine during exercise or certain movements such as coughing, sneezing and laughing. In women, it is most commonly associated with previous pregnancy, with or without recognised obstetric trauma. Previous urogynaecological surgery may also result in stress urinary incontinence.

2.2 A NICE clinical guideline describes recommendations for the management of urinary incontinence in women. Conventional treatment is conservative, and includes lifestyle changes such as weight loss and pelvic floor muscle training. Surgery is considered if these conservative measures do not help. Different

types of surgery may be used including intramural bulking procedures, insertion of a synthetic tension-free vaginal tape, insertion of a transobturator tape or other sling procedures, and colposuspension. When previous surgery has failed, insertion of an artificial urinary sphincter may be needed.

3 The procedure

3.1 Extraurethral (non-circumferential) retropubic adjustable compression device insertion aims to prevent stress urinary incontinence by increasing urethral resistance and providing support to the bladder neck.

3.2 With the patient under local, regional or general anaesthesia, an incision is made in the perineum. Specially designed introducers are used to insert 2 small silicone balloons. Under radiological guidance the balloons are positioned on either side of the urethra, close to the bladder neck. The balloons are filled with a mixture of water and radiocontrast medium to enable the positioning to be confirmed. Each balloon is then attached to a subcutaneous port sited in the labia major. These ports can be used to add or remove fluid to the balloon postoperatively, thereby achieving the best balance between voiding and leakage.

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 the interventional procedure overview.

4.1 In a systematic review of 8 studies, the mean number of pads used per day reduced from a range of 4.1 to 5.4 at baseline to a range of 1.1 to 1.2 at 2-year follow-up. In a case series of 57 patients (also included in the systematic review), there was a statistically significant decrease in the mean number of pads used per day from 5.6 (±2.3) at baseline (n=57) to 0.4 (±0.8) at 72-month follow-up (n=29; $p<0.001$).

4.2 In a case series of 52 patients, 14% (7/52) of patients were fully continent and 25% (13/52) of patients reported more than 80% improvement at last follow-up (median 10.5 months); 19% (10/52) of patients were still having successive balloon inflations. In the case series of 57 patients, 62% of patients reported

that they were fully continent at last follow-up (mean 72 months), 30% reported improvement of more than 50%, and 8% of patients reported no change or improvement of less than 50%. In a case series of 41 patients, 44% of patients were fully continent, 15% reported significant improvement, 29% reported slight improvement and 12% reported no change at last follow-up (mean 25 months).

4.3 In a case series of 162 patients (also included in the systematic review), 51% and 76% of patients were fully continent (<2 g on a provocative pad test) at 1- and 5-year follow-up respectively. The mean provocative pad weight decreased for 85% (107/126) of patients, with a mean improvement from 49.6 g to 11.2 g ($p<0.001$) at 1-year follow-up.

4.4 In the case series of 162 patients, the mean Incontinence Quality of Life (IQOL) score improved from 36.8 at baseline to 71.1 at 1-year and 74.3 at 5-year follow-up (p value not reported). In the same study, the mean Urogenital Distress Inventory (UDI) score improved from 60 at baseline to 37 at 1-year and 51 at 5-year follow-up. In the case series of 57 patients, there was a statistically significant improvement in the mean IQOL score from 27.2 at baseline to 65.9 at 1-year and 78.6 at 72-month follow-up ($p<0.001$ for both).

4.5 In the case series of 57 patients, there was a statistically significant increase in the mean Valsalva leak point pressure from 51 cmH_2O at baseline to 86 cmH_2O at 12-month follow-up ($n=30$; $p<0.01$). The mean urethral closure pressure increased from 47 cmH_2O at baseline to 51 cmH_2O at 12-month follow-up ($n=30$; p=not significant).

4.6 In the case series of 41 patients, explantation because of non-response was done in 15% (6/41) of patients.

4.7 The specialist advisers listed key efficacy outcomes as cure or improvement in urinary incontinence as measured by subjective outcome measures (validated questionnaires), and objective measures (pad tests and urodynamics).

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 the interventional procedure overview.

5.1 Intraoperative urethral or bladder perforation was reported in 3% to 17% of patients in a systematic review of 8 studies. Haematoma within 30 days of the procedure (first implantation) was reported in 1 patient in a case series of 52 patients; this was treated by deflation of the balloons.

5.2 Urethral erosion was reported in 2% to 15% of patients and cutaneous erosion of the port was reported in 3% to 8% of patients, during the first year of follow-up, in the systematic review of 8 studies. Balloon migration during the first year was reported in 7% to 18% of patients in the same study and balloon dysfunction during the first year was reported in 0.6% to 6% of patients.

5.3 Device infection during the first year was reported in 0.6% to 9% of patients in the systematic review of 8 studies. Urinary tract infection was reported in 2% of patients in a case series of 162 patients.

5.4 Dysuria or acute urinary retention was reported in 2% to 7% of patients in the systematic review of 8 studies. De novo urgency during the first year of follow-up was reported in 11% of patients in 1 study included in the systematic review of 8 studies.

5.5 The device was explanted in 18% (28/153) of patients during the first year of follow-up in the case series of 162 patients. Of these, 50% (14/28) were reimplanted within 12 months. Reasons for explantation included port erosion, balloon migration, balloon erosion, worsening incontinence, pain, device failure, infection and port migration. Balloons were removed in 21% (12/57) of patients (3 bilateral and 9 unilateral) in a case series of 57 patients.

5.6 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, specialist advisers did not describe any anecdotal adverse events. They considered that the following were

theoretical adverse events: urethrovaginal fistula formation, urethral stricture, vaginal erosion, pelvic or genital pain, dyspareunia, development of overactive bladder, and urethral stenosis. One adviser noted that the procedure may make established techniques (as a secondary procedure) more technically difficult.

6 Committee comments

6.1 The committee was informed that the procedure is not in widespread use in the UK.

6.2 The committee noted that most patients have had previous procedures before insertion of extraurethral retropubic adjustable compression devices for stress urinary incontinence.

7 Further information

7.1 For related NICE guidance, see the NICE website.

7.2 Patient commentary was not sought, because it was not possible to identify any patients who had treatment with by this procedure in the UK.

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

Information for patients

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

ISBN: 978-1-4731-2389-2

Endorsing organisation

This guidance has been endorsed by Healthcare Improvement Scotland.

Accreditation

port erosion, balloon migration, balloon erosion, worsening incontinence, pain, device failure, infection and port migration.

HERC staff summary:
Balloon continence devices have a limited evidence base of effectiveness, and appear to have significant harms associated with them.

HERC staff recommendation:

1) Add balloon continence device placement (HCPCS C9746) to GN173/line 660

GUIDELINE NOTE 173, INTERVENTIONS THAT ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS FOR CERTAIN CONDITIONS
The following Interventions are prioritized on Line 660 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
C9746	Transperineal implantation of permanent adjustable balloon continence device, with cystourethroscopy, when performed and/or fluoroscopy, when performed	Insufficient evidence of effectiveness; evidence of harm	May, 2018

Section 6.0

New Discussion Items

Coverage Of Developmental Diagnoses

Question: Should coverage of developmental delay diagnoses be modified?

Question source: OHA, school-based health systems

Issue: Since a change in the DMAP file types and transitions to ICD-10, there are a number of code pairings that previously were used by the schools to get medical services for children paid for by OHP that are being denied.

From Linda Williams, Policy Analyst at OHA

> Please note below coding that School districts and ESDs are puzzled they no longer are able to receive reimbursement for therapy services provided as part of Early Intervention and Early Childhood Special Education (EI/ECSE) for over a decade prior to changes made effective during the 2015-2016 school year (specifically since October 1, 2015, ICD-10 implementation)
>
> This has been and continues to be an issue for EI/ECSE leveraging Medicaid as of October 1, 2015 forward. I brought this forward and continue to struggle to get an explanation for this to ESDs and school districts mandated to provide health related services/therapies to Medicaid eligible children eligible under the IDEA for developmental delay.
>
> Districts and ESDs have been asking why the change that only allows only reimbursement for assessment/evaluation and not therapy to correct or ameliorate developmental delays in childhood or delayed milestones to help a child get on track with age appropriate growth and development and note that when OT, PT, Speech therapy is contraindicated confer with parent and refer the child to a physician for further evaluation and testing for diagnosis. This change has negatively impacted EI/ECSE Medicaid reimbursement as part of Federal Financial Participation/cost sharing.

In the IDEA program, schools are obligated to start providing services even if a diagnosis has not been established. The Individualized Education Program (IEP) program serves as the overseeing body and provides the prescription for the referrals. Schools are not able to discontinue these services or charge parents for the services.

The most common codes that are being denied are:

R62.0 Delayed milestone in childhood
R62.50 Unspecified lack of expected normal physiological development in childhood
R62.59 Other lack of expected normal physiological development in childhood

Other examples of denied codes include:

a. *F80.9 Developmental disorder of speech and language, unspecified*

b. *F81.89 Other developmental disorders of scholastic skills*
c. *G72.9 Myopathy, unspecified*
d. *G93.9 Disorder of brain, unspecified*
e. *G96.9 Disorder of central nervous system, unspecified*
f. *Q24.9 Congenital malformation of heart, unspecified*

In 2011, as part of the ICD-10 review, the Mental Health and Chemical Dependency Subcommittee reviewed several of the F80 codes and place them all on the DMAP Excluded File (now "Undefined")

HSC/HERC history

HOSC Minutes August 24, 1995

Deatherage presented the recommendation of the Task Force on Developmental Delay. She explained the process that had been followed and how consensus had been reached. The Task Force's recommendation was that 315.4X be added to the Posture and Movement line with criteria specifying that for age 3 and under it is an appropriate diagnosis and for ages greater than 3, the use is diagnostic and should be time limited. The Task Force also recommended a prior authorization protocol be adopted requiring documentation of expected outcomes after a specific period of treatment for 3 and under and for those over three, that authorization be for no more than 120 days. These recommendations were adopted by the Subcommittee.

September 23, 2004 HOSC Minutes

VII. Coordination Disorder Guideline - Alison Little
Dr. Little explained that the guideline for Line 336 (in packet), had been attached to that line for many years, and that she queried Dr. Kitchen about its origin, who did not recall. The diagnosis, 315.4, is also known as developmental coordination disorder, clumsiness syndrome, dyspraxia syndrome and specific motor development disorder. The current guideline for physical therapy is in conflict with this guideline. Delete the Coordination Disorder guideline from Line 336.

HOSC Minutes August 12, 2010

Dyspraxia
Smits introduced a summary document regarding dyspraxia. The discussion centered around whether there was effective treatments for dyspraxia syndrome (315.4), and the decision was there were not, and that the diagnosis was hard to define. However, the group felt that dyspraxia (781.3) should be kept on the Signs and Symptoms list to allow work up for a cause. There are no treatments included for diagnoses on the signs and symptoms list.

1) Advise DMAP to keep dyspraxia (781.3) on the Signs and Symptoms List.
2) Remove dyspraxia syndrome (315.4) from line 317 Neurological Dysfunction In Posture And Movement Caused By Chronic Conditions. Advise DMAP to place dyspraxia syndrome (315.4) on the Never Covered List.

November 2014 VBBS Minutes
DMAP/HSC Code Clean Up

Smits introduced an Excel spreadsheet with recommendations for placement of CPT codes which currently are duplicated on several lists or are otherwise in need

of revision. The supplemental issues Word document was also reviewed. There was no discussion; the subcommittee accepted the recommendations as presented.

May 2015

Remove ICD-9 315.4 (developmental coordination disorder, clumsiness syndrome, dyspraxia syndrome, or specific motor development disorder) and ICD-10 F82 (Specific developmental disorder of motor function) from lines 297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS and 381 DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF- DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION. Place ICD-9 315.4 and ICD-10 F82 on the DMAP "Undefined Conditions File"

Remove ICD-9 315.9 (Unspecified delay in development) from lines 297 and 381 and place on Undefined List.

Remove ICD-9 348.9 (Unspecified condition of brain) from the dysfunction lines. Place ICD-9 348.9 on the DMAP "Undefined" List

Current Prioritized List Status

Code	Code Description	Current Prioritized List Placement
R62.0	Delayed milestone in childhood	Diagnostic Workup File (DWF)
R62.50	Unspecified lack of expected normal physiological development in childhood	Diagnostic Workup File (DWF)
R62.59	Other lack of expected normal physiological development in childhood	Diagnostic Workup File (DWF)

Code	Code Description	Current Prioritized List Placement
F70.	Mild intellectual disabilities	345,377
F71.	Moderate intellectual disabilities	71,292,345,377
F72.	Severe intellectual disabilities	71,292,345,377
F73.	Profound intellectual disabilities	71,292,345,377
F78.	Other intellectual disabilities	71,292,345,377
F79.	Unspecified intellectual disabilities	71,292,345,377
F80.0	Phonological disorder	345
F80.1	Expressive language disorder	345

Coverage Of Developmental Diagnoses

Code	Code Description	Current Prioritized List Placement
F80.2	Mixed receptive-expressive language disorder	345
F80.4	Speech and language development delay due to hearing loss	345
F80.81	Childhood onset fluency disorder	345
F80.82	Social pragmatic communication disorder	345
F80.89	Other developmental disorders of speech and language	345
F80.9	Developmental disorder of speech and language, unspecified	Undefined Diagnosis File
F81.0	Specific reading disorder	Undefined Diagnosis File
F81.2	Mathematics disorder	Undefined Diagnosis File
F81.81	Disorder of written expression	Undefined Diagnosis File
F81.89	Other developmental disorders of scholastic skills	Undefined Diagnosis File
F81.9	Developmental disorder of scholastic skills, unspecified	Undefined Diagnosis File
F82.	Specific developmental disorder of motor function	Undefined Diagnosis File
F84.0	Autistic disorder	71,193,292,345,377
F84.2	Rett's syndrome	71,292,345,377
F84.3	Other childhood disintegrative disorder	71,193,292,345,377
F84.5	Asperger's syndrome	193 AUTISM SPECTRUM DISORDERS
F84.8	Other pervasive developmental disorders	71,193,292,345,377
F84.9	Pervasive developmental disorder, unspecified	193 AUTISM SPECTRUM DISORDERS
F88.	Other disorders of psychological development	Undefined Diagnosis File
F89.	Unspecified disorder of psychological development	Undefined Diagnosis File

Line: 71

Condition: NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES (See Coding Specification Below) (See Guideline Notes 6,64,65,129,170)

Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., G-TUBES, J-TUBES, RESPIRATORS, TRACHEOSTOMY, UROLOGICAL PROCEDURES)

Line: 193

Condition: AUTISM SPECTRUM DISORDERS (See Guideline Notes 65,75)

Treatment: MEDICAL THERAPY/BEHAVIORAL MODIFICATION INCLUDING APPLIED BEHAVIOR ANALYSIS

ICD-10: F84.0,F84.3-F84.9

CPT: 0359T-0374T,90785,90832-90840,90846-90849,90882,90887,93792,93793, 96118,98966-98969,99051,99060,99201-99215,99224-99226,99324-99355, 99366,99415,99416,99441-99449,99487-99490,99495-99498

HCPCS: G0176,G0177,G0248-G0250,G0406-G0408,G0425-G0427,G0459,G0463-G0467,G0469,G0470,G0511,G0513,G0514,H0004,H0023,H0032,H0034, H0038,H2010,H2014,H2027,H2032,S9484

Line: 292

Condition: NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS (See Coding Specification Below) (See Guideline Notes 6,64,65,170)

Treatment: MEDICAL AND SURGICAL TREATMENT (E.G., DURABLE MEDICAL EQUIPMENT AND ORTHOPEDIC PROCEDURE)

Line: 345

Condition: NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS (See Guideline Notes 6,64,65,90)

Treatment: MEDICAL THERAPY

Line: 377

Condition: DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION (See Guideline Notes 6,38,64,65,90)

Treatment: MEDICAL THERAPY (SHORT TERM REHABILITATION WITH DEFINED GOALS)

Evidence Summary

Galuschka, 2014

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3935956/

- All available randomized controlled trials looking at the diagnosis and treatment of reading and/or spelling disorders
- Twenty-two randomized controlled trials with a total of 49 comparisons of experimental and control groups could be included.
- Comparisons evaluated 5 reading fluency trainings, 3 phonemic awareness instructions, 3 reading comprehension trainings, 29 phonics instructions, 3 auditory trainings, 2 medical treatments, and 4 interventions with coloured overlays or lenses. One trial evaluated the effectiveness of sunflower therapy and another investigated the effectiveness of motor exercises.
- Results: Phonics instruction is the only approach whose efficacy on reading and spelling performance in children and adolescents with reading disabilities is statistically confirmed.
- Conclusions this analysis demonstrated that severe reading and spelling difficulties can be ameliorated with appropriate treatment.

Galuschka, 2016

- Guideline on the diagnosis and treatment of reading and/or spelling disorders
- 3-11% of children and adolescents have some form of reading or spelling disorder
- Based on Galuschka systematic review, meta-analysis and consensus conference
- Included 53 publications, 22 RCTs
- Evaluate for co-morbid attention deficit-hyperactivity disorder, anxiety disorder, or disorder of arithmetical skills
- Vision and hearing disorders can be an underlying treatable cause
- Reading and spelling performance should be reinforced with systematic instruction about letter-sound and sound-letter correspondences, letter-syllable-morpheme synthesis, and sound-syllablemorpheme analysis (g' = 0.32) (recommendation grade A).
- Spelling ability responds best to spelling-rule training (recommendation grade A).
- Irlen lenses, visual and/or auditory perceptual training, hemispheric stimulation, piracetam, and prism spectacles should not be used (recommendation grade A).

McArthur, 2012 https://www.ncbi.nlm.nih.gov/pubmed/23235670

- Cochrane systematic review
- Phonics training for English-speaking poor readers
- Inclusion criteria – randomized, quasi-randomized or studies with iminimzation, in those whose word reading was below the level of their expected age for no known reason.
- 11 studies, 736 participants

- The effect sizes for the outcomes were:
    - word reading accuracy standardised mean difference (SMD) 0.47 (95% confidence interval (CI) 0.06 to 0.88; 10 studies)
    - nonword reading accuracy SMD 0.76 (95% CI 0.25 to 1.27; eight studies)
    - word reading fluency SMD -0.51 (95% CI -1.14 to 0.13; two studies)
    - reading comprehension SMD 0.14 (95% CI -0.46 to 0.74; three studies)
    - spelling SMD 0.36 (95% CI -0.27 to 1.00; two studies)
    - letter-sound knowledge SMD 0.35 (95% CI 0.04 to 0.65; three studies)
    - phonological output SMD 0.38 (95% -0.04 to 0.80; four studies).
    - one result in a negative direction for nonword reading fluency SMD 0.38 (95% CI -0.55 to 1.32; one study), though this was not statistically significant.
    - Subgroup analyses that had no impact included training type (phonics alone versus phonics and phoneme awareness versus phonics and irregular word training), training intensity (less than two hours per week versus at least two hours per week), training duration (less than three months versus at least three months), training group size (one-on-one versus small group training), or training administrator (human administration versus computer administration).
- Conclusions: Phonics training appears to be effective for improving some reading skills. Specifically, statistically significant effects were found for nonword reading accuracy (large effect), word reading accuracy (moderate effect), and letter-sound knowledge (small-to-moderate effect).

Hendren, 2018
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5880915/pdf/fpsyt-09-00101.pdf

- Descriptive article addressing comorbidities and reading disorder
- With reading disorder, there is often comorbid ADHD, anxiety, depression, autism, impulse control and conduct disorders
- Treatment of reading disorder should take into account psychiatric comorbid conditions

HERC Staff Summary:

Schools are facing a number of rejected claims while providing services for children with developmental delay in schools. Some of this can be ameliorated by education around using more appropriate codes. Several reading disorder diagnoses are not currently funded, but there is evidence to support specific phonic instructions and these can be added to the funded region. Often, early intervention is indicated when the only diagnosis may be failing to meet developmental milestones. Currently, these are diagnostic codes just on the diagnostic file and ongoing treatment with these codes is not being permitted. A solution would need to allow for treatment to be offered

without necessarily a more specific diagnosis, but still subject to appropriate limitations and meeting medical necessity requirements.

There may be a need to emphasize greater coordination between schools, primary care, and mental health in order to comprehensively address learning issues at schools.

HERC Staff Recommendations:

Code	Code Description	Current Prioritized List Placement	Recommended Changes
R62.0	Delayed milestone in childhood – includes late talker, late walker, delayed attainment of expected physiological developmental stage	Diagnostic Workup File (DWF)	**Add to dysfunction lines. Subject to Guideline Note 6.**
R62.50	Unspecified lack of expected normal physiological development in childhood	Diagnostic Workup File (DWF)	No change, too vague for anything but diagnostic
R62.59	Other lack of expected normal physiological development in childhood	Diagnostic Workup File (DWF)	No change

Code	Code Description	Current Prioritized List Placement	
F80.9	Developmental disorder of speech and language, unspecified – Communication disorder NOS, Language disorder NOS	Undefined Diagnosis File	No change. Too vague
F81.0	Specific reading disorder – "backward reading" Developmental dyslexia, specific learning disorder, with impairment in reading, specific reading retardation. Def: Serious impairment of reading skills unexplained in relation to general intelligence and teaching processes.	Undefined Diagnosis File	**Consider adding this to line 345**
F81.2	Mathematics disorder – Developmental acalculia, Developmental arithmetical disorder	Undefined Diagnosis File	No change.

Code	Code Description	Current Prioritized List Placement	
F81.81	Disorder of written expression – Specific learning disorder, with impairment in written expression, specific spelling disorder	Undefined Diagnosis File	**Consider adding this to line 345**
F81.89	Other developmental disorders of scholastic skills	Undefined Diagnosis File	Too vague
F81.9	Developmental disorder of scholastic skills, unspecified – Knowledge acquisition disability NOS, Learning disability NOS, Learning disorder NOS	Undefined Diagnosis File	Too vague
F82.	Specific developmental disorder of motor function	Undefined Diagnosis File	Reviewed at May 2015 VbBS/HERC and removed from 2 dysfunction lines
F88.	Other disorders of psychological development – Developmental agnosia, Global developmental delay, other specific neurodevelopmental disorder	Undefined Diagnosis File	No change
F89.	Unspecified disorder of psychological development	Undefined Diagnosis File	No change

Code	Description	Current Prioritized List Placement	Recommended change
T1018	School-based individualized education program (iep) services, bundled	Ancillary	No change
T1024	Evaluation and treatment by an integrated, specialty team contracted to provide coordinated care to multiple or severely	Ancillary	No change

	handicapped children, per encounter		

1) **Add R62.0 *Delayed milestone in childhood* to dysfunction lines: 292, 345, and 377.**
    a. Guideline Note 6 will apply
    b. Add a coding specification
        R62.0 is only included on this line for the intent of community-based Early Intervention programs or school-based health services IDEA programs.

2) **Add the following codes to Line 345**
    a. F81.0 (Specific reading disorder)
    b. F81.81 (Disorder of written expression)

3) **Add a guideline**

    Guideline Note XXX Reading and writing disorder in children
    Line 345
    Reading and writing disorder (F81.0, F81.81) are included on this line for children and adolescents when there has been a clinical assessment to determine potential modifiable causes (such as hearing, vision screening and psychiatric comorbidities), phonics training is used, and the patient demonstrates progress towards goals as defined by a treatment plan or Individualized Education Program (IEP).

4) **HSD staff to work with schools to help with identifying appropriate diagnoses**

5) **Consider adding a Statement of Intent**
    Statement of Intent X Clinical and Educational Coordination
    HERC intends that children and adolescents with delays in attaining educational standards be clinically evaluated for potential pathophysiological etiologies (such as vision, hearing, and lead) and psychiatric etiologies (such as depression), and that interventions to address speech or developmental delay be coordinated between the school, primary care, and mental health setting, as appropriate.

Dermatochalasis and Blepharoplasty

Question: Should dermatochalasis be moved to a covered line for surgical repair in cases where it impairs vision? Should other "clean up" changes be made to the Prioritized List concerning blepharoplasty?

Question source: Dr. Tracy Muday, medical director of Advanced Health; ICD-10 Ophthalmology reviewers

Issue: Dermatochalasis is an excess of skin in the upper or lower eyelid, also known as "baggy eyes." It may be either an acquired or a congenital condition. The excess tissue can sometimes obstruct the visual field, especially the superior visual field. In severe cases, it may obstruct as much as 50 percent of the superior visual field. When it impairs vision, it can be treated with blepharoplasty in which excess skin, muscle and fat are removed. While the improvement of vision is an indication for blepharoplasty on the superior eyelid, if the visual fields are not obstructed, it may be performed for cosmetic reasons. In general, blepharoplasty of the inferior eyelid is considered cosmetic, as dermatochalasis in the lower eyelid does not interfere with vision. Blepharoplasty may also be done for certain ptosis conditions.

Currently, dermatochalasis (ICD-10 H02.83) is on line 567 BLEPHARITIS. Blepharoplasty of the upper eyelid (CPT 15822-15823) is only found on lines 351 STRABISMUS DUE TO NEUROLOGIC DISORDER and 469 ACQUIRED PTOSIS AND OTHER EYELID DISORDERS WITH VISION IMPAIRMENT. Blepharoplasty of the lower eyelid (CPT 15820-15821) is on the Services Recommended for Non-Coverage List. GN130 applies only to line 469 and restricts blepharoplasty to situations in which visual fields are impaired. Dr. Muday was asking about when dermatochalasis was a covered condition given that GN130 outlines when its treatment is covered.

Blepharoplasty was discussed as part of the 2010 ICD-10 Ophthalmology review. At that time, the ophthalmologists recommended moving dermatochalasis from the blepharitis line, where it had been for a very long time, to the line for acquired ptosis. There was a staff error in translating this recommendation, and the ICD-10 materials approved by HERC moved dermatochalasis from the ptosis line to the blepharitis line (the opposite of the reviewer's intent; this mistakenly resulted in no change from previous Lists). The reviewers crafted a guideline to govern the treatment of dermatochalasis for the ptosis line as shown below, as part of the intended move of dermatochalasis to that covered line.

GUIDELINE NOTE 130, BLEPHAROPLASTY

Line 469

Blepharoplasty is covered when 1) visual fields demonstrate an absolute superior defect to within 15 degrees of fixation, 2) upper eyelid position contributes to difficulty tolerating a prosthesis in an anophthalmic socket, 3) essential blepharospasm or hemifacial spasm is present, OR 4) when there is significant ptosis in the downgaze reading position.

HERC staff recommendations:

1) Add ICD-10 ICD-10 H02.83 (dermatochalasis) to line 469 ACQUIRED PTOSIS AND OTHER EYELID DISORDERS WITH VISION IMPAIRMENT and remove from line 567 BLEPHARITIS
    a. Will allow coverage of blepharoplasty when GN130 criteria are met
    b. Follows the ICD-10 Ophthalmology reviewer's intent
2) Add line 351 STRABISMUS DUE TO NEUROLOGIC DISORDER to GN130
    a. Has indications for blepharoplasty
3) Add CPT 15820-15821 (Blepharoplasty, lower eyelid) to line 660 and add the following entry to GN173:

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

The following Interventions are prioritized on Line 660 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
15820-15821	Blepharoplasty, lower eyelid	No clinically important benefit	May 2018

Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea

Question: Should hypoglossal nerve stimulation be added to the obstructive sleep apnea line?

Question source: OHA Hearings Division

Issue: Hypoglossal nerve stimulation is a new procedure for treatment of obstructive sleep apnea (OSA) for patients for whom CPAP is contraindicated or not effective/tolerated. The Hearings Division recently was involved in a case in which this procedure was requested. It is not currently included on the OSA line, and was not part of the extensive OSA treatment review and coverage guidance development done a couple of years ago. Several devices have received FDA approval and are currently commercially available.

The CPT code used for insertion of the hypoglossal nerve stimulator is CPT 64568 (Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator). This code is currently only on lines 174 GENERALIZED CONVULSIVE OR PARTIAL EPILEPSY WITHOUT MENTION OF IMPAIRMENT OF CONSCIOUSNESS and 440 TRIGEMINAL AND OTHER NERVE DISORDERS. OSA is on line 203 SLEEP APNEA, NARCOLEPSY AND REM BEHAVIORAL DISORDER.

Hypoglossal nerve stimulation aims to treat obstructive sleep apnea 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 anesthesia, 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 synchronized 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.

Evidence

1) **NICE 2017**, review of hypoglossal nerve stimulation for treatment of moderate to severe OSA
    a. Conclusion: 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. Evidence review
        i. Systematic review and meta-analysis of 200 patients in 6 prospective studies [**Certal 2015**]
            1. There was a statistically significant decrease in the apnea–hypopnea 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).
            2. 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).

3. 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). 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).

ii. 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).

iii. 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.

iv. In a prospective case series of 46 patients [**Friedman 2016**], there was a statistically significant improvement in the mean sleep apnea quality of life index from 4.3±1.0 at baseline to 4.7±1.2 at 6-month follow-up (p=0.019).

c. Safety:

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 meta-analysis of 200 patients.

ii. 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.

iii. Bleeding was reported in 1 patient within 30 days of implantation in a prospective case series of 46 patients. In the same study, haematoma was reported in 7% (3/46) of patients. 2 were classified as non-series and one as serious

iv. 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.
v. 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.
vi. Headache was reported in 6% (8/126) of patients in the prospective case series of 126 patients within 1 year of the procedure. 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.
vii. Dry mouth was reported in 13% (16/126) of patients in the prospective case series of 126 patients within 3 years of the procedure.
viii. 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.
ix. 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. 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.
x. 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.
xi. 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. Defective implanted pulse-generator connector was reported in 1 patient in the prospective case series of 13 patients from the systematic review and metaanalysis of 200 patients.
xii. 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.

Original STAR study

1) **Strollo 2014**
    a. Multicenter, prospective, single-group, cohort study of hypoglossal nerve stimulation in patients with difficulty either accepting or adhering to CPAP therapy (N=126)

   i. Mean BMI 28.4
b. The median AHI score at 12 months decreased 68%, from 29.3 events per hour to 9.0 events per hour (P<0.001); the ODI score decreased 70%, from 25.4 events per hour to 7.4 events per hour (P<0.001). Secondary outcome measures showed a reduction in the effects of sleep apnea and improved quality of life. In the randomized phase, the mean AHI score did not differ significantly from the 12-month score in the nonrandomized phase among the 23 participants in the therapy-maintenance group (8.9 and 7.2 events per hour, respectively); the AHI score was significantly higher (indicating more severe apnea) among the 23 participants in the therapy-withdrawal group (25.8 vs. 7.6 events per hour, P<0.001). The ODI results followed a similar pattern. The rate of procedure-related serious adverse events was less than 2%.
c. **CONCLUSIONS** In this uncontrolled cohort study, upper-airway stimulation led to significant improvements in objective and subjective measurements of the severity of obstructive sleep apnea.
d. Note: funded by manufacturer of a hypoglossal nerve stimulator device

Additional study not included in NICE review

1) Heiser 2017

a. A multicenter prospective single-arm study at three German centers (N=60)
b. Every subject reported improvement in sleep and daytime symptoms. The average usage time of the system was 42.9 ± 11.9 h/wk. The median apnea-hypopnea index was significantly reduced at 6 months from 28.6/h to 8.3/h. No patient required surgical revision of the implanted system.
c. Conclusion. Selective upper airway stimulation is a safe and effective therapy for patients with obstructive sleep apnea and represents a powerful option for its surgical treatment

Other coverage: Wellpoint and Aetna consider hypoglossal nerve stimulation to be experimental.

HERC staff summary: While promising, the evidence for hypoglossal nerve stimulation for the treatment of sleep apnea is limited to relatively small, non-controlled trials. Trusted sources consider this treatment to be experimental. There are harms reported for this procedure.

HERC staff recommendation:

1) Add hypoglossal nerve stimulation (CPT 64568 Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator) to line 660/GN173 as shown below
    a. Keep CPT 64568 on the two current lines and specify inclusion on line 660 only for use for hypoglossal nerve stimulation for OSA

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

The following Interventions are prioritized on Line 660 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
64568	Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator for **hypoglossal nerve stimulation for treatment of obstructive sleep apnea**	Insufficient evidence of effectiveness	May, 2018

NICE guidance

Hypoglossal nerve stimulation for moderate to severe obstructive sleep apnoea

Interventional procedures guidance
Published: 22 November 2017
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 (see section 7.3).

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 the interventional procedure overview.

4.1 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).

4.2 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 ($p<0.001$).

4.3 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).

4.4 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).

4.5 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 ($p<0.05$).

4.6 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.

4.7 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 ($p=0.019$).

4.8 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 the 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 an audit tool (which is for use at local discretion).

Information for patients

NICE has produced information on this procedure for patients and carers (information for the public). 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

The Laryngoscope

Systematic Review

Hypoglossal Nerve Stimulation in the Treatment of Obstructive Sleep Apnea: A Systematic Review and Meta-analysis

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Objectives/Hypothesis: Poor adherence to continuous positive airway pressure treatment in obstructive sleep apnea (OSA) adversely affects the effectiveness of this therapy. This study aimed to systematically review the evidence regarding the efficacy and safety of hypoglossal nerve stimulation as an alternative therapy in the treatment of OSA.

Data Sources: Scopus, PubMed, and Cochrane Library databases were searched (updated through September 5, 2014).

Methods: Studies were included that evaluated the efficacy of hypoglossal nerve stimulation to treat OSA in adults with outcomes for apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and effect on daytime sleepiness (Epworth Sleepiness Scale [ESS]). Tests for heterogeneity and subgroup analysis were performed.

Results: Six prospective studies with 200 patients were included in this review. At 12 months, the pooled fixed effects analysis demonstrated statistically significant reductions in AHI, ODI, and ESS mean difference of −17.51 (95% CI: −20.69 to −14.34); −13.73 (95% CI: −16.87 to −10.58), and −4.42 (95% CI: −5.39 to −3.44), respectively. Similar significant reductions were observed at 3 and 6 months. Overall, the AHI was reduced between 50% and 57%, and the ODI was reduced between 48% and 52%. Despite using different hypoglossal nerve stimulators in each subgroup analysis, no significant heterogeneity was found in any of the comparisons, suggesting equivalent efficacy regardless of the system in use.

Conclusions: This review reveals that hypoglossal nerve stimulation therapy may be considered in selected patients with OSA who fail medical treatment. Further studies comparing hypoglossal nerve stimulation with conventional therapies are needed to definitively evaluate outcomes.

Key Words: Hypoglossal nerve stimulation, sleep apnea.

Level of Evidence: NA

***Laryngoscope*, 125:1254–1264, 2015**

INTRODUCTION

Obstructive sleep apnea (OSA) is a serious, potentially life-threatening disorder characterized by recurrent episodes of upper-airway collapse during sleep that often lead to hypoxemia and hypercapnia.[1] Common symptoms include loud snoring, breathing interruptions, excessive daytime sleepiness, and cognitive impairment. Its association with an increased risk of cardiovascular complications is well described.[2]

The primary course of treatment for OSA is therapy with continuous positive airway pressure (CPAP) devices. Despite efforts to improve adherence, only 40% to 60% of patients continue to use CPAP long term or as prescribed, and many others do not seek medical attention. In cases where the effectiveness is not optimal, alternative therapies are often utilized after medical management has failed.[3]

In 1978, Remmers et al.[4] were the first to report the direct relationship between loss of genioglossus muscle activation during sleep and upper airway closure in patients with OSA. This finding led to early attempts to treat the disorder by electrical stimulation of the pharyngeal muscles with transcutaneous, intraoral, and intramuscular electrodes.[5–7]

Several subsequent projects since then have attempted to prove the usefulness of chronic hypoglossal nerve stimulation (HNS) as a novel therapeutic approach to sleep apnea. Selective HNS is less likely to produce arousal than direct intramuscular stimulation, which is associated with sensory stimulation, because the nerve is purely motor. Although the potential

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Editor's Note: This Manuscript was accepted for publication October 17, 2014.

The views herein are the private views of the authors and do not reflect the official views of the Department of the Army or the Department of Defense.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

DOI: 10.1002/lary.25032

ORIGINAL ARTICLE

Upper-Airway Stimulation for Obstructive Sleep Apnea

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ABSTRACT

BACKGROUND

Obstructive sleep apnea is associated with considerable health risks. Although continuous positive airway pressure (CPAP) can mitigate these risks, effectiveness can be reduced by inadequate adherence to treatment. We evaluated the clinical safety and effectiveness of upper-airway stimulation at 12 months for the treatment of moderate-to-severe obstructive sleep apnea.

METHODS

Using a multicenter, prospective, single-group, cohort design, we surgically implanted an upper-airway stimulation device in patients with obstructive sleep apnea who had difficulty either accepting or adhering to CPAP therapy. The primary outcome measures were the apnea–hypopnea index (AHI; the number of apnea or hypopnea events per hour, with a score of ≥15 indicating moderate-to-severe apnea) and the oxygen desaturation index (ODI; the number of times per hour of sleep that the blood oxygen level drops by ≥4 percentage points from baseline). Secondary outcome measures were the Epworth Sleepiness Scale, the Functional Outcomes of Sleep Questionnaire (FOSQ), and the percentage of sleep time with the oxygen saturation less than 90%. Consecutive participants with a response were included in a randomized, controlled therapy-withdrawal trial.

RESULTS

The study included 126 participants; 83% were men. The mean age was 54.5 years, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 28.4. The median AHI score at 12 months decreased 68%, from 29.3 events per hour to 9.0 events per hour ($P<0.001$); the ODI score decreased 70%, from 25.4 events per hour to 7.4 events per hour ($P<0.001$). Secondary outcome measures showed a reduction in the effects of sleep apnea and improved quality of life. In the randomized phase, the mean AHI score did not differ significantly from the 12-month score in the nonrandomized phase among the 23 participants in the therapy-maintenance group (8.9 and 7.2 events per hour, respectively); the AHI score was significantly higher (indicating more severe apnea) among the 23 participants in the therapy-withdrawal group (25.8 vs. 7.6 events per hour, $P<0.001$). The ODI results followed a similar pattern. The rate of procedure-related serious adverse events was less than 2%.

CONCLUSIONS

In this uncontrolled cohort study, upper-airway stimulation led to significant improvements in objective and subjective measurements of the severity of obstructive sleep apnea. (Funded by Inspire Medical Systems; STAR ClinicalTrials.gov number, NCT01161420.)

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*The complete list of investigators in the Stimulation Therapy for Apnea Reduction (STAR) Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on August 7, 2014, at NEJM.org.

N Engl J Med 2014;370:139-49.
DOI: 10.1056/NEJMoa1308659

Obstructive sleep apnea is a common disorder, characterized by recurrent narrowing and closure of the upper airway accompanied by intermittent oxyhemoglobin desaturation and sympathetic activation.[1] Sequelae include excessive sleepiness and impaired quality of life. Moderate-to-severe obstructive sleep apnea, defined as an apnea–hypopnea index (AHI) score of 15 or more apnea or hypopnea events per hour, is an independent risk factor for insulin resistance, dyslipidemia, vascular disease, and death.[2-7] Treatment with continuous positive airway pressure (CPAP) with the use of a mask favorably modifies these adverse health consequences.[8] However, the general effectiveness of CPAP therapy is dependent on patient acceptance of and adherence to the treatment.[9,10]

Alternative treatments to CPAP include custom-made oral-appliance therapy and a variety of upper-airway surgeries.[11,12] Since evidence-based reviews do not uniformly support the efficacy of these treatments for moderate-to-severe sleep apnea, new therapy is desirable.[13,14]

The onset of apnea is accompanied by a reduction in drive to the upper-airway muscles,[15,16] and upper-airway patency is strongly correlated with the activation of the genioglossus muscle.[17] Upper-airway stimulation with the use of unilateral stimulation of the hypoglossal nerve has been developed as a possible treatment option and has shown promise in feasibility trials.[18-23]

Using a multicenter, prospective, single-group trial design followed by a randomized, therapy-withdrawal trial that included only participants who had had a response to therapy, we addressed the clinical safety and effectiveness of upper-airway stimulation at 12 months after implantation. This technology permits stimulation to be synchronized with ventilatory effort during sleep.

Methods

Participants

Participants with moderate-to-severe obstructive sleep apnea were eligible for enrollment if they had difficulty accepting or adhering to CPAP treatment. Exclusion criteria were a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of more than 32.0, neuromuscular disease, hypoglossal-nerve palsy, severe restrictive or obstructive pulmonary disease, moderate-to-severe pulmonary arterial hypertension, severe valvular heart disease, New York Heart Association class III or IV heart failure, recent myocardial infarction or severe cardiac arrhythmias (within the past 6 months), persistent uncontrolled hypertension despite medication use, active psychiatric disease, and coexisting nonrespiratory sleep disorders that would confound functional sleep assessment.

Study Design and Oversight

The study was designed by the sponsor (Inspire Medical Systems), the investigators, and the Food and Drug Administration as a multicenter, prospective, single-group trial with participants serving as their own controls. There was no concurrent control group. The primary outcome evaluation was followed by a randomized, controlled therapy-withdrawal study that included a subgroup of consecutive participants selected from the population that had a response to therapy.

The trial protocol was approved by the institutional review board (in the United States) or medical ethics committee (in Europe) at each participating center. All the participants provided written informed consent before enrollment. An independent clinical-events committee and a data and safety monitoring board provided review and adjudication of safety data. Verification of source data was performed by independent monitors. The study investigators had full access to the data and had the right to submit the manuscript for publication without input from the sponsor. The writing committee (the first, second, and last authors), an independent statistician (Teri Yurik, NAMSA), and the sponsor vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol.

The primary outcome measures were assessed by means of overnight polysomnography and scored by an independent core laboratory with the use of standard criteria.[24] The data analysis was performed by the independent statistician, with the results reviewed by the first and last authors. The first author wrote the manuscript with assistance from the writing committee; no one who is not listed as an author contributed substantially to the study report.

SCREENING AND IMPLANTATION

In order for investigators to verify eligibility for the implantation, enrolled participants underwent screening that included polysomnography, medical and surgical consultation, and endoscopy during drug-induced sleep.[25] Participants were excluded if the AHI score from the screening polysomnography was less than 20 or more than 50 events per hour, if central or mixed sleep-disordered breathing events accounted for more than 25% of all apnea and hypopnea episodes, or if the AHI score while the person was not in a supine position was less than 10 events per hour. Participants were also excluded if pronounced anatomical abnormalities preventing the effective use or assessment of upper-airway stimulation were identified during the surgical consultation (e.g., tonsil size of 3 or 4 [tonsils visible beyond the pillars or extending to midline]) or if complete concentric collapse at the retropalatal airway was observed on endoscopy performed during drug-induced sleep.[25]

Qualified participants underwent a surgical procedure to implant the upper-airway stimulation system (Inspire Medical Systems)[20] (Fig. 1). The stimulation electrode was placed on the hypoglossal nerve to recruit tongue-protrusion function; the sensing lead was placed between the internal and external intercostal muscles to detect ventilatory effort; the neurostimulator was implanted in the right ipsilateral mid-infraclavicular region.

Approximately 1 month after implantation, all the participants underwent a second baseline diagnostic polysomnographic examination before activation of the device. Immediately after this polysomnography, all the participants had their device activated and were instructed regarding the use of a controller to initiate and terminate therapy on a nightly basis. After activation, participants had scheduled outpatient visits at months 2, 3, 6, 9, and 12; at each of these visits data on adverse events were obtained and device interrogation was performed.

OUTCOME MEASURES

The primary outcome was the change in the severity of obstructive sleep apnea in the study population, as assessed by means of the AHI and the oxygen desaturation index (ODI; the number of times per hour of sleep that the blood oxygen level drops by ≥4 percentage points from baseline). The coprimary outcome was the proportion of participants with a response from baseline to 12 months with respect to the primary outcome measures of the AHI and ODI scores. A response as measured by means of the AHI was defined as a reduction of at least 50% from baseline in the AHI score and an AHI score on the 12-month polysomnography of less than 20 events per hour.[26] The ODI was chosen as a stable integrative outcome value of all forms of sleep-disordered breathing. A response as measured by means of the ODI was defined as a reduction of at least 25% from baseline in the ODI score. The prespecified primary efficacy objectives were response rates of at least 50%, as assessed by means of the AHI and ODI. All participants who received an implant were included in the primary outcome analysis; participants who did not complete the 12-month visit were considered not to have had a response.

Secondary outcome measures included self-reported sleepiness and disease-specific quality of life as assessed with the use of the Epworth Sleepiness Scale (scores range from 0.0 to 24.0, with higher scores indicating more daytime sleepiness), disease-specific quality of life, as assessed with the use of the Functional Outcomes of Sleep Questionnaire (FOSQ; scores range from 5.0 to 20.0, with higher scores indicating greater functioning), and the percentage of sleep time with the oxygen saturation less than 90%.

FOLLOW-UP

The follow-up visits at months 2, 6, and 12 included a polysomnographic study and evaluation of daytime sleepiness by means of the Epworth Sleepiness Scale. An Epworth Sleepiness Scale score of less than 10.0 is considered to be the threshold for normal subjective sleepiness.[27] Participants also completed the FOSQ, on which a score of more than 17.9 is considered to be the threshold for persons with normal sleep-related quality of life. A change of 2.0 or more points in the FOSQ score is considered to indicate a clinically meaningful improvement in daily functioning.[28]

During the polysomnographic studies at 2 months and 6 months, device variables were adjusted with the use of a programmer unit that communicates with the device by means of telemetry. The adjusted variables included the

stimulation voltage, rate, and pulse width and the timing of electrical stimulation. No device adjustments were made in the 30 days before or during the polysomnographic study at 12 months.

At the 12-month visit, the first 46 consecutive participants who met the criterion of having a response to therapy were randomly assigned, in a 1:1 ratio, to the therapy-maintenance group or the

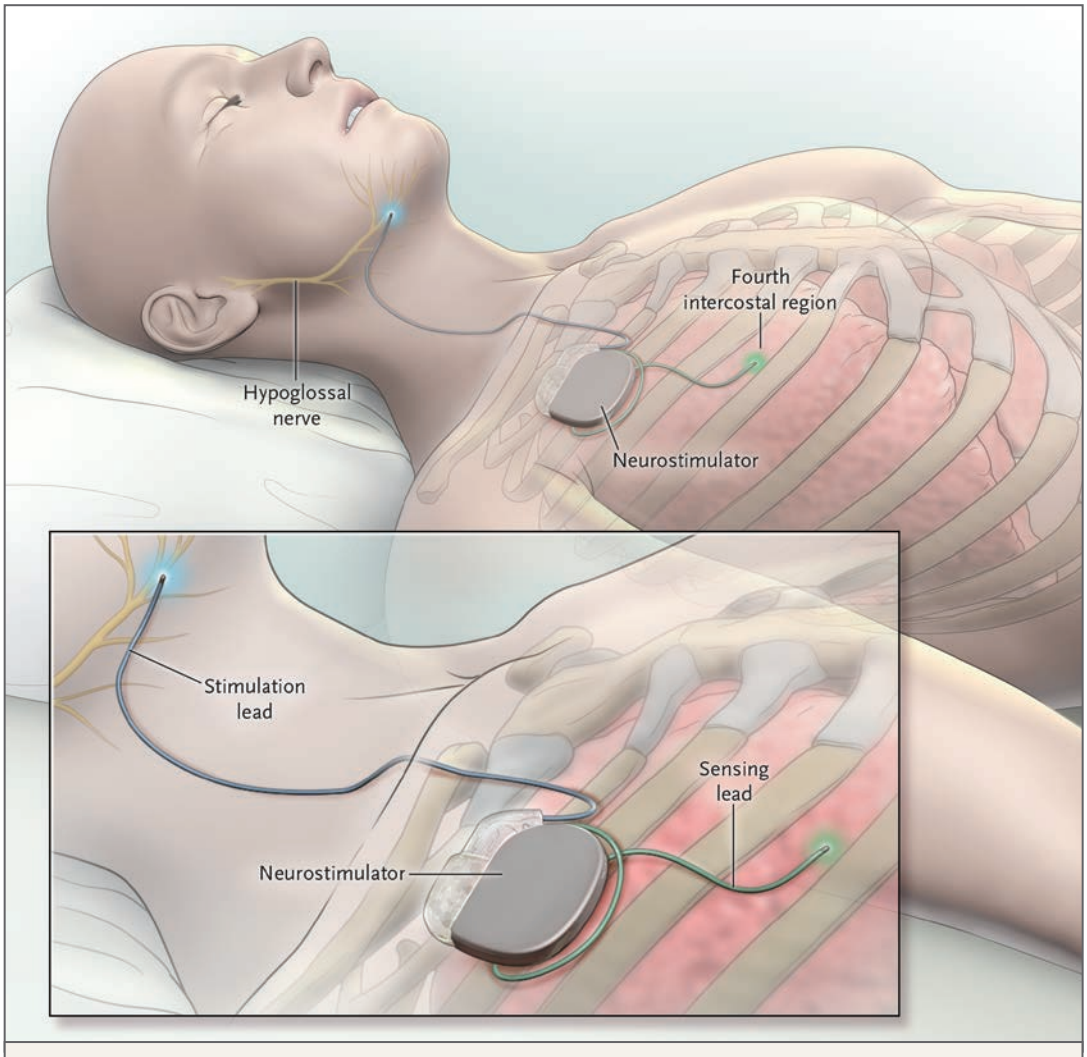

Figure 1. Upper-Airway Stimulation.

The neurostimulator delivers electrical stimulating pulses to the hypoglossal nerve through the stimulation lead; the stimulating pulses are synchronized with ventilation detected by the sensing lead. For implantation of the device, the main trunk of the hypoglossal nerve (XII) was exposed by means of a horizontal incision in the upper neck at the inferior border of the submandibular gland. The nerve was followed anteromedially until it branched into a lateral and a medial (m-XII) division. The stimulation lead was placed on the m-XII branch. The cuff section of the stimulation lead includes three electrodes that can be arranged in a variety of unipolar or bipolar configurations for stimulation of the upper airway. Appropriate placement of the stimulation lead was confirmed by observing tongue protrusion during stimulation and by electromyographic monitoring during surgery. A second incision was made horizontally at the fourth intercostal region. The dissection was aimed at the upper border of the underlying rib. A tunnel was created posteroanteriorly between the external and internal intercostal muscles. The ventilatory sensor was placed in the tunnel, with the sensing side facing the pleura. A third incision was made horizontally, 2 to 4 cm inferior to the right clavicle. A pocket was created inferior to the incision and superficial to the pectoralis major muscle to accommodate the neurostimulator (implanted pulse generator). With a subcutaneous tunneling device, the leads of the stimulation electrode and the pressure sensor were led into the infraclavicular pocket and connected to the implanted pulse generator. Adequate functioning of the system was confirmed before closure.

therapy-withdrawal group.[29] This design filtered out persons who had not had a response to therapy. The therapy-withdrawal group had the device turned off for 7 days, whereas the therapy-maintenance group continued with the device turned on. Polysomnography was performed after the randomization period to measure the effects of therapy withdrawal, as compared with continued use of the therapy. For the 12-month nonrandomized phase of the study, participant enrollment commenced on November 10, 2010, and ended on March 23, 2013.

ADVERSE EVENTS

Adverse events were reported and then reviewed and coded by the clinical-events committee. Serious adverse events were defined as any events that led to death, life-threatening illness, permanent impairment, or new or prolonged hospitalization with serious health impairment.

STATISTICAL ANALYSIS

For the coprimary outcomes, the AHI and ODI scores at the 12-month follow-up were compared with the baseline measurements, which were the averages of the measurements obtained before implantation and at the 1-month preactivation visit, to determine a binary outcome of status with respect to response to the therapy. We estimated that 108 participants would need to be enrolled for the study to have 80% power to evaluate the primary outcome, with the exact one-sided binomial test set at a significance level of 2.5%. The changes in the Epworth Sleepiness Scale and FOSQ scores from the preimplantation screening to the 12-month visit were calculated for each participant. P values from a paired t-test were calculated for the secondary outcome measures.

In the randomized controlled therapy-withdrawal trial, the difference in mean AHI scores (i.e., the difference between scores obtained at the 12-month visit in the nonrandomized phase and those obtained at the end of the randomized phase) was compared between the therapy-maintenance group and the therapy-withdrawal group. We estimated that 40 participants would need to undergo randomization in a 1:1 ratio in order for the study to have 80% power to detect a significant difference between groups, at the 5% significance level, with the use of a two-sided t-test.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

The study population consisted of 126 participants (83% of whom were men), with a mean age of 54.5 years (range, 31 to 80) and mean BMI of 28.4 (range, 18.4 to 32.5). Per protocol, all the participants had a history of nonadherence to CPAP therapy; 17% of the participants had undergone a uvulopalatopharyngoplasty (surgery to remove excess upper-airway tissue) for the treatment of obstructive sleep apnea.

The mean time from the diagnosis of obstructive sleep apnea to study enrollment was 5.6 years. The mean AHI score on preimplantation screening polysomnography was 32.0 events per hour, and the mean ODI score was 28.9 events per hour. At the baseline visit before implantation, the mean FOSQ score was 14.3, and the mean Epworth Sleepiness Scale score was 11.6. The mean AHI score on the second baseline polysomnography was 31.9 events per hour. There was no significant difference between the two baseline AHI assessments (P=0.83).

A total of 124 of 126 participants (98%) completed the follow-up at 12 months. The mean BMI at 12 months was 28.5, which did not differ significantly from the mean BMI at baseline. The characteristics of the study cohort at baseline are presented in Table 1. Information on study enrollment, randomization, and follow-up are shown in Figure 2.

SURGICAL IMPLANTATION

The upper-airway stimulation device was successfully implanted in all 126 participants. The median time for surgical implantation was 140 minutes (range, 65 to 360). Participants were discharged after surgery on the same day (16% of participants), the next day (79%), or the second day after surgery (5%).

PRIMARY OUTCOMES

The scores on the AHI and ODI (primary outcome measures) were lower (indicating fewer episodes of sleep apnea) at 12 months than at baseline. The median AHI score decreased 68%, from the baseline value of 29.3 events per hour to 9.0 events per hour. The median ODI score decreased 70%, from 25.4 events per hour to 7.4 events per hour. At the 12-month visit, the

Table 1. Characteristics of the Study Population at Baseline.*

Characteristic	Participants (N=126)
Age — yr	54.5±10.2
Male sex — no. (%)	105 (83)
White race — no. (%)†	122 (97)
Body-mass index‡	28.4±2.6
Neck size — cm	41.2±3.2
Blood pressure — mm Hg	
Systolic	128.7±16.1
Diastolic	81.5±9.7
Hypertension — no. (%)	48 (38)
Diabetes — no. (%)	11 (9)
Asthma — no. (%)	6 (5)
Congestive heart failure — no. (%)	2 (2)
Uvulopalatopharyngoplasty — no. (%)	22 (17)

* Plus–minus values are means ±SD.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

criteria for the coprimary outcome of a reduction of at least 50% in the AHI score from baseline and an AHI score of less than 20 events per hour were met by 66% of the participants (83 of 126 participants; lower boundary of the 97.5% confidence interval [CI], 57). The criterion for the coprimary outcome of a reduction of at least 25% in the ODI score from baseline was met by 75% of participants (94 of 126; lower boundary of the 97.5% CI, 66). Both primary efficacy outcomes exceeded the predefined study objectives (Table 2).

SECONDARY OUTCOMES

Scores on the FOSQ and Epworth Sleepiness Scale indicated significant improvement at 12 months, as compared with baseline. The increase in the FOSQ score (mean change, 2.9 points; 95% CI, 2.4 to 3.5) exceeded the 2.0-point increase that is typically considered to be a clinically meaningful improvement. Similarly, the Epworth Sleepiness Scale score at 12 months was consistent with normalization of the measure (i.e., score <10.0). The median percentage of sleep time with the oxygen saturation less than 90% decreased from a baseline value of 5.4% to 0.9% at 12 months (Table 2).

THERAPY-WITHDRAWAL STUDY

Among the 46 consecutive participants with a response to therapy who underwent randomization, the demographic and clinical characteristics at baseline were similar with regard to age, BMI, neck size, and AHI and ODI scores. By design, participants who had not had a response were not included in this part of the study.

The AHI and ODI scores were similar in the two groups at 12 months (baseline of the randomized portion of the trial). There was a significant difference between the therapy-withdrawal group and the therapy-maintenance group with respect to the change in AHI scores from the beginning of the randomization period at 12 months to the assessment 1 week later. Among the 23 participants in the therapy-withdrawal group, the AHI score was significantly higher at the 1-week assessment than it was at the start of the randomized phase (25.8 vs. 7.6 events per hour, P<0.001). The average increase in the AHI score in the therapy-withdrawal group was 18.2 events per hour, whereas the average increase in the therapy-maintenance group was 1.7 events per hour (difference in changes in mean scores, 16.4±12.0 events per hour; P<0.001). A similar effect was observed with respect to the mean ODI scores (Fig. 3).

ADVERSE EVENTS

Two participants had a serious device-related adverse event requiring repositioning and fixation of the neurostimulator to resolve discomfort. A total of 33 serious adverse events not considered to be related to the implantation procedure or implanted devices were reported. Most of nonserious adverse events related to the procedure (88%) occurred within 30 days after implantation and were expected postsurgical events, including sore throat from intubation, pain at the incision site, and muscle soreness.

A total of 18% of the participants had temporary tongue weakness after surgery, which resolved over a period of days to weeks. No permanent tongue weakness was reported during the study. Among device-related events that were not considered to be serious, 40% of the participants reported some discomfort associated with stimulation, and 21% reported tongue soreness, including abrasion on the lower side of the tongue. These events were related to the functional

stimulation of the tongue muscles and the resulting tongue motion over the lower teeth. Most of these events resolved after the participants acclimated to the upper-airway stimulation therapy or after the device was reprogrammed to adjust the stimulation variables. In nine participants, a tooth guard was used to resolve tongue soreness or abrasion related to the device.

The overall rate of serious adverse events was less than 2%. A detailed list of adverse events is provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

DISCUSSION

Patients with moderate-to-severe obstructive sleep apnea may not have consistent clinical benefit from CPAP therapy owing to poor adherence to treatment.[30] These patients, if left untreated, remain at considerable risk for cardiovascular complications and death. In the current study, unilateral stimulation of the hypoglossal nerve, synchronous with ventilation, resulted in significant and clinically meaningful reductions in the severity of obstructive sleep apnea and self-reported sleepiness and improvements in quality-of-life measures at 1 year. The observed response rates, which were based on the primary outcome measures of AHI and ODI, consistently exceeded the previously defined threshold for surgical success.[12] The reduction in sleepiness and improvement in quality-of-life measures at 12 months were similar to previously reported effects of CPAP on moderate-to-severe obstructive sleep apnea.[28]

The effect of stimulation of the hypoglossal nerve with respect to obstructive events was first described by Schwartz et al. in 1993 in a feline model.[31] Subsequent studies showed that stimulation of the genioglossal muscle or the hypoglossal nerve could reverse inspiratory flow limitation during sleep.[17] The current study extended the observations that were reported by Eastwood et al. over a period of 6 months in a single-group interventional trial.[18] The feasibility studies conducted by our team identified a BMI of 32 or lower or an AHI score of 50 events per hour or less as phenotypic risk factors that favorably affect the success of upper-airway stimulation.[22,25] This approach may not be appropriate for persons with excessive airway collapsibility.[32] Screening potential participants by means of

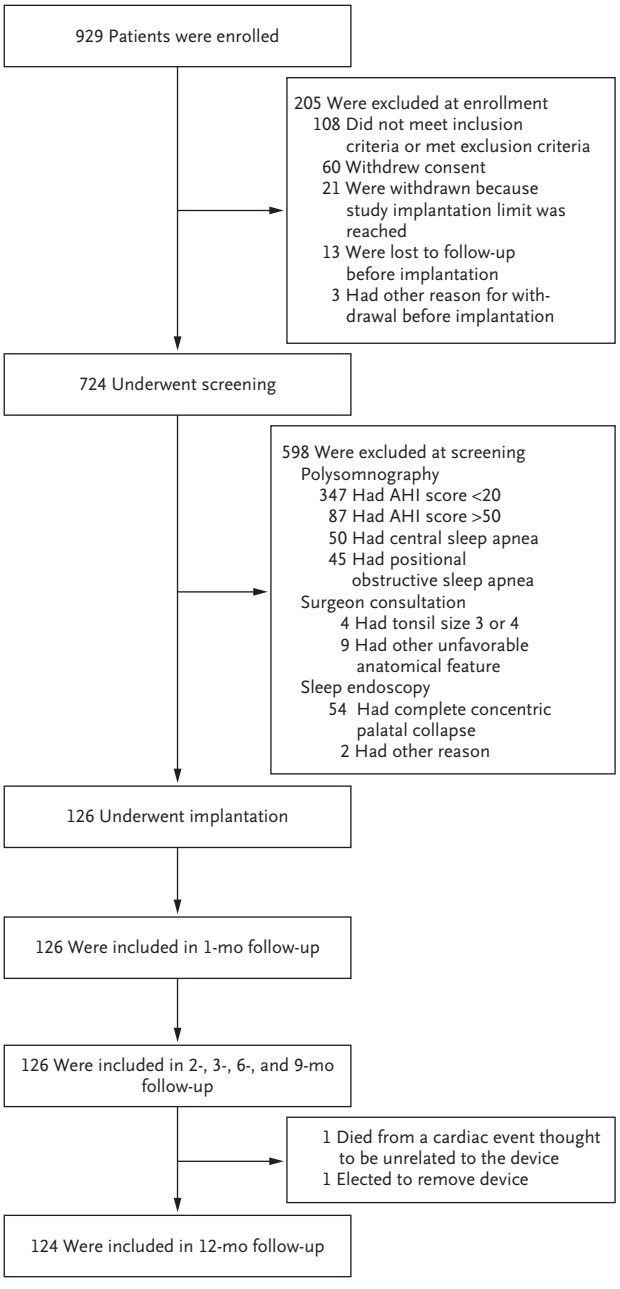

Figure 2. Study Enrollment.

Of 929 participants enrolled, 205 were excluded before undergoing a screening test. An additional 598 participants were excluded after the screening assessment, which included polysomnography, consultation with the surgeon, and endoscopy during sleep; 56 of these participants were excluded after the endoscopy was performed during drug-induced sleep (25% of the 222 participants who underwent the procedure). A total of 126 participants underwent implantation. The apnea–hypopnea index (AHI) measures the number of apnea or hypopnea events per hour. A tonsil size of 3 indicates that the tonsils are visible beyond the pillars, and a tonsil size of 4 that they extend to the midline.

endoscopy during drug-induced sleep helped to identify functional upper-airway collapse that was likely to be focused on the retrolingual region and therefore amenable to forward motion of the base of the tongue by means of neurostimulation.[25]

Surgical implantation of the upper-airway stimulation system was performed by otolaryngologists at 22 academic and private centers. None of the implantation procedures resulted in serious complications, participant rehospitalizations, or explantations because of infection. The serious adverse events in the two participants who required repositioning and fixation of the neurostimulator occurred 30 days after implantation and were related primarily to discomfort at the device location. The electrical stimulation of the hypoglossal nerve evokes a functional response of the tongue muscles and an anterior displacement of the tongue. The patient can feel the anterior displacement of the tongue during wakefulness when the stimulation is turned on. Similar to CPAP, therapeutic stimulation variables were determined during attended in-laboratory sleep studies.

The implanted upper-airway stimulation de-

Table 2. Primary and Secondary Outcome Measures.*

Outcome	Baseline	12 Months	Change	P Value
Primary outcomes				
AHI score†	32.0±11.8	15.3±16.1	−16.4±16.7	<0.001
Median	29.3	9.0	−17.3	
Interquartile range	23.7 to 38.6	4.2 to 22.5	−26.4 to −9.3	
ODI score‡	28.9±12.0	13.9±15.7	−14.6±15.8	<0.001
Median	25.4	7.4	−15.7	
Interquartile range	19.5 to 36.6	3.5 to 20.5	−24.0 to −8.6	
Secondary outcomes				
FOSQ score§	14.3±3.2	17.3±2.9	2.9±3.1	<0.001
Median	14.6	18.2	2.4	
Interquartile range	12.1 to 17.1	16.2 to 19.5	0.7 to 4.7	
Epworth Sleepiness Scale score¶	11.6±5.0	7.0±4.2	−4.7±5.0	<0.001
Median	11.0	6.0	−4.0	
Interquartile range	8.0 to 15.0	4.0 to 10.0	−8.0 to −1.0	
Percentage of sleep time with oxygen saturation <90%	8.7±10.2	5.9±12.4	−2.5±11.1	0.01
Median	5.4	0.9	−2.2	
Interquartile range	2.1 to 10.9	0.2 to 5.2	−6.6 to −0.3	

* Plus–minus values are means ±SD. Two participants did not complete follow-up at 12 months: one participant died unexpectedly 10 months after implantation owing to a cardiac event that was not thought to be related to the implant, and one requested explantation of the device because of personal choice. In the primary-outcome analysis, both participants were considered not to have had a response to therapy. Means, standard deviations, medians, and interquartile ranges are presented because some variables (e.g., the 12-month scores on the apnea–hypopnea index [AHI] and oxygen desaturation index [ODI]) show evidence of nonnormality.

† The AHI score indicates the number of apnea or hypopnea events per hour; a score of 15 or more events per hour indicates moderate-to-severe obstructive sleep apnea.

‡ The ODI score indicates the number of times per hour of sleep that the blood oxygen level drops by 4 percentage points or more from baseline.

§ Scores on the Functional Outcomes of Sleep Questionnaire (FOSQ) range from 5.0 to 20.0, with higher scores indicating better functioning. A score of more than 17.9 is considered to be the threshold for persons with normal sleep-related quality of life. A change of 2.0 or more points in the score is considered to indicate a clinically meaningful improvement of daily functioning.[28] Data at 12 months were missing for one participant in addition to the two who did not complete the 12-month follow-up.

¶ Scores on the Epworth Sleepiness Scale range from 0.0 to 24.0, with lower scores indicating less daytime sleepiness. Data at 12 months were missing for one participant in addition to the two who did not complete the 12-month follow-up.

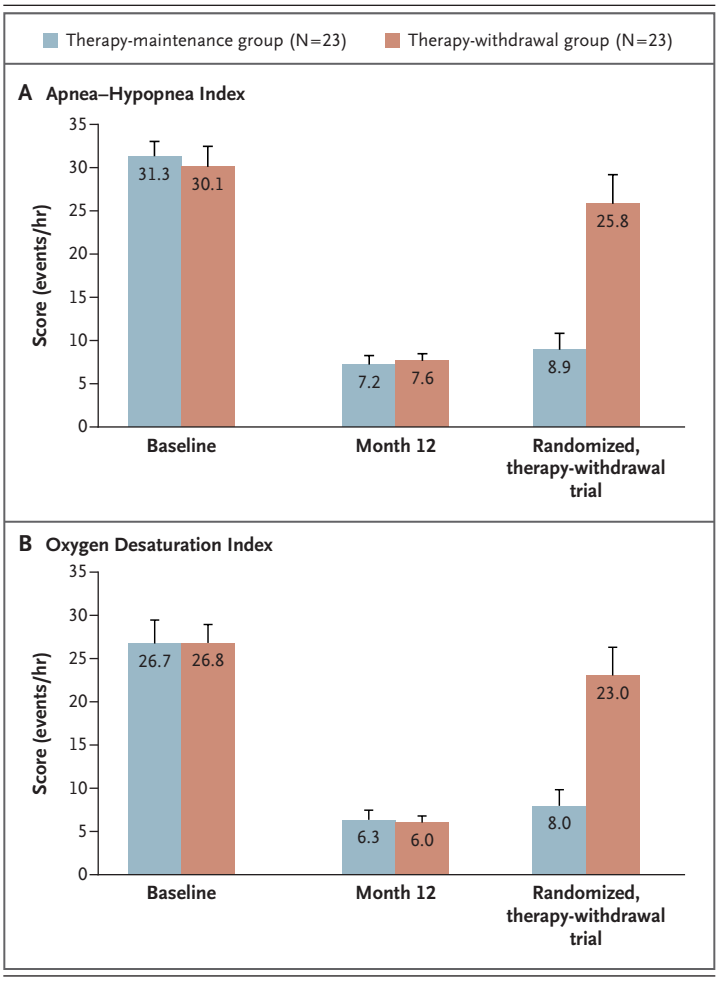

Figure 3. Primary Outcomes at 12 Months after Implantation and during the Randomized, Therapy-Withdrawal Trial.

After 12 months, 46 consecutive participants who had a response to therapy were randomly assigned, in a 1:1 ratio, to the therapy-maintenance group or the therapy-withdrawal group. The therapy-withdrawal group had the device turned off for at least 5 days during this phase, and it remained off until polysomnography was performed. The therapy-maintenance group continued nightly use of the device. There was a significant difference between the therapy-withdrawal group and the therapy-maintenance group with respect to the change in the apnea–hypopnea index score from the assessment at 12 months of the cohort study to the assessment at the end of the therapy-withdrawal study (difference in changes in mean scores, 16.4 events per hour; P<0.001) (Panel A). A similar effect was observed for the mean oxygen desaturation index scores (the number of times per hour of sleep that the blood oxygen level drops by ≥4 percentage points from baseline) (Panel B). Results are expressed as the mean values, with T bars representing standard errors.

vice eliminated adherence issues associated with wearing a CPAP mask. The daily use of upper-airway stimulation was 86%, as assessed on the basis of self-report (see the Supplementary Appendix). Objective use of the device, quantified as the time spent using the device each night, could not be directly reported with the current generation of the device. The average stimulation time per night was measured. This value accounts for the time predominately associated with the inspiratory phase of the breathing cycle. Assuming a normal duty cycle of 1:2.0 or 1:1.5, the average objective use would be in excess of 5 hours per night (see the Supplementary Appendix). Additional objective data on adherence will be required to confirm the findings of the current study.

The current study was designed to assess the severity and symptoms of obstructive sleep apnea before the implantation of the upper-airway stimulation device as compared with 12 months after implantation, with the use of a prospective single-group trial design in which the participants served as their own controls. Only participants who could not use CPAP, or who declined to do so, were recruited for the study. A control group of therapeutic CPAP users (i.e., a comparative-effectiveness design) would be impractical, given the current study design.

Some participants had a significant increase in the AHI score at month 12 (see the Supplementary Appendix). An additional analysis of the association between the baseline characteristics and outcome measures did not identify predictors that differentiated between participants who had a response and those who did not.

The randomized, controlled therapy-withdrawal study in which some participants had the therapy turned off for 1 week provided evidence that the therapeutic effect established at 12 months was attributable to the upper-airway stimulation therapy, rather than variability in the AHI score. The randomized phase included only consecutive participants who had had a response to therapy and, as a result, does not provide information on participants who did not have a response to therapy.

By design, this trial enrolled participants with moderate-to-severe obstructive sleep apnea who had various difficulties adhering to CPAP and who did not have clinically significant central or mixed sleep apnea or complete

concentric collapse at the retropalatal airway on endoscopy during drug-induced sleep. The cohort had a reduction in the severity of obstructive sleep apnea, and the adverse-event profile was acceptable.

Supported by Inspire Medical Systems.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Christopher P. O'Donnell, Ph.D., for comments on an earlier version of the manuscript.

APPENDIX

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Volcano National Park, Hawaii, 2012 Zia Farooki, M.D.

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Original Research—Sleep Medicine and Surgery

Otolaryngology–Head and Neck Surgery
2017, Vol. 156(2) 378–384

DOI: 10.1177/0194599816683378
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Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. Selective stimulation of the hypoglossal nerve is a new surgical therapy for obstructive sleep apnea, with proven efficacy in well-designed clinical trials. The aim of the study is to obtain additional safety and efficacy data on the use of selective upper airway stimulation during daily clinical routine.

Study Design. Prospective single-arm study.

Setting. Three tertiary hospitals in Germany (Munich, Mannheim, Lübeck).

Subjects and Methods. A multicenter prospective single-arm study under a common implant and follow-up protocol took place in 3 German centers (Mannheim, Munich, Lübeck). Every patient who received an implant of selective upper airway stimulation was included in this trial (apnea-hypopnea index $\geq$15/h and $\leq$65/h and body mass index $<$35 kg/m^2). Before and 6 months after surgery, a 2-night home sleep test was performed. Data regarding the safety and efficacy were collected.

Results. From July 2014 through October 2015, 60 patients were included. Every subject reported improvement in sleep and daytime symptoms. The average usage time of the system was 42.9 $\pm$ 11.9 h/wk. The median apnea-hypopnea index was significantly reduced at 6 months from 28.6/h to 8.3/h. No patient required surgical revision of the implanted system.

Conclusion. Selective upper airway stimulation is a safe and effective therapy for patients with obstructive sleep apnea and represents a powerful option for its surgical treatment.

Keywords

obstructive sleep apnea, surgical treatment, hypoglossal nerve, selective upper airway stimulation, German postmarket study

Received June 30, 2016; revised September 23, 2016; accepted November 18, 2016.

Obstructive sleep apnea (OSA) has an increased prevalence over the prior decades, present in 6% of women and 13% of men in the United States.[1] Continuous positive airway pressure (CPAP) is the gold standard therapy; however, it is limited by adherence and acceptance issues. Alternative treatment options have been developed, including upper airway stimulation (UAS) per the unilateral respiration-synchronized stimulation of the hypoglossal nerve.[2,3] This approach to electrical stimulation based on implanted neuromodulation technology was demonstrated to be a safe and effective treatment for OSA in a recent large clinical trial.[3] For selected patients with moderate to severe OSA who were CPAP intolerant, the UAS system reduced OSA severity both objectively, as measured by apnea-hypopnea index (AHI) and oxygen desaturation index (ODI), and subjectively, through improved quality-of-life measures—namely, the Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ)—all evaluated at 12 months postimplantation.[3] Randomized withdrawal of therapy for 1 week at 13 months resulted in return of AHI, ODI, ESS, and FOSQ to baseline levels, and reactivation reestablished therapeutic efficacy as measured at 18 months.[4] More recently, long-term follow-up of the study cohort reported sustained treatment effects and therapy adherence after 24 and 36 months of implantation.[5,6] In addition, 2 single-center studies in a clinical practice setting demonstrated that UAS was associated with high adherence, low morbidity, and significantly decreased AHI.[7,8]

Previous studies have identified specific selection criteria for patients who are likely to respond to UAS.[9-13] Individuals with body mass index $<$32 or $<$35 kg/m^2 had a lower AHI at 6

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This article was presented at the 2016 AAO-HNSF Annual Meeting & OTO EXPO; September 18-21, 2016; San Diego, California.

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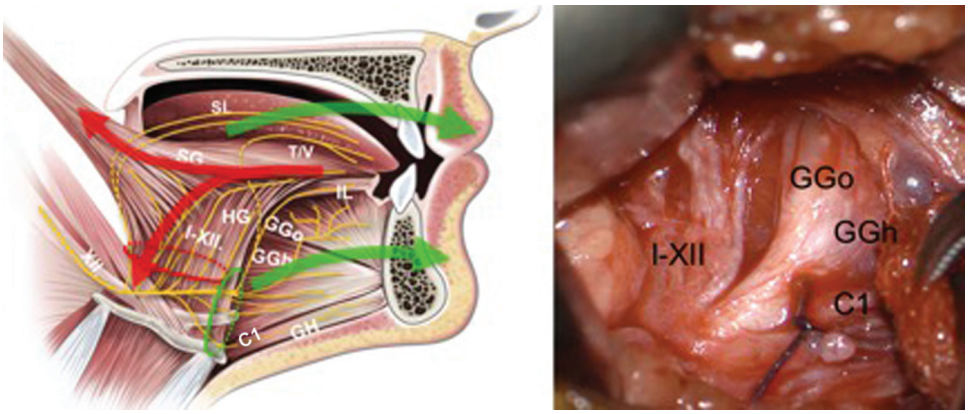

Figure 1. Schematic and intraoperative figure of the terminating hypoglossal nerve branches. Green ellipse indicates branches targeted for cuff placement. C1, first cranial nerve; GGo/GGh, oblique/horizontal genioglossus muscle; GH, geniohyoid muscle; HG, hyoglossus muscle; I-XII, lateral branches of hypoglossal nerve; SG, styloglossus muscle; SL/IL, superior/inferior longitudinal muscles; T/V, transversal/vertical intrinsic muscles; XII, hypoglossal nerve.

months with treatment.[3,9,12-14] A specific pattern of collapse—namely, complete concentric collapse at the retropalatal airway—during a screening drug-induced sedated endoscopy prior to implantation was associated with reduced level of response.[10] The complete concentric collapse pattern can be found in >20% of otherwise suitable candidates and is associated with higher body mass index and AHI.[15] These success/failure predictors merit additional supporting evidence from the clinical practice setting for their utility in ongoing patient selection.

This multicenter prospective study focuses on objective and patient-reported outcomes and therapy adherence of UAS for treatment of OSA in a clinical practice setting at 3 academic centers. The study intends to determine if treatment outcome reported in a previous controlled clinical trial setting can be achieved in a routine clinical setting.

Methods

This multicenter prospective clinical trial included OSA patients who received an implanted UAS system (Inspire Medical Systems, Minneapolis, Minnesota). The study was approved by the ethics committee at all 3 institutions and was registered as NCT02293746 on clinicaltrials.gov.

Patient Selection

Key study selection criteria were based on those established from the STAR trial.[3] Patients with a history of moderate to severe OSA and nonadherence to CPAP underwent screening for qualification of implantation as part of routine clinical practice. Patients with body mass index >35 kg/m^2 were excluded. Additional screening included a 2-night home sleep test and drug-induced sedated endoscopy. Patients were excluded if they presented with AHI <15 or >65, central sleep apnea >25% of total AHI, or complete concentric collapse at the velopharynx during drug-induced sedated endoscopy.

Implantation

The surgical implantation procedure was performed in accordance with previously established operative techniques.[16,17] The standardized operative procedure included (1) placing a cuff electrode on the distal branches of the hypoglossal nerve to stimulate the tongue protrusors, (2) inserting an implanted pulse generator in the right upper chest, and (3) placing a respiratory sensing lead between external and internal intercostal muscles of the ribs. The targeted stimulation site on the hypoglossal nerve aimed to recruit genioglossus and transversal/vertical muscles while excluding styloglossus and hyoglossus muscle activation. Furthermore, a branch of the first cranial nerve—which is responsible for the geniohyoid muscle activation and which runs parallel to the hypoglossal nerve—was also included when feasible. Both intraoperative nerve monitoring and visualization of tongue motion were used to confirm proper electrode placement,[17,18] as shown in **Figure 1**.

All patients were discharged on their regular diets and were advised to avoid strenuous physical activities involving the right arm—ipsilateral side of implant—for 2 weeks postoperatively.

Data Collection and Statistical Analysis

The device was activated 1 month after implantation, followed by a month of therapy acclimatization, with patients gradually increasing the stimulation amplitude to optimize both comfort and subjective effectiveness. Between months 2 and 6, in-laboratory titration studies were conducted to optimize therapy during polysomnography (ie, full polysomnography titration). While the majority of patients required only 1 titration night, some warranted a second titration to further optimize and individualize therapy. Fifteen patients had a second titration night after 3 months of implantation. This was conducted if the first titration night was not acceptable, and the decision was made at each implant center. During the second overnight polysomnography, advanced testing of specific electrode configurations, stimulation timing, and impulse settings was performed, all of which were not routinely tested during the first polysomnography. Two-night home sleep test studies were recorded with level III polygraphy systems to determine objective outcomes at 6

Figure 2. Treatment and follow-up pathway of selective upper airway stimulation for obstructive sleep apnea. DISE, drug-induced sedated endoscopy; PSG, polysomnography.

Table 1. Patients Characteristics at Enrollment (N = 60).[a]

Characteristic	Mean ± SD	Range
Age, y	56.8 ± 9.1	37-75
BMI, kg/m^2	28.8 ± 3.6	21.4-36.6
AHI, events/h	31.6 ± 14.4	13.4-64.5
ODI, events/h	28.5 ± 16.6	3.5-71.5
FOSQ score	13.2 ± 3.6	3.3-19.6
ESS	12.4 ± 5.7	2-24

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; ODI, oxygen desaturation index.
[a]Men, n = 58; women, n = 2.

months without device adjustment. The objective outcomes of AHI and ODI were scored with standard 2007 scoring criteria,[19] with hypopnea scored according to 30% airflow reduction and 4% oxygen desaturation. Patient-reported outcomes included ESS and the FOSQ at baseline (preimplant) and months 2 and 6 (postimplant). The treatment and follow-up pathway, as applied, is shown in **Figure 2**.

SPSS 23.0 software (IBM, Chicago, Illinois) was used. Descriptive statistics were calculated for demographic variables. Paired *t* test was used to compare baseline and postimplantation values. Data are given as median and mean ± SD. *P* values ≤.05 were considered statistically significant.

Results

Characteristics of the Participants

Patient characteristics are summarized in **Table 1**. The majority of participants presented with moderate to severe OSA during the screening sleep studies and moderate symptoms of daytime sleepiness and diminished OSA-relevant quality of life.

All patients had failed CPAP as a first-line treatment. Among them, 14 patients had also attempted oral appliance therapy but could not maintain adherence, primarily due to insufficient efficacy. A total of 15 patients had prior upper airway OSA operations, which included uvulopalatopharyngoplasty (UPPP), uvulopalatal flap, genioglossus advancement, tongue base reduction, advancement/stabilization of the tongue base, and epiglottoplasty.

Surgical Implantation

The average implantation procedures were 160.0 ± 35.9 minutes in duration, ranging from 113 to 329 minutes. Right tongue base or bilateral protrusion was confirmed with perioperative stimulation testing among all patients. Only 1 patient did not show a clear protrusion during the implant procedure but subsequently demonstrated right tongue base protrusion at postoperative visits.

Polygraphic Outcomes

The objective outcome from the polygraphic study consisted of 2-night at-home sleep studies at baseline for screening prior to implant and again at 6 months postoperatively for therapy efficacy validation (see **Table 2** and **Figure 3**). The average values of the 2 home sleep studies were used for comparison analysis. Out of 60 participants, 56 completed the 6-month polygraphy studies. Of the 4 patients who did not complete the 6-month visit, 4 underwent a UPPP surgery after the 2-month titration studies and missed the 6-month visit.

Among the 56 patients who completed the 6-month visit, an average AHI reduction of 61% ± 24% compared with baseline was achieved. At the 6-month visit, 25% of patients presented with an AHI ≤5 events per hour; 59% patients, AHI ≤10/h; and 70% patients, AHI ≤15/h. Per the Sher criteria (AHI <20 with at least 50% reduction), 68% patients were classified as responders.[20] With the 4 patients who underwent a UPPP and missed the 6-month visit, a success rate of 63% was found. There was a statistically significant reduction in ODI, apnea index, hypopnea index, and minimal SpO_2 nadir from baseline to 6 months. Total and percentage sleep time with SpO_2 <90% decreased, though neither achieved statistical significance.

Patient-Reported Outcomes

At the 2-month visit, there was significant reduction in daytime sleepiness as measured by the ESS and significant improvement in daytime functioning as measured by the FOSQ compared with baseline. Both ESS and FOSQ scores further improved at the 6-month visit from the baseline as well as the 2-month visit (see **Table 3**).

Adverse Events

Two procedure-related adverse events were recorded. In both cases, bleeding occurred during tunneling of the

Table 2. Polygraphic Outcomes at Baseline and 6 Months.[a]

	Baseline	6 mo	*P* Value
AHI, events/h			<.001
Mean ± SD	31.2 ± 13.2	12.0 ± 9.8	
Median (range)	28.6 (12.3-64.5)	8.3 (0.8-34)	
ODI, events/h			<.001
Mean ± SD	27.6 ± 16.4	13.5 ± 10.7	
Median (range)	27.0 (3.5-60.9)	9.6 (0.5-35.5)	
Apnea index, events/h			<.001
Mean ± SD	18.1 ± 14.7	7.6 ± 7.8	
Median (range)	14.2 (2.2 -64.5)	4.9 (0-33.7)	
Hypopnea index, events/h			<.001
Mean ± SD	13.0 ± 7.2	4.4 ± 4.1	
Median (range)	12.4 (0-33.7)	3.2 (0.2-20.4)	
Central + mixed apnea index, events/h			.27
Mean ± SD	1.2 ± 2.3	0.8 ± 1.1	
Median (range)	0.4 (0-11)	0.3 (0-4.6)	
Min SpO_2, %			<.001
Mean ± SD	71.4 ± 11.4	80.4 ± 7.6	
Median (range)	73.8 (50.5-88)	81 (65-90.5)	
Mean SpO_2, %			.41
Mean ± SD	92.8 ± 1.9	93.2 ± 3.4	
Median (range)	93 (86.5-97)	93.5 (73-97)	
Total sleep time SpO_2 <90%, min			.07
Mean ± SD	45.3 ± 60.5	25.8 ± 34.8	
Median (range)	13.4 (0-272)	8.8 (0-141)	
Percentage sleep time SpO_2 <90%			.26
Mean ± SD	10.7 ± 13.9	7.1 ± 12.1	
Median (range)	3.2 (0-56.7)	2 (0-75.5)	

[a]Averaged 2-night results from all 56 subjects who completed the 6-month visit. $P < .05$ vs baseline.

stimulation lead from the neck incision to the device pocket. Five patients reported postoperative pain related to the incisions. There was 1 instance of acute tongue numbness and 1 incidence of dysarthria, and both resolved within 2 months without further incident.

Three device-related adverse events were reported, all 3 relating to painful stimulation sensation in the period after therapy activation. One of these was a complaint of mild pain at all 3 device locations, and this patient continues to be monitored. The other instances of postactivation pain resolved without intervention or issue, resolving as patients acclimated to therapy use. One patient complained of speech difficulties after the therapy was activated, but this was resolved through reprogramming the stimulation energy field parameters, thereby improving the patient's subjective experience while maintaining suitable objective tongue motion as assessed by the managing physician.

Therapy Use

Device interrogation at the 6-month visit indicated 42.9 ± 11.9 h/wk (range, 9-64 h/wk) of therapy use among all patients, based on recording by the implanted device. The average stimulation amplitude was 1.9 ± 0.6 V (range, 1.0-3.5) and 1.9 ± 0.6 V (range, 1.0-3.9) at the 2- and 6-month visits, respectively.

Discussion

In this multicenter prospective study, UAS reduced OSA severity and improved patient-reported outcomes. Seventy percent of the study cohort reached AHI <15 at 6 months' postimplant. This result was consistent with the STAR trial outcomes reported at 12, 18, and 36 months of follow-up.[3,5] Patient-reported outcomes measured by ESS and FOSQ demonstrated a similar degree of improvement as in the STAR trial. No serious adverse events were observed, and minor complaints and side effects were either managed in the outpatient clinic setting or resolved spontaneously via therapy acclimatization. Therapy acceptance and adherence were high, as shown by objective device usage data.

The study followed the current routine clinical practice for patient selection, operative techniques, and therapy titration. The key patient selection criteria included body mass index <35, AHI between 15 and 65, and absence of complete concentric collapse at the soft palate during drug-induced sedated endoscopy. The implant techniques were standardized in this study as well as in clinical practice to

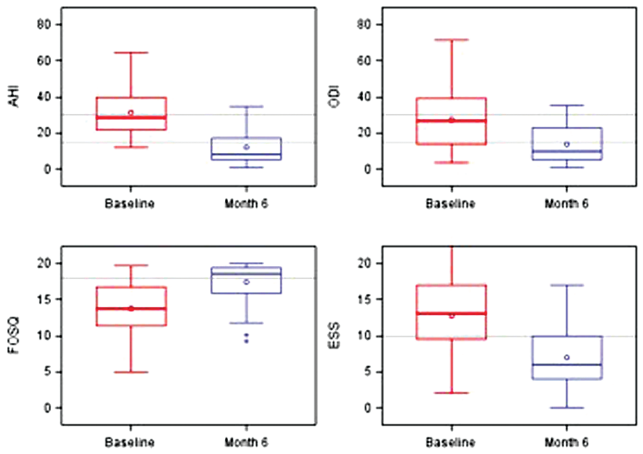

Figure 3. Primary outcomes of the clinical trial in terms of apnea-hypopnea index (AHI), oxygen desaturation index (ODI), Functional Outcomes of Sleep Questionnaire (FOSQ), and Epworth Sleepiness Scale (ESS) between baseline and 6-month visit. All results were statistically significant ($P < .05$ vs baseline).

include (1) the protrusor branches of the hypoglossal nerve, which innervate the genioglossus muscle, and (2) the stiffener branches of the transverse/vertical muscles, while excluding all retractor branches that innervate the styloglossus and hyoglossus muscles.[17] All patients enrolled in this study displayed either contralateral extension or bilateral protrusion of the tongue upon stimulation. Heiser et al showed a clear association of selective stimulation of protrusor muscles for better therapy outcomes, when excluding all branches of the retractor muscles.[18] The current study reflected a consistent implementation of the standardized operative techniques.[17] There is a considerable proportion of genioglossus muscle fibers that receive innervation from the hypoglossal nerve in the contralateral side, which may explain the bilateral protrusion observed, despite the overtly unilateral stimulation of the hypoglossal nerve (ie, crosstalk from right to left) seen in an extensive proportion of patients.[21]

Adverse events were rare. The surgical procedure was safe, and the few adverse events were solved without sequelae. Regarding the bleeding during tunneling, evidence with knowledge of patient anatomy would suggest that these minor bleeds are attributable to either an anterior branch of the external jugular vein or a prominent vein of the sternocleidomastoid muscle. Conservative management of such tunneling bleeds by external compression was the most appropriate approach to manage this complication. If necessary, a small fourth incision for direct visualization of the lacerated vein and accompanying closure with suture or equivalent may be performed. Neurapraxia of the hypoglossal and/or marginal mandibular nerves, potentially associated with this procedure, were infrequent and transient within this patient population, consistent with the STAR trial.

This multicenter study and an earlier single-center study reported objective therapy use of UAS of approximately 6 to 7 hours per night based on information retrieved from the implanted device after 6 months.[7,8] Although additional adherence data are needed for longer follow-up duration, the adherence of UAS at 6 months is considerably higher than the average 4.7 hours per night for CPAP use as reported in the APPLES study after 6 months[22] and 3.7 to 4.7 hours per night reported in the HomePAP study after 3 months.[23] This current study cohort included patients who previously could not adhere to CPAP. The improved adherence with UAS is suggestive of its clinical utility for longitudinal patient management for OSA symptoms and risks from OSA-related comorbidities, meriting further prospective study.

In addition, patients qualifying for this UAS therapy, a priori, skewed toward failure by virtue of being demonstrably refractory to successful treatment with CPAP, as a precondition to qualify for UAS. One plausible explanation may be that patients choosing to undergo significant surgery for such a device are probably better educated in terms of OSA and its sequelae with the necessity of treatment. It is widely accepted and reasonably well validated that patients who are recipients of concomitant educational, supportive, and behavioral interventions are improving their CPAP usage over time, and that is likely the case with UAS as well for this patient phenotype.[24] Finally, patients who are profound sufferers of untreated OSA would be more likely to select UAS versus patients with minimal symptoms and

Table 3. Patient-Reported Outcomes at Baseline and 2- and 6-Month Follow-up.

				P Value		
	Baseline	2 mo	6 mo	Baseline vs 2 mo	Baseline vs 6 mo	2 mo vs 6 mo
ESS				<.001	<.001	<.001
Mean ± SD	12.8 ± 5.4	9.0 ± 4.8	7.0 ± 4.5			
Median (range)	13.5 (2-24)	8.0 (0-21)	6.0 (0-17)			
FOSQ				<.001	<.001	.002
Mean ± SD	13.2 ± 3.5	15.2 ± 4.1	16.9 ± 2.9			
Median (range)	13.3 (5-19.8)	15.7 (5.1-20)	17.8 (9.2-20)			

Abbreviations: ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes Sleep Questionnaire.

OSA, who would probably not opt for this treatment, given the moderately invasive surgical procedure and permanent in-dwelling electrotherapeutic device system. Our data support the already-published UAS study results showing that patients nonadherent to CPAP can be adherent to UAS if properly selected.

Of further interest as it pertains to hypothesis generation, a recent systematic review found that a 1-hour-per-night increase in CPAP use was associated with an additional reduction of systolic blood pressure of 1.5 mm Hg.[25] The improved UAS therapy use may have clinical implications for reducing cardiovascular risks associated with untreated OSA. This area, of course, needs to be studied through further clinical trials.

In comparing the surgical treatment of UAS and its safety profile with other OSA operations, the procedure seems to be safe and without long-lasting side effects for typical patients. Two cases (3%) were reported with bleeding during tunneling, both of which were resolved without any sequelae. Another instance occurred during previous phases of UAS study and was similarly resolved. Numbness of tongue and dysarthria for a few days after surgery were reported in 2 other cases. As compared with similar types of nerve dissection/surgery, the incidence numbers are acceptably low. In parotid surgery, the temporary facial palsy rate is around 40.2% on the first postoperative day and 1.6% at 12 months.[26] If the subjective dysarthria is a result of a palsy of the hypoglossal nerve, then the equivalent risk is <2% for the first postoperative days and 0% for the long term, representing a suitably low morbidity for essential hypoglossal nerve functioning in the postsurgical and chronic settings. The small numbers of reported numbness of the tongue cannot readily be explained by the UAS surgery, due to its widely accepted functions for efferent-only motor innervation; yet, perhaps the lingual nerve may occasionally be encountered (eg, ptotic sublingual gland and accompanying nerve) and traumatized through retraction or other elements of accessing, visualizing, and placing the stimulation cuff around the hypoglossal nerve.

Furthermore, this clinical trial shows that even the self-reported outcomes of the patients significantly improved (as measured by the ESS and FOSQ). Polysomnography measures alone do not capture important aspects of OSA. The quality of life depending on daytime sleepiness could be enhanced. This effect has clinical and economic relevance.

Overall, surgical treatment with a fully implanted electrotherapeutic device system for selective UAS appears to be a safe procedure in the clinical setting. Additionally, in the event that the therapy is ultimately unsuitable for a particular patient, there is no overt anatomy-altering element to this procedure, and it is essentially reversible for such patients who may choose to have an underperforming system completely explanted (ie, reversible vs a failed UPPP).

Conclusion

Selective UAS reduced OSA severity and improved patient-reported quality-of-life outcome measures. Therapy adherence was high after 6 months of follow-up. Surgical and stimulation-related morbidity were low. This multicenter study further strengthened the evidence that the treatment can be successfully translated from the previous controlled trial setting into routine clinical practice.

Author Contributions

Clemens Heiser, conception and design, data acquisition, data analysis and interpretation, drafting the article, final approval, accountability for all aspects of the work; **Joachim T. Maurer**, conception and design, data acquisition, data analysis and interpretation, drafting the article, final approval, accountability for all aspects of the work; **Benedikt Hofauer**, data analysis, drafting, final approval, accountability for all aspects of the work; **J. Ulrich Sommer**, data analysis, drafting, final approval, accountability for all aspects of the work; **Annemarie Seitz**, data analysis, drafting, final approval, accountability for all aspects of the work; **Armin Steffen**, conception and design, data acquisition, data analysis and interpretation, drafting the article, final approval, accountability for all aspects of the work.

Disclosures

Competing interests: Clemens Heiser—study investigator and consultant of Inspire Medical Systems (received personal fees, travel expenses, and research grants); Joachim T. Maurer—study investigator and consultant of Inspire Medical Systems (received personal fees, travel expenses, and research grants), consultant for Nyxoah, an invited speaker for Revent and ImThera; Benedikt Hofauer—study investigator of Inspire Medical Systems (received personal fees and travel expenses); J. Ulrich Sommer—study investigator of Inspire Medical Systems (received personal fees and travel expenses); Armin Steffen—study investigator and consultant of Inspire Medical Systems (received personal fees, travel expenses, and research grants).

Sponsorships: Inspire Medical Systems (Maple Grove, Minnesota).

Funding source: Inspire Medical Systems (Maple Grove, Minnesota).

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Incisional Hernias

Question: Should incisional hernias be added to the lower, unfunded hernia line?

Question source: OHA Hearings Division; Dr. Alison Little, CCO medical director

Issue: Incisional hernias located in the abdomen are classified as ventral hernias. From the American College of Surgeons: "A ventral hernia is a bulge through an opening in the muscles on the abdomen. The hernia can occur at a past incision site (incisional), above the naval (epigastric) or other weak muscles sites (primary abdominal)." Ventral hernias without obstruction or gangrene are located on the lower hernia line. Incisional hernias are only on the upper hernia line. OHA Hearings had a recent case involving an incisional hernia and asked for clarification about whether these hernias should be treated as ventral hernias.

Dr. Little requested that ICD-10 K43.0 (Incisional hernia with obstruction, without gangrene) be added to the lower hernia line, as one sub-diagnosis for this code is "Incarcerated incisional hernia, without gangrene." ICD-10 K46.0 (Unspecified abdominal hernia with obstruction, without gangrene) also should be added to the lower hernia line, as it has a similar sub-diagnosis: "Unspecified incarcerated abdominal hernia." Similarly, K43.3 (Parastomal hernia with obstruction, without gangrene) can be used to code for "Incarcerated parastomal hernia, without gangrene" and K43.6 (Other and unspecified ventral hernia with obstruction, without gangrene) can be used to code for "Incarcerated hypogastric hernia (and similar types of hernia) without gangrene."

Current Prioritized List status:

ICD-10 Code	**Code Description**	**Placement**
K43.0	Incisional hernia with obstruction, without gangrene	168 COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER; PERSISTENT HYDROCELE
K43.1	Incisional hernia with gangrene	168
K43.2	Incisional hernia without obstruction or gangrene	522 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER OR DIAPHRAGMATIC HERNIA)
K43.3	Parastomal hernia with obstruction, without gangrene	168
K43.6	Other and unspecified ventral hernia with obstruction, without gangrene	168
K43.9	Ventral hernia without obstruction or gangrene	522
K46.0	Unspecified abdominal hernia with obstruction, without gangrene	168

HERC staff recommendations:

1) Add the following ICD-10 codes to line 522 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER OR DIAPHRAGMATIC HERNIA) and keep on line 168
    a. K43.0 (Incisional hernia with obstruction, without gangrene)
    b. K43.3 (Parastomal hernia with obstruction, without gangrene)
    c. K43.6 (Other and unspecified ventral hernia with obstruction, without gangrene)
    d. K46.0 (Unspecified abdominal hernia with obstruction, without gangrene)
2) Modify GN24 as shown below:

GUIDELINE NOTE 24, COMPLICATED HERNIAS

Lines 168,522

Complicated hernias are included on Line 168 if they cause symptoms of intestinal obstruction and/or strangulation. Incarcerated hernias (defined as non-reducible by physical manipulation) are also included on Line 168, excluding incarcerated ventral hernias. Incarcerated ventral hernias (including incarcerated abdominal incisional hernias) are included on Line 522, because the chronic incarceration of large ventral hernias does not place the patient at risk for impending strangulation. ICD-10 K43.0, K43.3, K43.6 and K46.0 are included on line 522 when used to designate incarcerated abdominal incisional hernias without intestinal obstruction or gangrene.

Robotic Assist Surgery

Question: Should robotic assist surgery be placed on the non-cost effective services line?

Question source: Holly Jo Hodges, MD, CCO medical director

Issue: HCPCS S2900 (Surgical techniques requiring use of robotic surgical system) is currently Ancillary, but closed to payment. CCOs have been routinely denying these claims due to lack of a fee schedule entry. However, Dr. Hodges is concerned that if the codes remains on the Ancillary List, it will be open to claims and hard to deny payment. She is requesting a review of this technology.

In robotic-assisted surgery, the same instruments used in laparoscopic surgery are connected to a robotic device that allows for 3-dimensional visualization, greater range of motion of the instruments, and improved ergonomics for the surgeon. Extensive marketing and competition among hospitals have led to widespread use of robotic surgery for a broad range of procedures, but it remains controversial because of its increased costs and lack of evidence of improved outcomes compared with non-robotic minimally invasive approaches.

Evidence:
Note: systematic reviews and meta-analyses are included for various types of surgeries

1) **Liu 2016**, Cochrane review of robotic assisted gynecologic surgery: http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD011422/epdf
    a. N=6 RCTs (517 patients).
        i. N=4 for hysterectomy (317 patients)
        ii. N=2 sacrocopopexy (146 women)
        iii. Compared robotic assist to conventional laparoscopic surgery (CLS) or vaginal hysterectomy
    b. Moderate-quality evidence was found for the effects of RAS on intraoperative injury when compared with CLS (RR 1.23, 95% CI 0.44 to 3.46; participants = 415; studies = 5; I2 = 0%), along with low-quality evidence for bleeding and infection complications.
    c. Mean total operating time was consistent across procedures and on average was about 42 minutes longer in the RAS arm compared with the CLS arm (95%CI 17 to 66 minutes; participants = 294; studies = 4; I2 = 82%; moderate-quality evidence).
    d. Mean hospital stay for hysterectomy procedures was on average about seven hours shorter in the RAS arm than in the CLS arm (mean difference (MD) -0.30 days, 95% CI -0.54 to -0.06; participants = 217; studies = 2; I2 = 0%; low-quality evidence).
    e. Limited data from two studies suggest that RAS for sacrocolpopexy may be associated with increased postoperative pain compared with CLS; this needs further investigation.
    f. **Authors' conclusions** We are uncertain as to whether RAS or CLS has lower intraoperative and postoperative complication rates because of the imprecision of the effect and inconsistency among studies when they are used for hysterectomy and sacrocolpopexy. Moderate-quality evidence suggests that these procedures take longer with RAS but may be associated with a shorter hospital stay following hysterectomy. We found limited evidence on the effectiveness and safety of RAS compared with CLS or open surgery for surgical procedures performed for gynaecological cancer; therefore its use should be limited to clinical trials.

2) **Ilic 2017**, Cochrane review of laparoscopic (LRP) and robotic assist radical prostatectomy (RARP) surgery vs open surgery
    a. N=2 RCTs (446 patients)
    b. Based on data from one trial, RARP likely results in little to no difference in urinary quality of life (MD -1.30, 95% CI -4.65 to 2.05) and sexual quality of life (MD 3.90, 95% CI - 1.84 to 9.64). We rated the quality of evidence as moderate for both quality of life outcomes, downgrading for study limitations.
    c. Based on one trial, RARP may result in little to no difference in overall surgical complications (RR 0.41, 95%CI 0.16 to 1.04) or serious postoperative complications (RR 0.16, 95% CI 0.02 to 1.32). We rated the quality of evidence as low for both surgical complications, downgrading for study limitations and imprecision.
    d. Based on two studies, LRP or RARP may result in a small, possibly unimportant improvement in postoperative pain at one day (MD - 1.05, 95% CI -1.42 to -0.68) and up to one week (MD -0.78, 95% CI -1.40 to -0.17).We rated the quality of evidence for both time points as low, downgrading for study limitations and imprecision.
    e. Based on one study, RARP likely results in little to no difference in postoperative pain at 12 weeks (MD 0.01, 95% CI -0.32 to 0.34). We rated the quality of evidence as moderate, downgrading for study limitations.
    f. Based on one study, RARP likely reduces the length of hospital stay (MD -1.72, 95% CI -2.19 to -1.25). We rated the quality of evidence as moderate, downgrading for study limitations.
    g. Based on two studies, LRP or RARP may reduce the frequency of blood transfusions (RR 0.24, 95% CI 0.12 to 0.46). Assuming a baseline risk for a blood transfusion to be 8.9%, LRP or RARP would result in 68 fewer blood transfusions per 1000 men (95% CI 78 fewer to 48 fewer). We rated the quality of evidence as low, downgrading for study limitations and indirectness.
    h. **Authors' conclusions** There is no high-quality evidence to inform the comparative effectiveness of LRP or RARP compared to ORP for oncological outcomes. Urinary and sexual quality of life-related outcomes appear similar. Overall and serious postoperative complication rates appear similar. The difference in postoperative pain may be minimal. Men undergoing LRP or RARP may have a shorter hospital stay and receive fewer blood transfusions. All available outcome data were short-term, and this study was unable to account for surgeon volume or experience.
3) **Lang 2014**, Systematic Review and Meta-analysis Comparing Robotic-Assisted Thyroidectomy (RT) and Conventional Open Thyroidectomy (COT)
    a. N=11 studies (no RCTs), 2,375 patients
    b. RT was significantly associated with longer operating time ($p<0.001$), hospital stay ($p = 0.023$) and higher temporary recurrent laryngeal nerve (RLN) injury ($p = 0.016$)
    c. Blood loss ($p = 0.485$), temporary ($p = 0.333$) and permanent ($p = 0.599$) hypocalcemia, hematoma ($p = 0.602$), and overall morbidity ($p = 0.880$) appeared comparable. Two (0.2 %) brachial plexus injuries in RT were reported in one study.
    d. Conclusions. Relative to OT, RT was associated with significantly longer operating time, longer hospital stay, and higher temporary RLN injury rate but comparable permanent complications and overall morbidity. Given some of the limitations with the literature and the potential added surgical risks and morbidity in RT, application of the robot in thyroid surgery should be carefully and thoroughly discussed before one decides on the procedure.

4) **Hyun 2013**, Systematic review and meta-analysis of robotic surgery compared with conventional laparoscopic and open resections for gastric carcinoma
    a. N=9 non-randomized observational studies (7200 patients)
    b. Robotic assisted gastrectomy (RAG) was associated with longer operating times than laparoscopically assisted gastrectomy (LAG) and open gastrectomy (OG; weighted mean difference 61.99 and 65.73 min respectively; *P* ≤0.001).
    c. The number of retrieved lymph nodes and the resection margin length in RAG were comparable with those of LAG and OG.
    d. Estimated blood loss was significantly less in RAG than in OG (*P* =0.002), but not LAG. Mean hospital stay for RAG was similar to that for LAG (*P* =0.14). In contrast, hospital stay was significantly shorter, by a mean of 2.18 days, for RAG compared with OG (*P* <0.001). Postoperative complications were similar for all three operative approaches.
    e. Conclusion: Short-term oncological outcomes of RAG were comparable with those of the other approaches. LAG was a shorter procedure and less expensive than RAG. Future studies involving RAG should focus on minimizing duration of operation and reducing cost.
5) **Marcus 2014**, systematic review of fluoroscopy guided vs robotic assist pedicle screw placement
    a. N=5 studies (1,308 pedicle screw placements; 729 robot-assisted, 579 fluoroscopy-guided).
    b. The findings of these studies are mixed, with limited higher level of evidence data favoring fluoroscopy-guided procedures, and remaining comparative studies supporting robot-assisted pedicle screw placement.
    c. Conclusions There is insufficient evidence to unequivocally recommend one surgical technique over the other. Given the high cost of robotic systems, and the high risk of spinal surgery, further high quality studies are required to address unresolved clinical equipoise in this field.

Non-systematic reviews with large numbers of patients

1) **Jeong 2017**: Observational cohort study of robotic assist vs laparoscopic radical nephrectomy
    a. N=23,753 (robotic assisted radical nephrectomy N=5180 patients; laparoscopic radical nephrectomy N=18,573 patients).
    b. The use of robotic-assisted nephrectomy increased substantially over the course of the study, from 1.5% (39 of 2676 cases) in 2003 to 27% (862 of 3194 cases) by 2015.
    c. In the weighted-adjusted analysis, there were no significant differences between robotic-assisted and laparoscopic radical nephrectomy in the incidence of any (Clavien grades 1-5) postoperative complications (adjusted rates, 22.2% vs 23.4%, difference, −1.2%; 95%CI, −5.4 to 3.0%) or major (Clavien grades 3-5) complications (adjusted rates, 3.5% vs 3.8%, difference, −0.3%; 95%CI, −1.0% to 0.5%).
    d. The rate of prolonged operating time (>4 hours) for patients undergoing the robotic-assisted procedure was higher than for patients receiving the laparoscopic procedure in the adjusted analysis (46.3%vs 25.8%; risk difference, 20.5%; 95%CI, 14.2%to 26.8%).
    e. Robotic-assisted radical nephrectomy was associated with higher mean 90-day direct hospital costs ($19 530 vs $16 851; difference, $2678; 95%CI, $838 to $4519), mainly accounted for operating room ($7217 vs $5378; difference, $1839; 95%CI, $1050 to $2628) and supply costs ($4876 vs $3891; difference, $985; 95%CI, $473 to $1498).
    f. CONCLUSIONS AND RELEVANCE The use of robotic-assistance was not associated with increased risk of any or major complications but was associated with prolonged operating time and higher hospital costs compared with laparoscopic surgery.

Other coverage policies: CMS does not have a NCD for robotic assisted surgery, but does not pay for this service. Private insurers are mixed on payment for robotic assist surgery. Most hospitals are absorbing the additional cost of this surgery.

Currently, CCOs and HSD are not paying for robotic assisted surgery.

HERC staff summary:
There is a consistent finding in the literature that robotic assisted surgery have similar outcomes to the equivalent laparoscopic surgery for a variety of types of surgery, but at a higher cost and longer operating times.

HERC staff recommendation:

1) Add HCPCS S2900 (Surgical techniques requiring use of robotic surgical system) to line 500 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS and GN172 as shown below
    a. Advise HSC to remove HCPCS S2900 from the Ancillary List

GUIDELINE NOTE 172, INTERVENTIONS WITH MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS FOR CERTAIN CONDITIONS

Line 500

The following interventions are prioritized on Line 500 CONDITIONS FOR WHICH INTERVENTIONS RESULT IN MARGINAL CLINICAL BENEFIT OR LOW COST-EFFECTIVENESS:

Procedure Code	Intervention Description	Rationale	Last Review
S2900	Surgical techniques requiring use of robotic surgical system	More cost-effective treatments are available	May, 2018

Cochrane Library

Cochrane Database of Systematic Reviews

Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer (Review)

Ilic D, Evans SM, Allan CA, Jung JH, Murphy D, Frydenberg M

Ilic D, Evans SM, Allan CA, Jung JH, Murphy D, Frydenberg M.
Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer.
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD009625.
DOI: 10.1002/14651858.CD009625.pub2.

www.cochranelibrary.com

WILEY

[Intervention Review]

Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer

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Editorial group: Cochrane Urology Group.
Publication status and date: New, published in Issue 9, 2017.

Citation: Ilic D, Evans SM, Allan CA, Jung JH, Murphy D, Frydenberg M. Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD009625. DOI: 10.1002/14651858.CD009625.pub2.

ABSTRACT

Background

Prostate cancer is commonly diagnosed in men worldwide. Surgery, in the form of radical prostatectomy, is one of the main forms of treatment for men with localised prostate cancer. Prostatectomy has traditionally been performed as open surgery, typically via a retropubic approach. The advent of laparoscopic approaches, including robotic-assisted, provides a minimally invasive alternative to open radical prostatectomy (ORP).

Objectives

To assess the effects of laparoscopic radical prostatectomy or robotic-assisted radical prostatectomy compared to open radical prostatectomy in men with localised prostate cancer.

Search methods

We performed a comprehensive search using multiple databases (CENTRAL, MEDLINE, EMBASE) and abstract proceedings with no restrictions on the language of publication or publication status, up until 9 June 2017. We also searched bibliographies of included studies and conference proceedings.

Selection criteria

We included all randomised controlled trials (RCTs) with a direct comparison of laparoscopic radical prostatectomy (LRP) and robotic-assisted radical prostatectomy (RARP) to ORP, including pseudo-RCTs.

Data collection and analysis

Two review authors independently classified studies and abstracted data. The primary outcomes were prostate cancer-specific survival, urinary quality of life and sexual quality of life. Secondary outcomes were biochemical recurrence-free survival, overall survival, overall surgical complications, serious postoperative surgical complications, postoperative pain, hospital stay and blood transfusions. We performed statistical analyses using a random-effects model and assessed the quality of the evidence according to GRADE.

Main results

We included two unique studies with 446 randomised participants with clinically localised prostate cancer. The mean age, prostate volume, and prostate-specific antigen (PSA) of the participants were 61.3 years, 49.78 mL, and 7.09 ng/mL, respectively.

Primary outcomes

We found no study that addressed the outcome of prostate cancer-specific survival. Based on data from one trial, RARP likely results in little to no difference in urinary quality of life (MD -1.30, 95% CI -4.65 to 2.05) and sexual quality of life (MD 3.90, 95% CI -1.84 to 9.64). We rated the quality of evidence as moderate for both quality of life outcomes, downgrading for study limitations.

Secondary outcomes

We found no study that addressed the outcomes of biochemical recurrence-free survival or overall survival.

Based on one trial, RARP may result in little to no difference in overall surgical complications (RR 0.41, 95% CI 0.16 to 1.04) or serious postoperative complications (RR 0.16, 95% CI 0.02 to 1.32). We rated the quality of evidence as low for both surgical complications, downgrading for study limitations and imprecision.

Based on two studies, LRP or RARP may result in a small, possibly unimportant improvement in postoperative pain at one day (MD -1.05, 95% CI -1.42 to -0.68) and up to one week (MD -0.78, 95% CI -1.40 to -0.17). We rated the quality of evidence for both time-points as low, downgrading for study limitations and imprecision. Based on one study, RARP likely results in little to no difference in postoperative pain at 12 weeks (MD 0.01, 95% CI -0.32 to 0.34). We rated the quality of evidence as moderate, downgrading for study limitations.

Based on one study, RARP likely reduces the length of hospital stay (MD -1.72, 95% CI -2.19 to -1.25). We rated the quality of evidence as moderate, downgrading for study limitations.

Based on two study, LRP or RARP may reduce the frequency of blood transfusions (RR 0.24, 95% CI 0.12 to 0.46). Assuming a baseline risk for a blood transfusion to be 8.9%, LRP or RARP would result in 68 fewer blood transfusions per 1000 men (95% CI 78 fewer to 48 fewer). We rated the quality of evidence as low, downgrading for study limitations and indirectness.

We were unable to perform any of the prespecified secondary analyses based on the available evidence. All available outcome data were short-term and we were unable to account for surgeon volume or experience.

Authors' conclusions

There is no high-quality evidence to inform the comparative effectiveness of LRP or RARP compared to ORP for oncological outcomes. Urinary and sexual quality of life-related outcomes appear similar.

Overall and serious postoperative complication rates appear similar. The difference in postoperative pain may be minimal. Men undergoing LRP or RARP may have a shorter hospital stay and receive fewer blood transfusions. All available outcome data were short-term, and this study was unable to account for surgeon volume or experience.

PLAIN LANGUAGE SUMMARY

Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer

Review question

How does laparoscopic and robot-assisted laparoscopic surgery compare in the treatment of men with prostate cancer?

Background

Prostate cancer is a common cancer in men, often treated by surgical removal. Traditionally, surgeons used to make an incision on the lower abdomen to take the prostate. This procedure is called open radical prostatectomy (ORP). More recently, surgeons have started to use other ways to perform the same operation. Laparoscopic radical prostatectomy (LRP) allows surgeons to work inside the patient with long instruments and a tiny camera through small incisions. Laparoscopic surgery can be done with the use of a robotic device, which allows the surgeon to have a magnified, three-dimensional view and operate from a console, away from the patient. This procedure is called robotic-assisted radical prostatectomy (RARP). It is unclear whether the newer LRP and RARP approaches are better for patients.

Study characteristics

This review identified two randomised controlled trials of 446 men with prostate cancer, with an average age of approximately 60 years, that compared LRP or RARP to ORP.

Key results

We found no evidence as to how LRP or RARP compared to ORP in terms of reducing the risk of dying from prostate cancer, preventing the cancer from coming back or dying of any cause. Mens' quality of life was likely similar related to their urinary and sexual function. There appears to be no differences in postoperative surgical complications. LRP or RARP may have a small possibly unimportant effect on postoperative pain at one day and up to one week. However, no difference between RARP and ORP was found at 12 weeks postoperatively. Men having LRP or RARP likely have a shorter hospital stay and may need fewer blood transfusions.

Quality of evidence

We found no trial evidence for any cancer outcome. The evidence for quality of life were moderate; that for overall and serious surgical complications were low quality. Postoperative pain were low (up to one week) and moderate (at 12 weeks) quality of evidence. The quality of evidence for hospital stay and blood transfusions were moderate and low, respectively. Collectively, the most outcomes were low to moderate quality of evidence. This means that our estimates are likely to be close to the truth but that there is a possibility that they may be different.

Ann Surg Oncol (2014) 21:850–861
DOI 10.1245/s10434-013-3406-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

A Systematic Review and Meta-analysis Comparing Surgically-Related Complications between Robotic-Assisted Thyroidectomy and Conventional Open Thyroidectomy

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ABSTRACT

Background. Despite gaining popularity, robotic-assisted thyroidectomy (RT) remains controversial. This systematic review and meta-analysis is aimed at comparing surgically-related complications between RT and conventional open thyroidectomy (OT).

Methods. A systematic review of the literature was performed to identify studies comparing surgically-related outcomes between RT and OT. Studies that compared ≥ 1 surgically-related outcomes between RT and OT were included. Outcomes included operating time, blood loss, complications, and hospital stay. Meta-analysis was performed using a fixed-effects model.

Results. Eleven studies were eligible but none were randomized controlled trials. Of the 2,375 patients, 839 (35.3 %) underwent RT, while 1,536 (64.7 %) underwent OT. RT was significantly associated with longer operating time ($p < 0.001$), hospital stay ($p = 0.023$) and higher temporary recurrent laryngeal nerve (RLN) injury ($p = 0.016$). Although there was no correlation between the number of RTs reported in the study and the rate of temporary RLN injury ($p = -0.486$, $p = 0.328$, respectively), routine perioperative laryngoscopy was performed in only 2 of 11 studies. Blood loss ($p = 0.485$), temporary ($p = 0.333$) and permanent ($p = 0.599$) hypocalcemia, hematoma ($p = 0.602$), and overall morbidity ($p = 0.880$) appeared comparable. Two (0.2 %) brachial plexus injuries in RT were reported in one study.

Conclusions. Relative to OT, RT was associated with significantly longer operating time, longer hospital stay, and higher temporary RLN injury rate but comparable permanent complications and overall morbidity. Given some of the limitations with the literature and the potential added surgical risks and morbidity in RT, application of the robot in thyroid surgery should be carefully and thoroughly discussed before one decides on the procedure.

Thyroidectomy is a common surgical procedure, and the standard cervical open thyroidectomy (OT) is a safe and effective procedure.[1] However, to improve cosmesis and patient satisfaction, various endoscopic approaches have been developed.[2] Unlike OT, these endoscopic approaches often require making incisions away from the neck so as to leave no visible neck scar.[2,3] In experienced hands, similar outcomes to OT have been reported.[3] However, these endoscopic techniques are generally technically challenging because of the small working space and limitations with current endoscopic instruments.[3] To overcome these problems, a South Korean group pioneered the use of the *da Vinci* robot (i.e. 'robotic-assisted thyroidectomy', or RT). Despite higher cost, it offers better manipulations and stereoscopic visual field.[4] Since 2009[5] there has been much interest both in the US and other parts of the world, with several groups publishing their initial successful experience.[6–9] However, despite the initial enthusiasm, RT remains controversial. In October 2011, the US FDA revoked the approval on the use of the robot for thyroidectomy.[10] This has led some to abandoning RT and

First Received: 8 August 2013;
Published Online: 23 November 2013

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Systematic review

Systematic review and meta-analysis of robotic surgery compared with conventional laparoscopic and open resections for gastric carcinoma

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Background: **Robot-assisted gastrectomy (RAG) has been developed in the hope of improving surgical quality and overcoming the limitations of conventional laparoscopically assisted gastrectomy (LAG) and open gastrectomy (OG) for gastric cancer. The aim of this study was to determine the extent of evidence in support of these ideals.**

Methods: **A systematic review of the three operation types (RAG, LAG and OG) was carried out to evaluate short-term outcomes including duration of operation, retrieved lymph nodes, estimated blood loss, resection margin status, technical postoperative complications and hospital stay.**

Results: **Nine non-randomized observational clinical studies involving 7200 patients satisfied the eligibility criteria. RAG was associated with longer operating times than LAG and OG (weighted mean difference 61·99 and 65·73 min respectively; $P \leq 0{\cdot}001$). The number of retrieved lymph nodes and the resection margin length in RAG were comparable with those of LAG and OG. Estimated blood loss was significantly less in RAG than in OG ($P = 0{\cdot}002$), but not LAG. Mean hospital stay for RAG was similar to that for LAG ($P = 0{\cdot}14$). In contrast, hospital stay was significantly shorter, by a mean of 2·18 days, for RAG compared with OG ($P < 0{\cdot}001$). Postoperative complications were similar for all three operative approaches.**

Conclusion: **Short-term oncological outcomes of RAG were comparable with those of the other approaches. LAG was a shorter procedure and less expensive than RAG. Future studies involving RAG should focus on minimizing duration of operation and reducing cost.**

Paper accepted 26 June 2013
Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9242

Introduction

Since the first minimally invasive distal gastrectomy was reported in 1994[1], laparoscopically assisted gastrectomy (LAG) has become widely used for the treatment of gastric cancer because of shorter hospital stays and lower postoperative complication rates compared with open gastrectomy (OG)[2,3]. A considerable proportion of patients with advanced gastric cancers are still treated with OG, however, especially in Western countries, because of concerns regarding the potential for inadequate lymphadenectomy during LAG[4–6]. To overcome the technical limitations of laparoscopic surgery, robotic surgical systems that allow motion scaling, three-dimensional visualization and a high degree of freedom have been introduced[7,8]. Since robot-assisted gastrectomy (RAG) was first reported in 2003[9], a number of studies have examined the feasibility of this new technology for gastrectomy[10–19].

Despite the higher costs of robotic surgery, it has generally been expected that the initial cost of robotic technology would be offset by surgery of better quality and the ability to overcome some of the limitations of LAG[20]. No randomized clinical trials involving RAG with long-term follow-up data have been reported. The aim of this study was to analyse the effectiveness of RAG in comparison with LAG and OG by evaluating the available short-term results. In the present three-arm comparisons (RAG *versus* LAG, RAG *versus* OG), meta-analysis of the available data was performed using sophisticated subgroup analyses to increase statistical power and resolve inconsistencies.

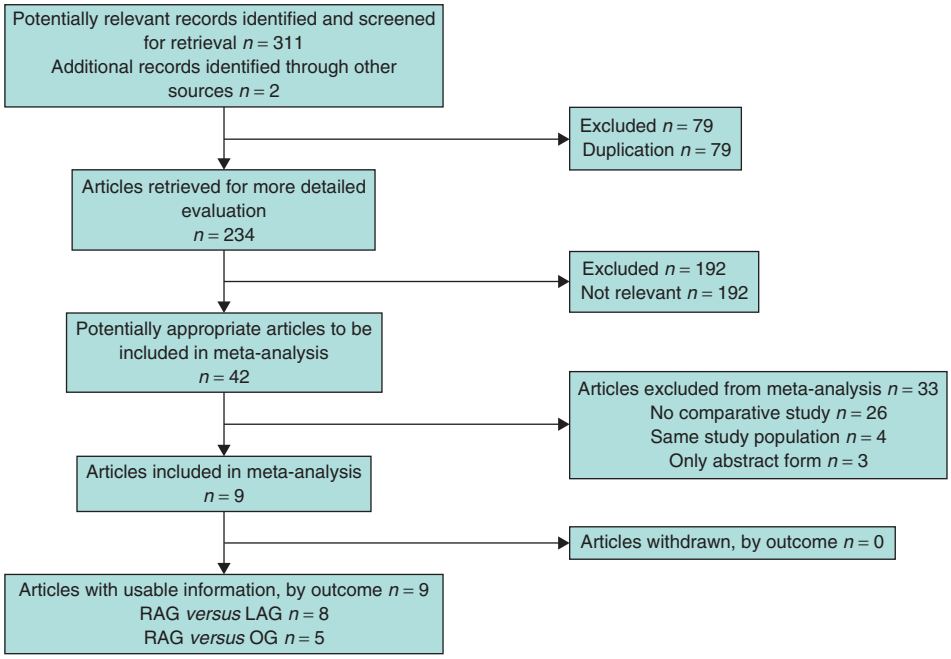


Fig. 1 PRISMA diagram showing selection of articles for review. Of nine included studies, four reported three-arm comparisons of robot-assisted gastrectomy (RAG), laparoscopically assisted gastrectomy (LAG) and open gastrectomy (OG).

Methods

Search strategy

Systematic searches of MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) were performed to identify articles published up to October 2012 that compared outcomes with and without the use of robotic technology for the treatment of gastric cancer. The search terms 'robot', 'robotic', 'robot-assisted', 'da Vinci', 'gastrectomy', 'gastric resection', 'stomach resection', 'Roux-en-Y', 'Billroth', 'gastroduodenostomy', 'gastroenterostomy' and 'gastrojejunostomy' were utilized. Both free-text and medical subject heading (MeSH) searches were used for keywords. The links of every search result and all references in the original articles identified were reviewed to identify additional literature that was not indexed. Only studies written in English were considered for inclusion.

Eligibility criteria

Studies meeting the following criteria were included: comparative, peer-reviewed studies of RAG *versus* LAG or OG for patients with gastric cancer for which the full text of the article was available and that included objective evaluations of at least one of the perioperative outcome measures mentioned below. If two studies from the same group were identified, the most recent study or that including more subjects was selected unless the reports were from different time periods.

Methodological quality appraisal

The methodological quality of the selected studies was assessed using a checklist based on a modified version of the Methodological Index for Non-randomized Studies (MINORS)[3,21]. This validated quality assessment system for non-randomized controlled trials is based on eight items: consecutive patients, prospective data collection, reported primary endpoints, unbiased postoperative evaluation, appropriate control intervention, contemporary groups, group equivalents and sample size. A maximum score of 16 points is possible with these eight items. Studies scoring 12 or more points were considered high quality.

Data extraction

Data were extracted from the original studies by two independent reviewers who were blinded to journal names, institutions and funding grants. Differences were resolved by consensus or by a third reviewer. Authors with incomplete reporting of outcomes of interest were contacted via e-mail. If no response was received, a

Table 1 Summary of studies included in the meta-analysis

Reference	Enrolment interval (country)	Study design	No. of patients (M : F)	Age (years)*	BMI (kg/m^2)*	Conversion (%)	Mortality (%)	TNM stage I/II (%)	Type of gastrectomy	Matched factors†
Kim *et al.*[33] (2010)	2007–2008 (Korea)	OCS (P)	RAG 16 (10 : 6)	53·8(15·6)	21·3(3·4)	0	0	n.r.§	S	–
			LAG 11 (10 : 1)	57·9(13·1)	25·3(2·5)	0	0	n.r.§	S	1,2,4,5
			OG 12 (9 : 3)	56·0(12·4)	25·2(1·9)	–	0	n.r.§	S	1,2,4,5
Pugliese *et al.*[34] (2010)	2006–2009 (Italy)	OCS (n.r.)	RAG 18 (11 : 7)	65·7	n.r.	12·5	5·5	n.r.	S	–
			LAG 48 (n.r.)	n.r.	n.r.	6·2	2·0	n.r.	S	4,5
Caruso *et al.*[35]‡ (2011)	2006–2010 (Italy)	OCS (P)	RAG 29 (18 : 11)	64·8(12·4)	27·0(3·0)	0	0	45/31	S/T	
			OG 120 (65 : 55)	65·1(11·0)	28·0(4·0)	–	3·3	48/15	S/T	1,2,3,4,5
Yoon *et al.*[36]‡ (2012)	2009–2011 (Korea)	OCS (P)	RAG 36 (18 : 18)	53·9(11·7)	23·2(2·5)	0	0	81/19	T	–
			LAG 65 (31 : 34)	56·9(12·3)	23·6(3·4)	0	0	85/11	T	1,2,3,4,5
Eom *et al.*[37]‡ (2012)	2009–2010 (Korea)	OCS (P)	RAG 30 (21 : 9)	52·8(11·5)	24·2(4·0)	0	0	83/10	S	–
			LAG 62 (41 : 21)	57·9(10·6)	24·1(2·3)	0	0	90/10	S	2,3,4,5
Huang *et al.*[38]‡ (2012)	2006–2012 (Taiwan)	OCS (P)	RAG 39 (19 : 20)	65·1(15·9)	24·2(3·7)	n.r.	2·6	74/18	S/T	–
			LAG 64 (43 : 21)	65·6(14·8)	24·7(3·3)	n.r.	1·6	86/14	S/T	1,2,3,5
			OG 586 (406 : 180)	67·9(30·1)	23·7(3·6)	–	1·3	34/18	S/T	1,3,5
Son *et al.*[39] (2012)	2007–2011 (Korea)	OCS (R)	RAG 21 (14 : 7)	52·3(13·1)	23·7(3·7)	n.r.	0	76/14	S/T	–
			LAG 42 (26 : 16)	52·8(13·0)	22·6(3·2)	n.r.	0	79/17	S/T	1,2,3,4,5
Kim *et al.*[40] (2012)	2005–2010 (Korea)	OCS (P)	RAG 436 (265 : 171)	54·2(12·5)	23·6(3·1)	n.r.	0·4	80/12	S/T	–
			LAG 861 (550 : 311)	58·8(12·0)	23·5(2·8)	n.r.	0·3	83/11	S/T	2,3
			OG 4542 (3008 : 1534)	54·2(12·5)	57·7(11·8)	–	0·4	52/18	S/T	3,5
Hyun *et al.*[41]‡ (2013)	2009–2010 (Korea)	OCS (P)	RAG 38 (25 : 13)	54·2(12·7)	23·8(2·6)	0	0	79/13	S/T	–
			LAG 83 (55 : 28)	60·3(12·3)	23·8(2·9)	0	0	81/11	S/T	2,3,4,5
			OG 41 (28 : 13)	57·7(11·9)	22·7(2·4)	–	0	34/22	S/T	1,2,3,5

*Values are mean(s.d.). †Factors matched with robot-assisted gastrectomy (RAG) group: 1, age; 2, sex; 3, body mass index; 4, extent of lymphadenectomy; 5, type of gastrectomy. ‡Unpublished data obtained from author. §Reported only surgical indication; less than clinical T2 N1 M0 in tumour node metastasis (TNM) staging system. BMI, body mass index; OCS, observational clinical study; P, prospectively collected data; LAG, laparoscopically assisted gastrectomy; OG, open gastrectomy; n.r., not reported; S, subtotal gastrectomy; T, total gastrectomy; R, retrospectively collected data.

Table 2 Summary of primary outcomes for included studies: robot-assisted *versus* laparoscopically assisted gastrectomy

	No. of data sets	No. of patients	Effect estimate*	*P*	Heterogeneity I^2 (%)	Heterogeneity *P*
Duration of operation (min)	8	1870	61·99 (43·12, 80·86)	< 0·001	85	< 0·001
No. of retrieved LNs	8	1870	−0·25 (−3·72, 3·22)	0·89	81	<0·001
Estimated blood loss (ml)	8	1870	−6·08 (−25·73, 13·58)	0·54	83	<0·001
Proximal resection margin (cm)	5	1674	−0·06 (−0·32, 0·19)	0·63	49	0·10
Distal resection margin (cm)	5	1674	−1·14 (−1·55, −0·72)	< 0·001	0	0·92
Hospital stay (days)	8	1870	−0·60 (−1·39, 0·20)	0·14	56	0·03
Total postoperative complications	8	1870	1·12 (0·83, 1·52)	0·44	0	0·84
Leakage†	8	1870	1·06 (0·57, 1·94)	0·86	0	0·74
Stenosis‡	8	1870	0·90 (0·29, 2·77)	0·85	0	0·50

*Weighted mean difference (WMD) for continuous variables and odds ratio (OR) for complications, all with 95 per cent confidence interval; negative WMD and OR below 1 favour robot-assisted gastrectomy. †Anastomotic site leakage, anastomotic failure, duodenal stump leakage. ‡Stenosis, stricture, intestinal obstruction. LN, lymph node.

second e-mail was sent a week later. If an e-mail address was not valid, either the senior investigator or another investigator listed in the article was contacted. The six primary outcomes analysed were: duration of operation, number of retrieved lymph nodes, estimated blood loss, resection margin, hospital stay and technical postoperative complications. Hospital stay was defined as the interval from operation to discharge. Postoperative complications were confined to leaks and stenoses.

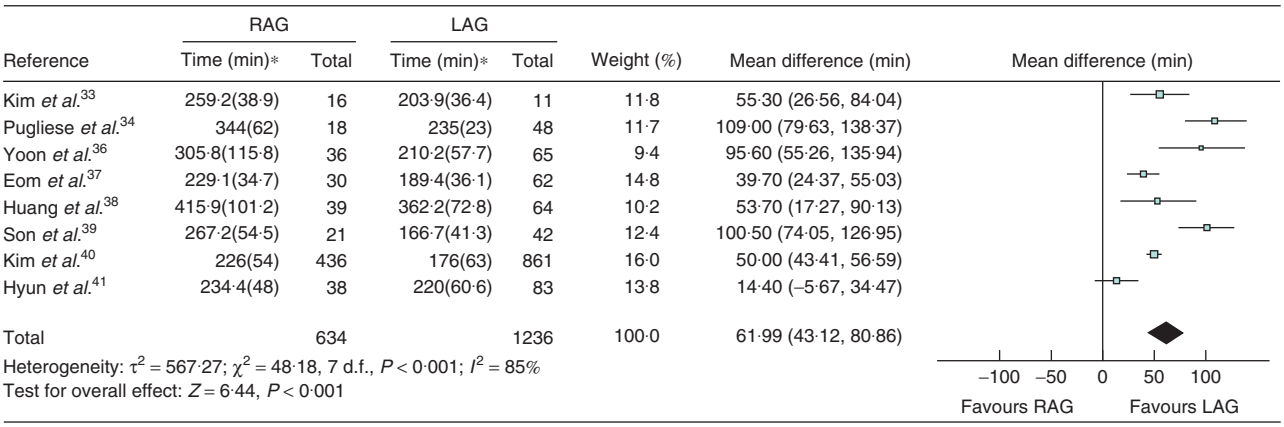
Statistical analysis

This study was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement using Review Manager (RevMan) version 5.0 (The Nordic Cochrane Centre, Copenhagen, Denmark)[22]. Continuous variables were evaluated to obtain the weighted mean difference (WMD) and pooled using an inverse variance model. Dichotomous variables were evaluated for

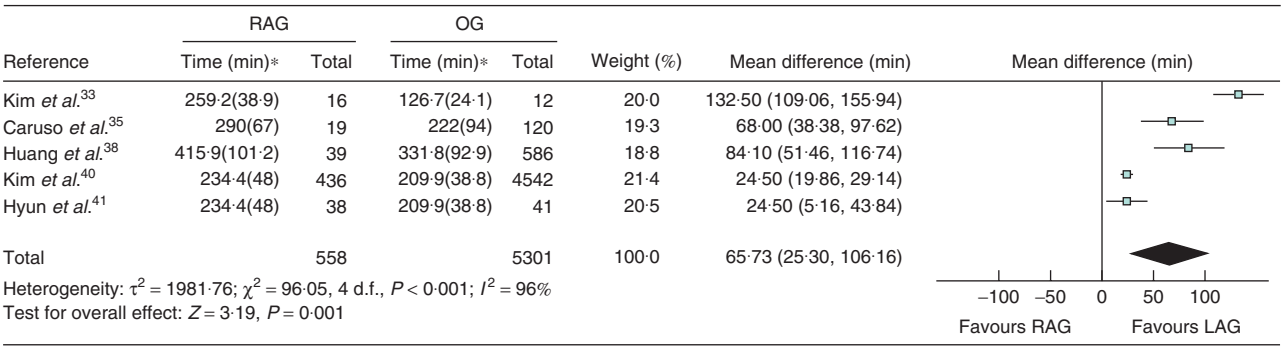
Table 3 Summary of primary outcomes for included studies: robot-assisted *versus* open gastrectomy

	No. of data sets	No. of patients	Effect estimate*	*P*	Heterogeneity	
					I^2 (%)	*P*
Duration of operation (min)	5	5859	65·73 (25·30, 106·16)	0·001	96	< 0·001
No. of retrieved LNs	5	5859	−1·13 (−2·47, 0·21)	0·10	49	0·10
Estimated blood loss (ml)	5	5859	−154·18 (−250·11, −58·25)	0·002	99	< 0·001
Proximal resection margin (cm)	3	5206	−0·41 (−1·64, 0·82)	0·52	62	0·07
Hospital stay (days)	5	5859	−2·18 (−2·81, −1·54)	< 0·001	46	0·12
Total postoperative complications	5	5859	1·37 (0·92, 2·06)	0·12	0	0·56
Leakage†	5	5859	1·82 (1·07, 3·09)	0·03	0	0·78
Stenosis‡	5	5859	0·96 (0·06, 15·70)	0·98	76	0·02

*Weighted mean difference (WMD) for continuous variables and odds ratio (OR) for complications, all with 95 per cent confidence interval; negative WMD and OR below 1 favour robot-assisted gastrectomy. †Anastomotic site leakage, anastomotic failure, duodenal stump leakage. ‡Stenosis, stricture, intestinal obstruction. LN, lymph node.



a RAG *versus* LAG

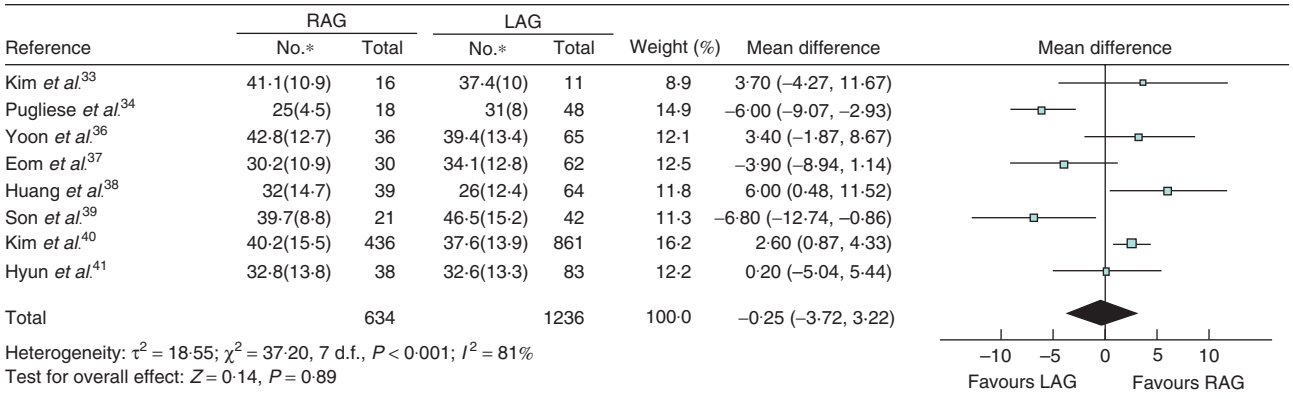


b RAG *versus* OG

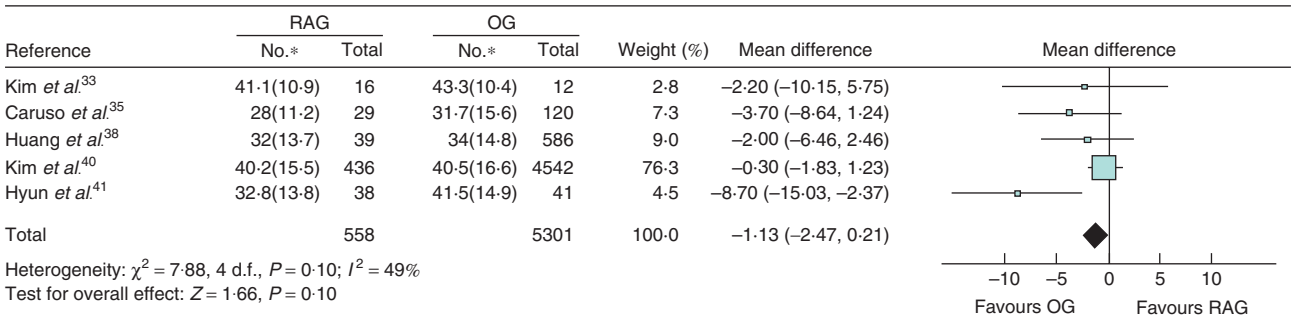
Fig. 2 Forest plot comparing duration of operation for **a** robot-assisted gastrectomy (RAG) *versus* laparoscopically assisted gastrectomy (LAG) and **b** RAG *versus* open gastrectomy (OG). An inverse variance random-effects model was used for meta-analysis. *Values are mean(s.d.). Mean differences are shown with 95 per cent confidence intervals

the odds ratio (OR) and pooled using the Mantel–Haenszel model. ORs and WMDs are presented with 95 per cent confidence intervals (c.i.).

Statistical heterogeneity, which indicated between-study variance, was evaluated according to the Higgins I^2 statistic[23]. I^2 values of less than 25 per cent, 25–50 per cent and more than 50 per cent indicated low, moderate and high heterogeneity respectively[24]. If the heterogeneity was high (I^2 above 50 per cent or $P < 0{\cdot}100$), a random-effects model was used for analysis.



a RAG *versus* LAG



b RAG *versus* OG

Fig. 3 Forest plot comparing number of retrieved lymph nodes for **a** robot-assisted gastrectomy (RAG) *versus* laparoscopically assisted gastrectomy (LAG) and **b** RAG *versus* open gastrectomy (OG). An inverse variance random-effects (**a**) and fixed-effect (**b**) model was used for meta-analysis. *Values are mean(s.d.). Mean differences are shown with 95 per cent confidence intervals

Otherwise, a fixed-effect model was used for pooled estimation[25].

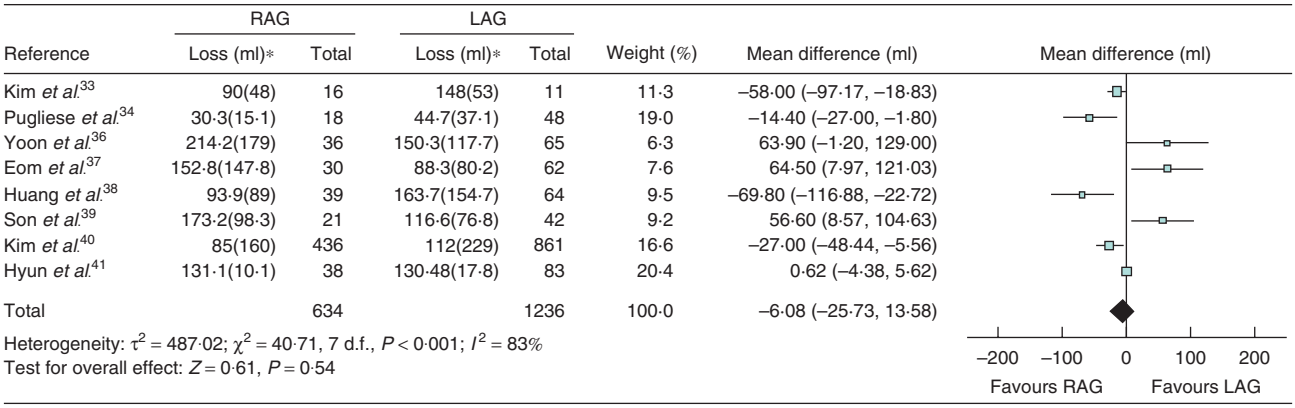
For three-arm comparison studies (RAG, LAG and OG), differences in baseline characteristics were recalculated with MedCalc® (MedCalc Software, Mariakerke, Belgium) using Student's *t* test, χ^2 test and Fisher's exact test.

Subgroup analyses were performed using studies with large numbers of procedures (more than 20 RAGs), matched patient characteristics (age, sex and body mass index), matched operation characteristics (extent of lymphadenectomy and type of gastrectomy), and high-quality studies (score 12 or more). Influence analysis, in which meta-analysis estimates were computed after each study had been omitted in turn, was used to identify individual studies affecting the pooled analysis.

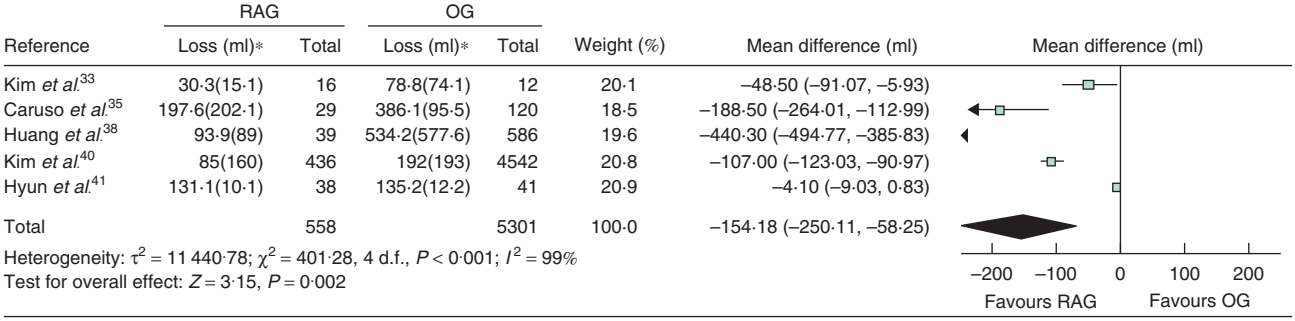
Begg's rank correlation method was used to assess publication bias by testing for Kendall's τ using Stata® version 12 (StataCorp LP, College Station, Texas, USA), and a graphical funnel plot was generated using RevMan[26]. $P < 0{\cdot}050$ was considered statistically significant.

Results

The combined searches identified 313 abstracts (*Fig. 1*). After elimination of 79 duplicates and exclusion of irrelevant articles, 42 articles were considered for peer review. Among these, four[18,27–29] were superseded by other articles with overlapping data sets and three[30–32] were available only in abstract form. In total, nine[33–41] articles (Korea 6, Italy 2, Taiwan 1) with a total of 7200 patients were eligible for inclusion. Data were analysed as reported by the authors. Four authors were contacted for additional unpublished information. Eom *et al.*[37] and Huang and co-workers[38] provided non-extractable data such as means and standard deviations that were described as medians and ranges in the original papers. Yoon and colleagues[36] provided information regarding overlapping patients, and Caruso *et al.*[35] provided subgroup data according to the type of surgery. In addition, baseline characteristics of OG were used, including type of gastrectomy and tumour node metastasis (TNM) stage, which were described incompletely in the original article from this centre[41].



a RAG *versus* LAG



b RAG *versus* OG

Fig. 4 Forest plot comparing estimated blood loss in **a** robot-assisted gastrectomy (RAG) *versus* laparoscopically assisted gastrectomy (LAG) and **b** RAG *versus* open gastrectomy (OG). An inverse variance random-effects model was used for meta-analysis. *Values are mean(s.d.). Mean differences are shown with 95 per cent confidence intervals

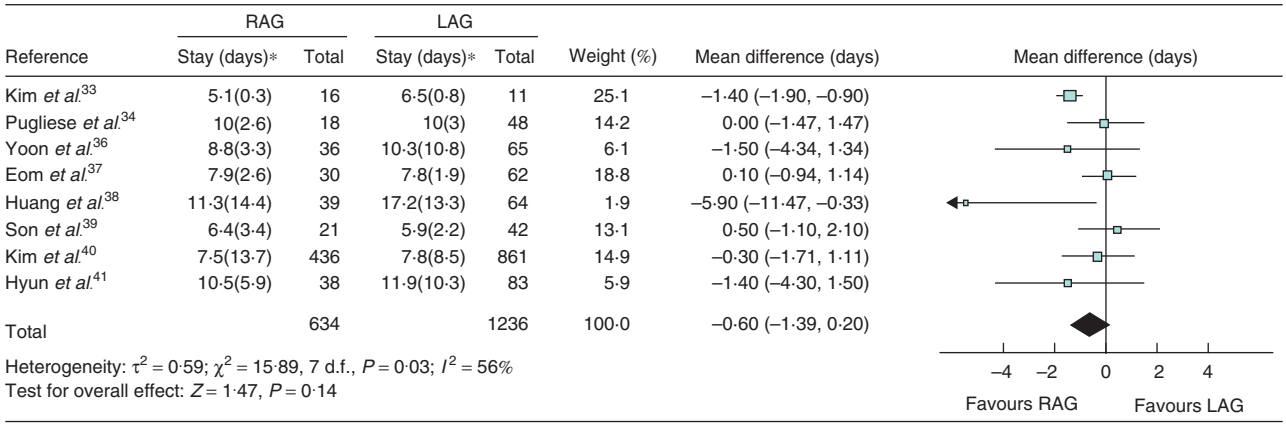
Study characteristics and quality assessment

The included studies are summarized in *Table 1*. Of the nine studies, four[33,38,40,41] were three-arm comparisons (RAG, LAG and OG), four[34,36,37,39] compared RAG and LAG and one[35] compared RAG and OG. Overall, eight articles[33,34,36–41] including 1870 patients compared RAG (634) and LAG (1236). Five articles[33,35,38,40,41] including 5859 patients compared RAG (558) and OG (5301). All robotic procedures used the da Vinci™ surgical system (Intuitive Surgical, Sunnyvale, California, USA). The included studies all had recent publication dates (2010 or later).

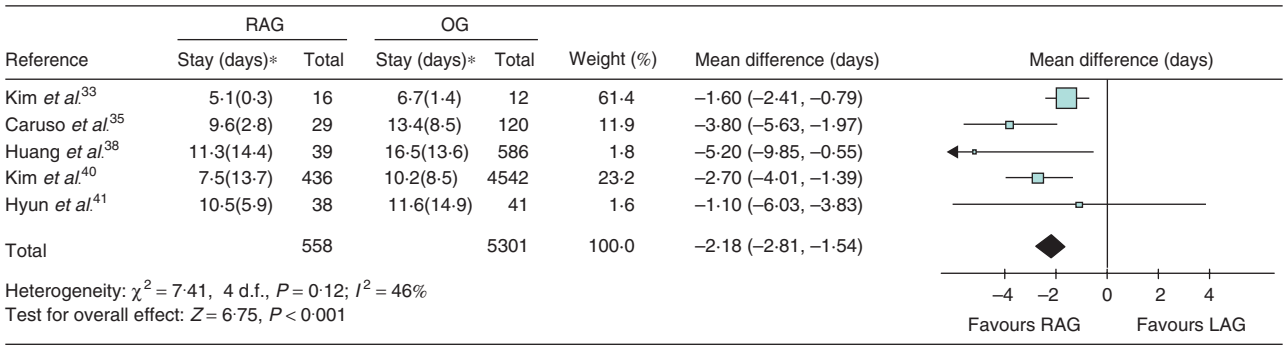
Conversion and mortality rates were reported in six and nine studies respectively (range 0–12·5 and 0–5·5 per cent). A higher proportion of patients in the RAG and LAG groups had stage I cancer than those randomized to OG (overall: 78·2, 83·2 and 50·0 per cent respectively). The baseline characteristics in three studies[35,36,39] were adequately matched for all the factors reviewed. Five studies[33,34,37,40,41] were not completely matched with regard to patient factors (age, sex and body mass index), and three studies[38,40,41] had differences in more than one surgical factor (extent of lymphadenectomy and type of gastrectomy). All trials were observational studies. All except two involved data collection using a prospective database; one study[39] used retrospective data and one[34] did not report on this. In general, the quality of the included studies was satisfactory. The median quality score was 12, and six[35–38,40,41] had a score of 12 or more. Details of the quality assessment are shown in *Table S1* (supporting information).

Evidence from primary outcomes

Tables 2 and *3* summarize the primary outcomes of the included studies. All studies provided information on duration of operation. Mean differences in operating time varied widely between RAG and LAG ($I^2 = 85$ per cent). Forest plots showed that robotic surgery took longer than LAG: WMD 61·99 (95 per cent c.i. 43·12 to 80·86) min ($P < 0·001$) (*Fig. 2*). There was similar wide variation in



a RAG *versus* LAG



b RAG *versus* OG

Fig. 5 Forest plot comparing duration of hospital stay after **a** robot-assisted gastrectomy (RAG) *versus* laparoscopically assisted gastrectomy (LAG) and **b** RAG *versus* open gastrectomy (OG). An inverse variance random-effects (**a**) and fixed-effect (**b**) model was used for meta-analysis. *Values are mean(s.d.). Mean differences are shown with 95 per cent confidence intervals

operating times between RAG and OG ($I^2 = 96$ per cent). All five involved studies showed a longer duration of operation for RAG than OG, and meta-analysis showed a shorter mean operating time for OG: WMD 65·73 (25·30 to 106·16) min ($P = 0·001$).

The mean number of harvested lymph nodes was reported in all studies (*Fig. 3*). There was wide variation in the number of retrieved lymph nodes for RAG and LAG ($I^2 = 81$ per cent), and no significant difference was found between the groups: WMD −0·25 (−3·72 to 3·22) ($P = 0·89$). The number of retrieved lymph nodes in OG was comparable with that in RAG: WMD −1·13 (−2·47 to 0·21) ($P = 0·10$); there was a low degree of heterogeneity between studies ($I^2 = 49$ per cent).

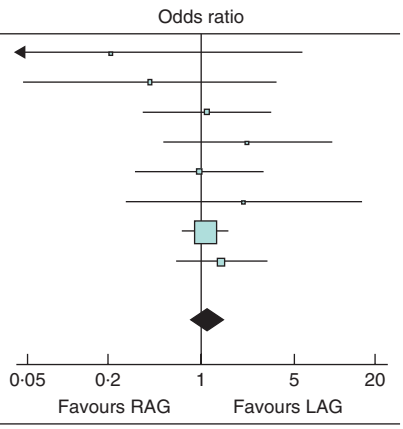
Eight of nine studies reported estimated blood loss and one[36] provided incomplete data. The meta-analysis revealed significant heterogeneity between RAG and LAG or OG ($I^2 = 83$ and 99 per cent respectively). There was no difference in intraoperative blood loss between RAG and LAG: WMD −6·08 (−25·73 to 13·58) ml ($P = 0·54$); however, estimated blood loss was significantly lower after RAG compared with OG: WMD −154·18 (−250·11 to −58·25) ml ($P = 0·002$) (*Fig. 4*).

Proximal (PRM) and distal (DRM) resection margin distances were compared between RAG and LAG in five studies[36,37,39–41]. There was low heterogeneity for PRM ($I^2 = 49$ per cent) and combined results in a fixed-effect model showed no difference between RAG and LAG: WMD −0·06 (−0·32 to 0·19) ($P = 0·63$). However, analysis of the DRM showed homogeneity between studies ($I^2 = 0$) and there was a significantly greater DRM margin with RAG: WMD −1·14 (−1·55 to −0·72) cm ($P < 0·001$). Conversely, pooled analysis showed similar PRM values for RAG and OG: WMD −0·41 (−1·64 to 0·82) cm ($P = 0·52$); heterogeneity was high ($I^2 = 62$ per cent)[35,40,41].

The duration of postoperative hospital stay was reported in all studies (*Fig. 5*). The meta-analysis revealed significant

Reference	Complication rate RAG	Complication rate LAG	Weight (%)	Odds ratio
Kim *et al.*[33]	0 of 16	1 of 11	2·1	0·21 (0·01, 5·71)
Pugliese *et al.*[34]	1 of 18	6 of 48	3·9	0·41 (0·05, 3·68)
Yoon *et al.*[36]	6 of 36	10 of 65	7·4	1·10 (0·36, 3·32)
Eom *et al.*[37]	4 of 30	4 of 62	2·8	2·23 (0·52, 9·62)
Huang *et al.*[38]	6 of 39	10 of 64	8·0	0·98 (0·33, 2·95)
Son *et al.*[39]	2 of 21	2 of 42	1·5	2·11 (0·28, 16·10)
Kim *et al.*[40]	44 of 436	81 of 861	61·1	1·08 (0·73, 1·59)
Hyun *et al.*[41]	18 of 38	32 of 83	13·2	1·43 (0·66, 3·11)
Total	81 of 634	146 of 1236	100·0	1·12 (0·83, 1·52)

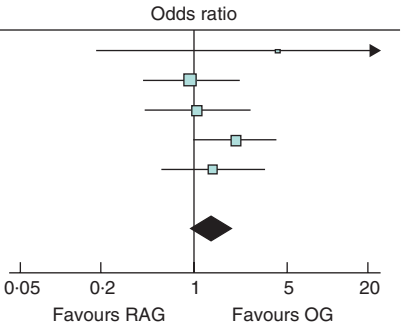
Heterogeneity: $\chi^2 = 3{\cdot}48$, 7 d.f., $P = 0{\cdot}84$; $I^2 = 0\%$
Test for overall effect: $Z = 0{\cdot}77$, $P = 0{\cdot}44$



a RAG *versus* LAG

Reference	Complication rate RAG	Complication rate OG	Weight (%)	Odds ratio
Kim *et al.*[33]	2 of 16	0 of 12	1·3	4·31 (0·19, 98·51)
Caruso *et al.*[35]	12 of 29	51 of 120	30·6	0·96 (0·42, 2·17)
Huang *et al.*[38]	6 of 39	86 of 586	23·9	1·06 (0·43, 2·60)
Kim *et al.*[40]	10 of 436	51 of 4542	23·0	2·07 (1·04, 4·10)
Hyun *et al.*[41]	18 of 38	16 of 41	21·3	1·41 (0·58, 3·44)
Total	48 of 558	204 of 5301	100·0	1·37 (0·92, 2·06)

Heterogeneity: $\chi^2 = 2{\cdot}96$, 4 d.f., $P = 0{\cdot}56$; $I^2 = 0\%$
Test for overall effect: $Z = 1{\cdot}54$, $P = 0{\cdot}12$



b RAG *versus* OG

Fig. 6 Forest plot comparing postoperative complications after **a** robot-assisted gastrectomy (RAG) *versus* laparoscopically assisted gastrectomy (LAG) and **b** RAG *versus* open gastrectomy (OG). A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

heterogeneity between RAG and LAG or OG ($I^2 = 56$ and 46 per cent respectively). Hospital stay was shorter after RAG than LAG, although this result did not reach statistical significance: WMD −0·60 (−1·39 to 0·20) days ($P = 0{\cdot}14$). Patients undergoing RAG had a significantly shorter hospital stay than those having OG: WMD −2·18 (−2·81 to −1·54) days ($P < 0{\cdot}001$).

Short-term postoperative complications were recorded in all studies (*Fig. 6*). Overall, the incidence of total postoperative complications was similar after RAG and LAG (OR 1·12, 95 per cent c.i. 0·83 to 1·52; $P = 0{\cdot}44$), without heterogeneity ($I^2 = 0$ per cent), in a fixed-effect model. There were no differences in rates of leakage (OR 1·06, 0·57 to 1·94; $P = 0{\cdot}86$) or stenosis (OR 0·90, 0·29 to 2·77; $P = 0{\cdot}85$) between the two groups ($I^2 = 0$ per cent for both). Meta-analysis of RAG and OG showed similar total postoperative complication rates (OR 1·37, 0·92 to 2·06; $P = 0{\cdot}12$), with low heterogeneity ($I^2 = 0$ per cent), and similar rates of stenosis (OR 0·96, 0·06 to 15·70; $P = 0{\cdot}98$). The leak rate was, however, significantly higher for RAG than for OG (OR 1·82, 1·07 to 3·09; $P = 0{\cdot}03$) in a fixed-effect model ($I^2 = 0$ per cent).

Sensitivity analysis and publication bias

The results of subgroup analysis for the primary outcomes are shown in *Table S2* (supporting information). A large sample size (more than 20 RAG procedures), matched patient factors (age, sex and body mass index), matched surgical factors (extent of lymphadenectomy and type of gastrectomy) and inclusion of only high-quality studies (modified MINORS score at least 12) did not influence the duration of operation, hospital stay or total postoperative complications for either LAG or OG compared with RAG,

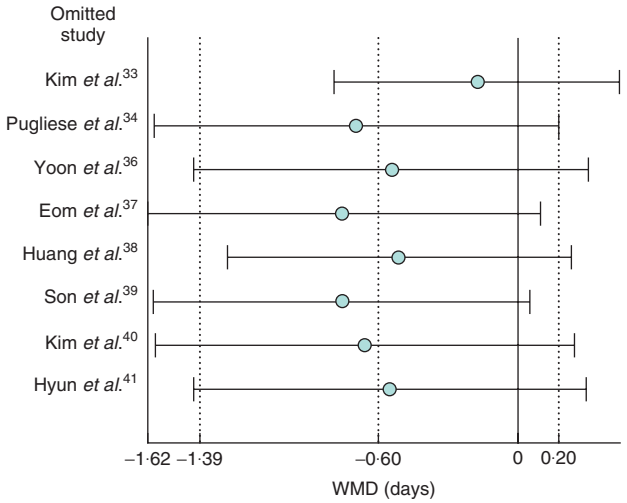


Fig. 7 Influence analysis of weighted mean difference (WMD) for hospital stay after robot-assisted gastrectomy (RAG) *versus* laparoscopically assisted gastrectomy. Each row represents a reanalysis of the data with exclusion of one study at a time to assess the influence of that particular study on the overall result. WMDs are shown with 95 per cent confidence intervals; negative values favour RAG

indicating robust and consistent results across studies. In contrast to LAG, OG showed inconsistent results in terms of the number of retrieved lymph nodes and estimated blood loss compared with RAG, although only two studies satisfied matching criteria. There were no significant differences in PRM between the RAG and LAG groups matched for type of gastrectomy: WMD −0·01 (−0·94 to 0·92) cm ($P = 0·98$). Conversely, RAG had a longer DRM than LAG, when matched for type of gastrectomy: WMD −0·98 (−1·75 to −0·22) cm ($P = 0·01$).

The influence analysis of hospital stay for RAG and LAG indicated that the studies with the greatest positive and negative influence on the overall pooled estimates seemed to be the data reported by Son and colleagues[39] (after omission: WMD −0·76 (95 per cent c.i. −1·58 to 0·06) days; $P = 0·07$) and Kim *et al.*[33] (after omission: WMD – 0·16 (−0·79 to 0·47) days; $P = 0·62$) (*Fig.* 7).

The funnel plots for all primary outcomes were relatively symmetrical, suggesting that publication biases were not present. Begg's test did not indicate publication bias for any primary outcomes, including duration of operation, number of retrieved lymph nodes, estimated blood loss, resection margin, hospital stay and total postoperative complications (all $P > 0·100$) (*Fig.* 8).

Discussion

A number of pilot series studies examining the feasibility of RAG have been reported, although the effectiveness and oncological safety of this procedure are still unclear given the limited number of observational studies[10–18]. Because randomized clinical trials of RAG have not yet been performed and long-term survival data are not available, meta-analysis of non-randomized observational clinical trials was used to evaluate the safety and short-term efficacy of robotic surgery for the treatment of gastric carcinoma, compared with conventional laparoscopic and open approaches to gastrectomy.

The most consistent finding in this meta-analysis was the long operating time for RAG. Robotic procedures generally take longer than conventional operations because

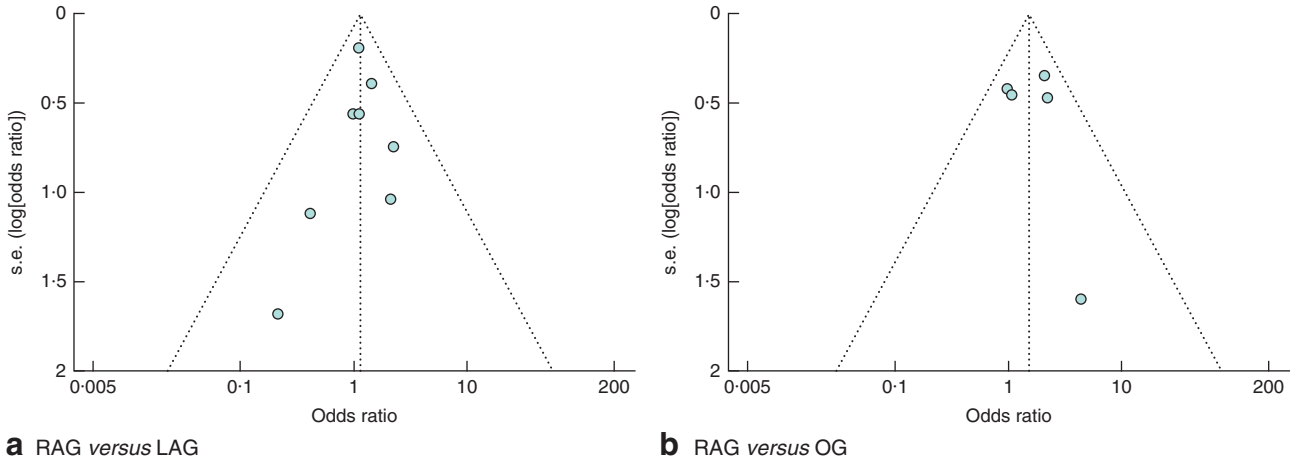


Fig. 8 Funnel plot for results from all studies comparing overall complication rate: **a** robot-assisted gastrectomy (RAG) *versus* laparoscopically assisted gastrectomy (LAG) and **b** RAG *versus* open gastrectomy (OG). s.e., Standard error

of the additional set-up procedures, including preparing and docking[42]. However, robotic set-up times are often less than 30 min[43,44], so a difference of greater than 60 min is notable. Hyun and colleagues[41] excluded the first 20 procedures completed during the initial RAG learning period to establish an equivalent comparison of surgical quality, and reported a similar operating time for RAG and LAG (234 *versus* 220 min; $P = 0{\cdot}198$). In contrast, studies including procedures completed during the RAG training or learning period consistently reported a significantly longer operating time[33–40]. This suggests that duration of surgery is influenced by learning curve effects. It has been suggested that experienced laparoscopic surgeons reach a plateau in operating time after about 20 operations[19]. As most of the studies in the present analysis did not explicitly describe the surgeon's level of proficiency, a subgroup analysis was carried out by selecting studies with more than 20 RAG operations as a surrogate marker of proficiency. This analysis failed to demonstrate a significant reduction in operating time for RAG.

Oncological outcome is a critical measure of success in gastric cancer surgery. With short follow-up times, numbers of retrieved lymph nodes and surgical resection margin were used as indicators of oncological acceptability. The analysis showed that the number of retrieved lymph nodes with RAG was similar to that for LAG and OG. To reduce heterogeneity, a subgroup analysis matched for the extent of lymphadenectomy and type of gastrectomy was performed[33–37,39,41]; this confirmed that similar numbers of lymph nodes were harvested. Only a limited number of studies reported on PRM[35–37,39–41]. There were no significant differences between the groups overall or in subgroup analysis matched for type of gastrectomy. Conversely, RAG had a longer DRM than LAG, overall and in subgroup analysis matched for type of gastrectomy. Both PRM and DRM lengths demonstrate that RAG is oncologically acceptable for proximal or distally located tumours[45,46].

The mean estimated blood loss in RAG was similar to that for LAG, but significantly less than in OG. Similar differences in blood loss between RAG and LAG were observed consistently in all subgroup analyses, which were conducted using large sample sizes, matched patients, matched operation type and high-quality studies[33,34,36–41]. The biological effect of blood loss on perioperative morbidity is still controversial[47,48]. As the variation in blood loss between RAG studies was high (range 30·3–214·2 ml), with heterogeneity as a result of different methods of estimating blood loss, this result should be interpreted with caution[33–41].

There were no differences in total postoperative complication rates between RAG and the other procedures, but RAG had a significantly higher rate of anastomotic leakage than OG. Although the overall incidence of anastomotic leak was low in all these studies (2·8, 2·5 and 1·7 per cent for RAG, LAG and OG respectively), leakage was the considered the major cause of morbidity and death[40]. Other studies have reported higher leakage rates after laparoscopic surgery compared with open procedures[49]. Both limited tactile feedback and the role of staple-line reinforcement have been considered relevant issues[50,51]. Only two of the studies examined here[40,41] used previously validated complication grading systems such as the Clavien–Dindo classification[52], highlighting the need for objective and reproducible methods to evaluate postoperative complications more accurately after this type of surgery.

The duration of hospital stay was shorter by 0·60 days in patients undergoing RAG than in those having LAG, although influence and subgroup analysis showed that this difference was not statistically significant. Hospital stay for RAG was, however, significantly shorter (by 2·18 days) than that for OG and consistent across all studies. It has been suggested that a shorter hospital stay for LAG compared with OG could offset the increased operation costs[53]. So far, only two studies[29,36] have performed a cost analysis of RAG compared with LAG from a single centre, indicating that RAG costs €3189 more per patient than LAG[29]. Of this, €2831 per patient resulted solely from depreciation of the da Vinci™ system and maintenance of capital equipment. If this is eliminated from the total, then the cost of RAG is comparable to that for LAG (€5130 *versus* €4772 respectively)[29].

There have been two earlier meta-analyses related to RAG[54,55]. Maeso and colleagues[54] performed a meta-analysis of the use of the da Vinci™ surgical system compared with laparoscopic surgery for different types of abdominal intervention, but this included only two articles[18,33] with a limited number of patients (87). A meta-analysis comparing RAG with LAG[55] involved only three studies[28,33,34], and did not assess the risk of bias with sensitivity and subgroup analyses. The present meta-analysis included nine studies[33–41] with a total of 7200 patients (663 RAG, 1236 LAG, 5301 OG) and used refined subgroup analysis to produce reliable results and reduce bias.

This analysis has some limitations. All included studies were observational, with the likelihood of selection bias. Although sensitivity analysis using matched data should reduce this bias, it cannot be eliminated. Robotic procedures included the initial learning period, which may have resulted in an unequal surgical quality comparison. Most of the studies had small sample sizes with fewer than 50 RAG procedures. Results with marginal statistical significance should be interpreted with caution.

The uneven distribution in the number of patients contributed to heterogeneity. One single, high-volume centre contributed more than half of the total number of RAG operations[40]. Most operations were conducted in East Asia and the results may not represent clinical outcomes in the West. Ethnic differences may introduce bias and should be taken into consideration.

Future work should focus on the balance between minimizing operating time and reducing cost, but high-quality controlled clinical trials to compare RAG with LAG and OG can now be undertaken.

Acknowledgements

The authors thank A. Patriti (Hospital Matteo degli Infermi, Spoleto, Italy), S. Caruso (University of Siena, Siena, Italy), B.-W. Eom, K.-W. Ryu, H.-M. Yoon and Y.-W. Kim (National Cancer Centre, Seoul, Korea), and W.-L. Fang and K.-H. Huang (Taipei Veterans General Hospital, Tapei, Taiwan) for providing additional unpublished data; and E.-J. Lee and K.-S. Jung (Korea University College of Medicine, Seoul, Korea) for their editorial contributions. This study was supported by a grant from the National Research and Development Programme for Cancer Control, Ministry of Health and Welfare, Republic of Korea (1020410) and the National Research Foundation of Korea from the Korean Government (2010-0024825).

Disclosure: The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

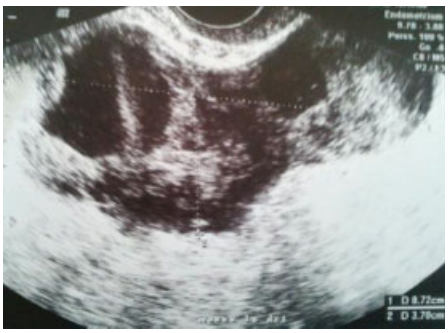
Table S1 Modified Methodological Index for Non-randomized Studies score for quality assessment in the meta-analysis (Word document)

Table S2 Subgroup analyses performed using large patient numbers, matched patient factors, matched operation factors and high-quality studies (Word document)

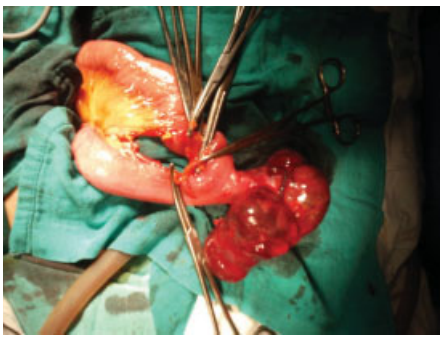
Snapshot quiz

Snapshot quiz 13/37

Question: The pelvic ultrasound scan (**a**) suggested a right adnexal mass, but what is the differential diagnosis of the laparotomy findings (**b**)?



a



b

The answer to the above question is found on p. 1605 of this issue of *BJS*.

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Eur Spine J (2014) 23:291–297
DOI 10.1007/s00586-013-2879-1

REVIEW ARTICLE

Robot-assisted and fluoroscopy-guided pedicle screw placement: a systematic review

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Received: 27 March 2013 / Revised: 14 June 2013 / Accepted: 18 June 2013 / Published online: 26 June 2013

Abstract
Purpose At present, most spinal surgeons undertake pedicle screw implantation using either anatomical landmarks or C-arm fluoroscopy. Reported rates of screw malposition using these techniques vary considerably, though the evidence generally favors the use of image-guidance systems. A miniature spine-mounted robot has recently been developed to further improve the accuracy of pedicle screw placement. In this systematic review, we critically appraise the perceived benefits of robot-assisted pedicle screw placement compared to conventional fluoroscopy-guided technique.
Methods The Cochrane Central Register of Controlled Trials, PubMed, and EMBASE databases were searched between January 2006 and January 2013 to identify relevant publications that (1) featured placement of pedicle screws, (2) compared robot-assisted and fluoroscopy-guided surgery, (3) assessed outcome in terms of pedicle screw position, and (4) present sufficient data in each arm to enable meaningful comparison (>10 pedicle screws in each study group).
Results A total of 246 articles were retrieved, of which 5 articles met inclusion criteria, collectively reporting placement of 1,308 pedicle screws (729 robot-assisted, 579 fluoroscopy-guided). The findings of these studies are mixed, with limited higher level of evidence data favoring fluoroscopy-guided procedures, and remaining comparative studies supporting robot-assisted pedicle screw placement.
Conclusions There is insufficient evidence to unequivocally recommend one surgical technique over the other. Given the high cost of robotic systems, and the high risk of spinal surgery, further high quality studies are required to address unresolved clinical equipoise in this field.

Keywords Robotics · Robot assisted · SpineAssist · Fluoroscopy guided · Pedicle screw · Bone screw · Spine · Spinal surgery · Neurosurgery · Systematic review

Introduction

Pedicle screw placement is a common surgical procedure to achieve fusion in the thoraco-lumbar spine. The anatomical proximity of the vertebral pedicles to associated neurovascular structures means that surgical misplacement of pedicle screws may result in serious morbidity. It has been estimated using a geometric model of spinal anatomy that a maximal translational error of less than 1 mm and rotational error of less than 5° are permissible to ensure satisfactory screw implantation [16]. The clinical corollary is that tools improving the accuracy and precision of pedicle screw placement can improve the outcome of patients undergoing spinal fusion.

At present, most spinal surgeons performing pedicle screw implantation do so using either anatomical landmarks or C-arm fluoroscopy [13]. The accuracy of pedicle screw implantation using these techniques varies considerably in the literature (from 28 to 94 %), though the evidence generally favors the use of image-guidance systems [5, 10, 25, 27]. A miniature spine-mounted robot has

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recently been developed to further improve the accuracy of pedicle screw placement [2, 4, 22]. Since 2006, a number of studies have individually supported its use [1, 9, 11, 12, 14, 20–22, 24, 26].

In this systematic review, we collect and critically appraise the evidence to evaluate whether, in patients undergoing pedicle screw implantation, robot-assisted surgery offers an advantage over conventional fluoroscopy-guided procedures in terms of pedicle screw position.

Materials and methods

The review protocol was registered on the PROSPERO international prospective register of systematic reviews. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was used in the preparation of this manuscript.

Search methods

The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and EMBASE databases were searched between January 2006 and January 2013. Relevant combinations of free-text search terms [(robot*) AND (pedicle OR screw)] and MeSH terms ["Robotics" AND ("Spine" OR "Bone Screws")] were used. An English language restriction was applied. References lists of selected papers were also reviewed, and expert opinion sought, to identify additional eligible manuscripts. Two authors (HM and TPC) independently identified articles using the above search criteria.

Inclusion and exclusion criteria

Titles and abstracts were screened to identify publications that met criteria of (1) featuring placement of pedicle screws, (2) comparing SpineAssist® (Mazor Surgical Technologies Ltd., Caesarea, Israel) and fluoroscopy-guided surgery, (3) assessing outcome in terms of pedicle screw position, and (4) presenting sufficient data in each arm to enable meaningful comparison (more than ten pedicle screws in each study group). Full articles were subsequently obtained and further assessed for eligibility. Discrepancies were resolved by discussion with a senior author.

Data extraction

The following data were extracted from eligible full articles: (1) study design, (2) study group characteristics including number of subjects and pedicle screws implanted in each arm, (3) outcome measures used to assess pedicle screw position, (4) key results, and (5) other results, such as radiation exposure and duration of operation.

Corresponding authors were contacted to provide supplemental data when required. In circumstances when this was not possible, data were extrapolated using the original results reported.

Appraisal of evidence

The Jadad and Methodological Index for Non-Randomized Studies (MINORS) scoring systems were used to guide evaluation of the quality of randomized and non-randomized studies, respectively, [8, 23]. Studies of greater quality were given appropriately greater weighting in the qualitative analysis.

Raw data on screw positions were used to determine the odds ratio in each study. The odds ratio for the key results was calculated using MedCalc version 12.3.0.0.

Results

A total of 246 retrieved articles were pooled from electronic library databases and other sources, of which 65 were duplicates (Fig. 1). We excluded 159 articles on the basis of their title and abstract because they did not present original data, did not feature pedicle screws, did not have both a robot-assisted and a control group, or had insufficient data in each arm to enable meaningful comparison. Full text screening of the remaining 22 articles led to the exclusion of a further 17 articles. In all, 5 articles were identified that satisfied our inclusion criteria, comprising two randomized controlled trials (of which one reported preliminary findings), one prospective cohort, one retrospective cohort, and one cadaveric study (Table 1) [9, 11, 17, 18, 20]. A total of 1,308 pedicle screws were reported—729 using robot-assistance, and 579 using fluoroscopy-guidance.

Pedicle screw placement

All included studies assessed pedicle screw position using post-operative fine-cut computed tomography (CT). In all, 94.1 % (686/729) of pedicle screws placed with robot-assistance were satisfactory, compared with 92.7 % (537/579) of pedicle screws placed with fluoroscopy-guidance. Ringel et al. [17] favored fluoroscopy-guidance ($p = 0.019$), and the remaining studies supported robot-assistance (albeit often not reaching statistical significance) [9, 11, 18, 20]. A forest plot summarizing the odds ratios of the included studies is illustrated in Fig. 2.

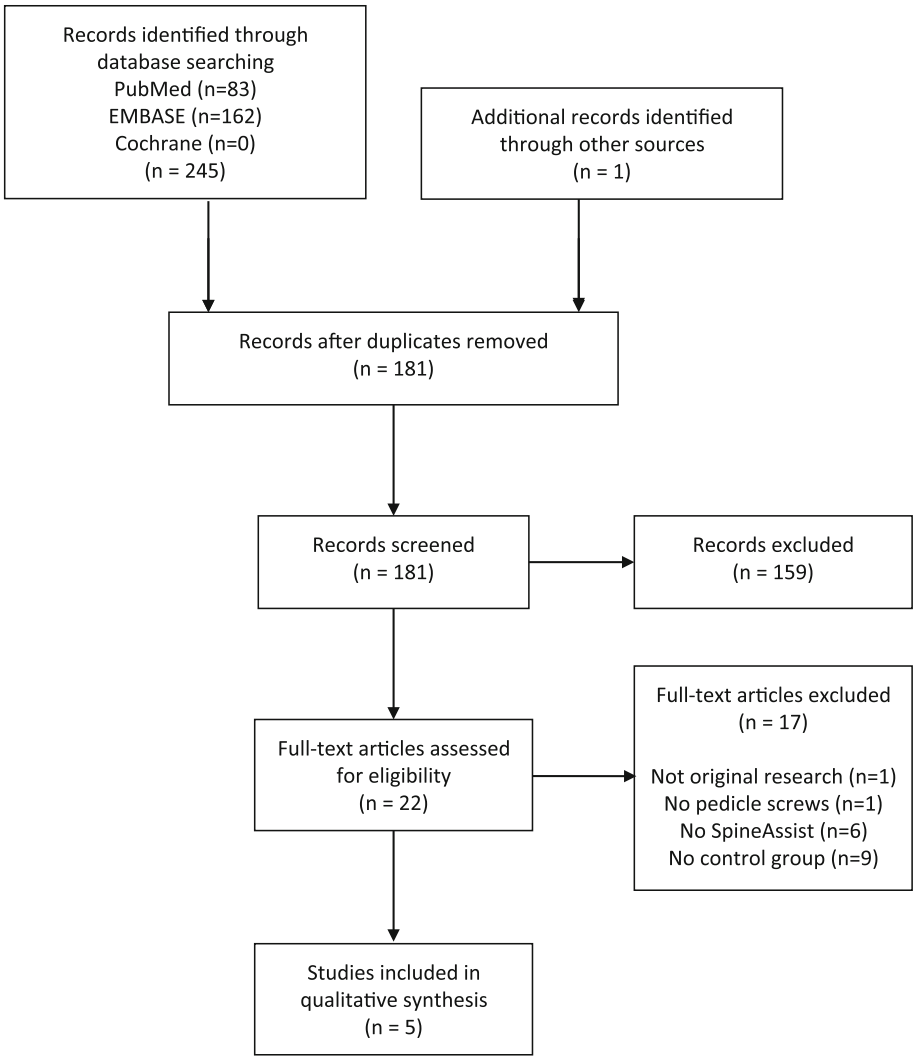

Fig. 1 Flow chart of search and selection process

Duration of surgery

The duration of surgery in the robot-assisted and fluoroscopy-guided groups was not reported as being significantly different in any of the three studies that analyzed this data [9, 11, 17].

Radiation exposure

All included studies commented on radiation exposure of patients and surgeons during pedicle screw implantation, though radiation doses during additional planning CT were not included in statistical significance testing. Kantelhardt et al. and Lieberman et al. [9, 11] reported radiation exposure to be significantly less during robot-assisted pedicle screw insertion compared to fluoroscopy-guided procedures, while Ringel et al. and Schizas et al. [17, 20] observed no significant difference in radiation exposure. Roser et al. [18] did not perform a statistical comparison on their preliminary findings, but a trend towards reduced radiation exposure in the robot-assisted group was observed.

Appraisal of quality of evidence

The Jadad system was used to evaluate the quality of the studies by Roser et al. and Ringel et al. [8, 17, 18]. Both studies were randomized but the methods to generate the sequence of randomization were not described. The Roser et al. study presents the preliminary results of 37 patients and the groups were therefore not balanced, with fewer patients undergoing fluoroscopy-guided ($n = 10$) than robot-assisted ($n = 18$) pedicle screw placement. Neither study fully addressed blinding. Although in the Ringel et al. study the position of pedicle screws was evaluated post-operatively by an independent neuroradiologist blinded to the technique used, it is unclear whether patients were also blinded. No participant withdrawal or loss to follow-up was reported.

Table 1 Summary of included studies

Reference	Level of evidence	Study group	Outcome	Key results	Other
Ringel et al. [17]	Single centre randomized controlled trial (Level 2)	60 pts undergoing lumbosacral pedicle screw implantation randomized into two equal groups: 30 pts FG ($n = 152$ screws), and 30 pts RA ($n = 146$ screws)	Pedicle screw position using Gertzbein and Robbins scale (positions A or B considered satisfactory)	FG: 142/152 (93 %) screws satisfactory RA: 124/146 (85 %) screws robot-assisted ($p = 0.019$)	Ten RA screws required intra-operative revision, one FG screw required post-operative revision. Duration of surgery and radiation exposure was not significantly different
Roser et al. [18]	Single centre randomized controlled trial (Level 2)	37 pts undergoing lumbosacral pedicle screw implantation randomized into three groups: 10 pts FG ($n = 40$ screws), 9 pts IG ($n = 36$ screws), and 18 pts RA ($n = 72$ screws)	Pedicle screw position using Gertzbein and Robbins scale (position A considered satisfactory)	FG: 39/40 (98 %) screws satisfactory IG: 33/36 (92 %) screws satisfactory RA: 71/72 (99 %) screws satisfactory	Study aims to recruit 30 pts per group. As preliminary results are reported here, statistical analysis was not performed
Schizas et al. [20]	Single centre prospective cohort study (Level 3)	34 consecutive pts undergoing thoraco-lumbar pedicle screw implantation divided into two groups: 23 pts FG ($n = 64$ screws) and 11 pts RA ($n = 64$ screws)	Pedicle screw position using the Rampersaud scale (positions A or B considered satisfactory)	FG: 59/64 (92 %) screws satisfactory RA: 61/64 (95 %) screws satisfactory ($p = 0.71$)	Radiation exposure was not significantly different
Kantelhardt et al. [9]	Single centre retrospective cohort study (Level 3)	112 consecutive pts undergoing thoraco-lumbar pedicle screw implantation divided into two groups: 57 pts FG ($n = 286$ screws), and 55 pts RA ($n = 250$ screws)	Pedicle screw position using Wiesner and Schizas scale (positions 0 or 1 considered satisfactory)	FG: 262/286[a] (92 %) screws satisfactory RA: 236/250[a] (95 %) screws satisfactory ($p < 0.05$)	Radiation exposure was significantly less in robot-assisted cases ($p = 0.0001$). Duration of surgery was not significantly different
Lieberman et al. [11]	Cadaveric study	12 cadavers underwent pedicle screw implantation divided into two groups: 2 cadavers FG ($n = 37$ screws), and 10 cadavers RA ($n = 197$ screws)	Pedicle screw position using the Rampersaud scale (position A considered satisfactory)	FG: 35/37[a] (95 %) screws satisfactory RA: 194/197[a] (99 %) screws satisfactory ($p = 0.082$)	Radiation exposure was significantly less in robot-assisted cases ($p < 0.001$). Duration of surgery was not significantly different

Pts patients, *FG* fluoroscopy-guided, *IG* image-guided (BrainLab VectorVision), *RA* robot-assisted (SpineAssist)

[a] Numbers calculated using percentages reported

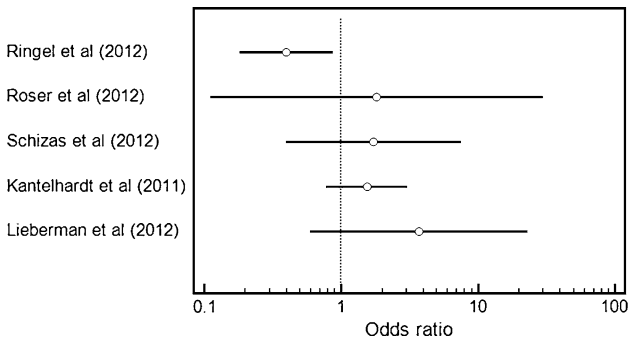

Fig. 2 Forest plot of pedicle screw accuracy comparing robot-assisted and fluoroscopy-guided insertion (>1 favors robot-assisted; <1 favors fluoroscopy-guided)

The quality of the studies by Schizas et al. and Kantelhardt et al. were evaluated using the MINORS system [9, 20, 23]. Neither study prospectively calculated the study size. The Schizas et al. [20] study did not report on the baseline equivalence of the control and intervention groups with respect to patient demographic factors such as age, sex and body mass index (BMI). The Kantelhardt et al. [9] study was retrospective.

Lieberman et al. [11] utilized human cadavers in a study that did not report pre-hoc power calculation, but otherwise was well designed.

Discussion

The evidence for robot-assisted pedicle screw placement is both limited and inconclusive. Five comparative studies were identified only. The findings of these studies are mixed, with the largest randomized controlled trial favoring fluoroscopy-guided procedures, and the other studies advocating robot-assisted pedicle screw placement. There

is therefore insufficient evidence to unequivocally recommend one surgical technique over the other.

The randomized controlled trial by Ringel et al. [17] represents the highest level of evidence study identified in this review. Applying the Jadad criteria, the method of randomization was not described, and patients did not appear to have been blinded to the procedure they underwent, though this is unlikely to have influenced the primary outcome of pedicle screw position. Notwithstanding these limitations, the study was generally well constructed and demonstrated significantly poorer screw placement in the robot-assisted group compared to the fluoroscopy-guided group (85 vs. 93 %). Moreover, ten screws placed using robot-assistance required intra-operative revision compared to only one in the control group. Duration of surgery and radiation exposure was not significantly different in the two groups, though patients undergoing robot-assisted surgery did require an additional planning CT.

The other randomized controlled trial by Roser et al. [18] reported preliminary findings of a three-arm study comparing fluoroscopy-guided, image-guided (BrainLab VectorVision 2, Feldkirchen, Germany), and robot-assisted pedicle screw placement. The study aims to enroll 90 patients with 4 screws per patient, but has so far recruited 37 patients, with fewer patients undergoing fluoroscopy-guided ($n = 10$) or image-guided ($n = 9$) surgery than robot-assisted ($n = 18$) pedicle screw placement. Statistical evaluation was not performed on these interim findings, but image-guided and robot-assisted pedicle screw placement had a comparable accuracy to conventional fluoroscopy-guided surgery, with a trend towards reduced radiation time and dosage.

The studies by Schizas et al. and Kantelhardt et al. [9, 20] are prospective and retrospective non-randomized cohort studies, respectively. In both studies, pedicle screws implanted using robot-assistance were better positioned than those placed using fluoroscopy-guidance (95 vs. 92 % in both cohorts). The Kantelhardt et al. study also reported reduced radiation exposure in the robot-assisted group, though the length of surgery did not differ significantly. Schizas et al. did not report on the equivalence of confounding variables in the intervention and control groups. Neither study acknowledged a prospective power calculation.

Despite being a human cadaver study, the study by Lieberman et al. [11] satisfied our inclusion criteria and was incorporated in our analysis. Although the authors did not prospectively calculate the study size, it was otherwise of high quality. As with the aforementioned cohort studies, pedicle screws placed using robot-assistance were better positioned than those placed using fluoroscopy-guidance (99 vs. 95 %); however, this did not reach statistical significance ($p = 0.082$). Radiation exposure was significantly less in screws placed using robot-assistance, but the length of surgery did not differ significantly.

A number of potential sources of bias were identified. Firstly, it is possible that certain patients were more likely to undergo robot-assisted pedicle screw placement in the cohort studies. For example, it may be that following the introduction of the robot into surgical practice, fairly straightforward cases were selected in the first instance while the operating team was still becoming more familiar with the technique. This selection bias is an inherent limitation of these non-randomized studies.

Secondly, intra- and inter-study variation in patient groups was noted. Not all studies reported on potential confounders such as unbalanced age, sex and BMI. While the studies by Ringel et al. and Roser et al. limited their participants to patients undergoing lumbosacral pedicle screw implantation the remaining studies included those undergoing thoracic pedicle screw implantation too. The anatomical differences between the lumbar and thoracic vertebra result in different maximal tolerable translational and rotational errors in these regions [16]. Interestingly, none of the studies included patients with thoracic scoliosis, and it could be argued that these cases, which have a very high rate of screw malposition [7], have the most to gain from the use of robot-assistance.

Thirdly, the nature of the robot-assisted operative technique varied considerably, including percutaneous pedicle screw implantation via a paramedian Wiltse approach [11, 17, 18], open pedicle screw implantation [20], and a combination of the two techniques [9]. In one study that compared robot-assisted percutaneous and open pedicle screw implantation, the accuracy of screw placement did not appear to differ significantly [9]. The robot itself may be attached to the spine in various ways, which may also influence accuracy. Ringel et al. [17] describe a platform that was fixed to a cranial spinal process with a K-wire, and attached to the operating table by a bed mount. They speculate that this may have been an insufficient method of fixation because, as the robot was only attached to the patient via a single K-wire, relative slippage might have occurred. Alternative methods of attaching the robot to the spine, such as the use of a platform connected to a spinous process clamp, with additional K-wires to cranial and caudal spinous processes, or to the iliac crests, may have therefore improved accuracy. The fluoroscopy-guided (control group) surgical technique of the control group also differed between studies depending on the use of a 2-C-arm set up or a single rotating C-arm, and either percutaneous or open approach. Surgical proficiency in the robot-assisted and fluoroscopy groups is difficult to quantitatively assess. All studies reported that operating surgeons were familiar with both robot-assisted and fluoroscopy-guided techniques, though it is suspected that experience and learning curve progression would be more advanced with the latter.

Lastly, all included studies involved independent blinded investigators to assess pedicle screw position using post-operative fine-cut CT. Unfortunately the metric tools used to satisfactorily determine screw placement varied widely including the Gertzbein and Robbins scale, Rampersaud scale, and Wiesner and Schizas scale [6, 15, 19, 28]. In the instance when the same scale was shared, criteria for a satisfactory position varied; for example, while the Schizas et al. and Lieberman et al. studies both adopted the Rampersaud scale, the former considered positions A and B adequate (completely in pedicle, or <2 mm breach), while the latter considered only position A acceptable (completely in pedicle only). The requirement for a universally adopted method of gauging pedicle screw position is widely acknowledged in the literature.

In addition to pedicle screw position numerous other factors may influence the choice of surgical technique. The high cost of robotic systems may limit availability of this technology for widespread use. In addition, the use of such systems requires additional training to the surgeon and operating team. Surgeons performing spinal fusion may be attracted to the use of robot-assistance if in addition to improving the accuracy and precision of pedicle screw implantation, there is associated reduction in radiation exposure without significantly lengthened operating times. The safety of such systems is paramount, and surgeons must be reassured that in the event of malfunction or failure, patient risk is minimal. Large forces are exerted during pedicle screw placement that can lead to skidding of the implantation cannula, or shift of the vertebrae, resulting in malposition if not appreciated during surgery. An often ignored additional prerequisite to the diffusion of robotic systems is their acceptability to patient population. To this end, although most studies have found attitudes to be generally positive, female and elderly patients may be more cautious about accepting robot-assisted surgery over conventional techniques [3].

In conclusion, given the high risk of spinal surgery, and the high cost of robotic systems, further studies to justify the clinical benefit and healthcare economics are required.

Acknowledgments H. J. Marcus is supported by the Wellcome Trust.

Conflict of interest None.

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JAMA | Original Investigation

Association of Robotic-Assisted vs Laparoscopic Radical Nephrectomy With Perioperative Outcomes and Health Care Costs, 2003 to 2015

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IMPORTANCE Use of robotic surgery has increased in urological practice over the last decade. However, the use, outcomes, and costs of robotic nephrectomy are unknown.

OBJECTIVES To examine the trend in use of robotic-assisted operations for radical nephrectomy in the United States and to compare the perioperative outcomes and costs with laparoscopic radical nephrectomy.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used the Premier Healthcare database to evaluate outcomes of patients who had undergone robotic-assisted or laparoscopic radical nephrectomy for renal mass at 416 US hospitals between January 2003 and September 2015. Multivariable regression modeling was used to assess outcomes.

EXPOSURES Robotic-assisted vs laparoscopic radical nephrectomy.

MAIN OUTCOMES AND MEASURES The primary outcome of the study was the trend in use of robotic-assisted radical nephrectomy. The secondary outcomes were perioperative complications, based on the Clavien classification system, and defined as any complication (Clavien grades 1-5) or major complications (Clavien grades 3-5, for which grade 5 results in death); resource use (operating time, blood transfusion, length of hospital stay); and direct hospital cost.

RESULTS Among 23 753 patients included in the study (mean age, 61.4 years; men, 13 792 [58.1%]), 18 573 underwent laparoscopic radical nephrectomy and 5180 underwent robotic-assisted radical nephrectomy. Use of robotic-assisted surgery increased from 1.5% (39 of 2676 radical nephrectomy procedures in 2003) to 27.0% (862 of 3194 radical nephrectomy procedures) in 2015 (*P* for trend <.001). In the weighted-adjusted analysis, there were no significant differences between robotic-assisted and laparoscopic radical nephrectomy in the incidence of any (Clavien grades 1-5) postoperative complications (adjusted rates, 22.2% vs 23.4%, difference, −1.2%; 95% CI, −5.4 to 3.0%) or major (Clavien grades 3-5) complications (adjusted rates, 3.5% vs 3.8%, difference, −0.3%; 95% CI, −1.0% to 0.5%). The rate of prolonged operating time (>4 hours) for patients undergoing the robotic-assisted procedure was higher than for patients receiving the laparoscopic procedure in the adjusted analysis (46.3% vs 25.8%; risk difference, 20.5%; 95% CI, 14.2% to 26.8%). Robotic-assisted radical nephrectomy was associated with higher mean 90-day direct hospital costs ($19 530 vs $16 851; difference, $2678; 95% CI, $838 to $4519), mainly accounted for operating room ($7217 vs $5378; difference, $1839; 95% CI, $1050 to $2628) and supply costs ($4876 vs $3891; difference, $985; 95% CI, $473 to $1498).

CONCLUSIONS AND RELEVANCE Among patients undergoing radical nephrectomy for renal mass between 2003 and 2015, the use of robotic-assisted surgery increased substantially. The use of robotic-assistance was not associated with increased risk of any or major complications but was associated with prolonged operating time and higher hospital costs compared with laparoscopic surgery.

JAMA. 2017;318(16):1561-1568. doi:10.1001/jama.2017.14586

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Supplemental content

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Radical nephrectomy for renal cancer remains the standard of care for large tumors with curative intent and has become the preferred treatment option for T1 and T2 tumors not amenable to nephron-sparing surgery.[1] Evidence suggests that there are no significant differences in oncological outcomes between laparoscopic and open radical nephrectomy, although laparoscopic procedures confer certain advantages over the open approach in terms of morbidity, blood loss, hospital length of stay, and postoperative analgesic requirements.[2,3]

Robotic surgery, in particular, has been rapidly adopted for a wide range of procedures over the last decade in the United States. While increasingly preferred for procedures that required open surgery, such as prostatectomy, it has also gradually replaced conventional laparoscopic surgery. This has largely been driven by extensive marketing and competition among hospitals to offer the most advanced technology.[4-7] However, the introduction and rapid adoption of the robotic platform has resulted in increased costs without significantly improving outcomes compared with nonrobotic minimally invasive approaches.[7-10]

Since the first use of robotic-assisted radical nephrectomy for renal cancer was reported in 2005, several small, single institutional observational studies have reported limited evidence on oncological and perioperative outcomes, which may not have true clinical relevance.[11] Some studies have shown equivalent perioperative outcomes despite increased costs of robotic-assisted compared with laparoscopic radical nephrectomy, yet most of these studies were limited by small sample sizes, lack of randomization, and antiquated data.[12-14] The objective of this study was to examine the utilization of robotic-assisted radical nephrectomy in the United States from 2003 to 2015 and to compare the in-hospital outcomes and costs between the 2 procedures.

Key Points

Questions Has the use of robotic-assisted vs laparoscopic radical nephrectomy changed from 2003 to 2015?

Findings The proportion of radical nephrectomies using robotic-assisted operations increased from 1.5% in 2003 to 27.0% in 2015. Although there was no significant difference between robotic-assisted vs laparoscopic radical nephrectomy in major postoperative complications, robotic-assisted procedures were associated with longer operating time and higher direct hospital costs.

Meaning The use of robotic-assisted radical nephrectomy increased substantially from 2003 to 2015 and was associated with prolonged operating time and increased costs.

Methods

Data Source

A retrospective cohort study was performed using the Premier Healthcare database (Premier), an all-payer, fee-supported database developed to measure resource use and quality, to assess the usage of the robotic platform for radical nephrectomy. This database captures approximately 20% of all hospitalizations from more than 700 acute care hospitals in the United States (>530 million hospital visits and 6 million inpatient discharges per year since 2011). This database also contains information on demographic and clinical characteristics, such as pharmaceuticals administered, laboratory and other diagnostic tests performed, and therapeutic services provided during admission. The Premier Healthcare database uses a reconciliation process that allows for verification and validation of hospital reporting for the use of resources and cost. Data audits are performed, and if reported costs submitted do not match the hospital's financial statement, Premier works with the hospital to correct the discrepancy.[15] Procedure and comorbidity data are provided by *International Classification of Diseases, Ninth Revision (ICD-9)* codes. This method has been used in other studies.[6,8,16,17] This investigation was deemed exempt from informed consent requirements by the Stanford University Medical Center institutional review board.

Patients

Patients receiving radical nephrectomy between January 2003 and September 2015 were identified by *ICD-9* code (55.51) and included in the analysis. Affiliated codes were identified and reviewed to ensure that radical nephrectomy was the primary procedure performed based on the diagnosis or concern for kidney cancer (eTable 1 in the Supplement). For example, cases of upper tract urothelial carcinoma (*ICD-9* codes 189.1 or 189.2), which have unique postoperative complication profiles stemming from the need for concurrent ureterectomy and cystotomy were excluded. Only patients receiving either robotic-assisted or laparoscopic radical nephrectomy were included. Patients undergoing open radical nephrectomy or nonelective surgeries were excluded. The inclusion and exclusion methodology is further depicted in the eFigure in the Supplement.

Main Exposures

Patients receiving robotic-assisted or laparoscopic radical nephrectomy were identified using the Charge Description Master, a catalog of all billable items eventually charged to the patient, to avoid possible inaccuracies stemming from the use of the *ICD-9* coding system in identifying robotic-assisted surgery.[17] The utilization of supplies unique to robotic procedures, as specified by the EndoWrist Instrument & Accessory Catalog from Intuitive Surgical, was used as an indicator for the use of robotic-assistance.[18] Nonrobotic cases were identified in a similar manner.

Demographic and Clinical Characteristics

Hospital-level data collected directly by Premier included size (<300, 300-500, and >500 beds), location (urban, rural), and teaching status (teaching, nonteaching). Patient-related data included year of surgery, age, race (white, black, and other), sex, and insurance status (private, Medicare, Medicaid, and other). Race determination was based on self-reporting by the patient and included in the demographics analysis to further

characterize the patient population.[6,17,19] Patients were also categorized based on the Charlson comorbidity index (0, 1, ≥2).

Outcomes

The primary outcome of the study was the trend in use of the robotic-assisted radical nephrectomy. The secondary outcomes of interest were perioperative complications, resource use, and direct hospital costs. Postoperative complications were classified based on the Clavien classification system.[20] These complications were defined as any (Clavien grades 1-5) or major (Clavien grades 3-5). Grade 1 complications include "Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological intervention." Grade 2 complications "[require] pharmacologic treatment with drugs other than such allowed for grade 1 complications." Grade 3 complications "[require] surgical, endoscopic or radiological intervention." Grade 4 describes "Life-threatening complications requiring intermediate care/intensive care unit." Grade 5 complications result in the "[d]eath of a patient." To identify events defined by the Clavien classification system, we used *ICD-9* codes as previously described.[6,21] Resource use variables analyzed included blood transfusion (packed red blood cells), operating time (hours), and length of stay (days). Operating time (≤4 hours vs >4 hours) and length of stay (≤4 days vs >4 days) were categorized as dichotomous variables.[19,22]

Two types of direct hospital costs were provided by the Premier Healthcare database. A total of 78.5% of all patients included in the study were treated by hospitals providing procedural costs (or "reported costs") and the remainder were treated by hospitals providing estimates based on Medicare cost-to-charge ratios (MCCR or "estimated costs").[17,23,24] If hospitals have their own cost-accounting system, they assign relative value units to procedures to estimate cost. These hospitals are then able to provide Premier with both charge and cost data. If hospitals do not have a cost-accounting system or do not use relative value units to estimate cost, they provide only charge data. Hospital departments are mapped to a specific line on the Medicare Cost Report to determine the appropriate MCCR, which is then used to determine cost at a given resource level. All costs were adjusted to 2015 US dollars using the consumer price index.

Statistical Analyses

Categorical variables were presented as numbers and percentages and were compared using the χ^2 test. Linear trends in the proportion of robotic-assisted radical nephrectomies over 13 years were assessed using a logistic regression model. To reduce potential confounding, we performed an adjustment for differences in baseline patient characteristics by using a weighted logistic regression model with inverse probability of treatment weighting (IPTW).[25] Using this technique, the weights used for patients undergoing laparoscopic radical nephrectomy were the inverse of 1 minus the propensity score, and weights used for patients receiving robotic-assisted radical nephrectomy were the inverse of the propensity score alone. The propensity scores were estimated by multiple logistic regression analysis without regard to outcomes. A full nonparsimonious model was developed including all variables shown in **Table 1**.

Log-binomial regression models were used to estimate risk ratios (RRs) for each exposure on perioperative outcomes. Since it was determined that the outcome variables related to direct hospital costs were not normally distributed, a generalized linear model with gamma distribution was generated, allowing for a link function to connect the predictor with the response variables.[26] All models were adjusted for clustering of patients within hospitals using robust standard errors to account for interhospital variability. An analysis was also conducted to determine if the costs related to each surgical approach (robotic-assisted and laparoscopic radical nephrectomy) were related to the source of cost obtained within the Premier Hospital database. For these analyses, the propensity score analyses were re-performed to obtain a new IPTW for each patient. These analyses were not prespecified but rather post hoc and thus interpreted as exploratory. Statistical analysis was performed using 2-sided tests, with a significance level of <.05 and Stata 14 statistical software (StataCorp).

Results

A cohort of 23 753 patients undergoing elective laparoscopic radical nephrectomy (n = 18 573) or robotic-assisted radical nephrectomy (n = 5180) for the management of renal masses at 416 US hospitals between 2003 and 2015 was evaluated. The **Figure** shows the trend in surgical approach for radical nephrectomy over time. Use of robotic-assisted surgery for radical nephrectomy increased from 1.5% to 27.0% in the entire radical nephrectomy cohort from 2003 to 2015 (*P* for trend <.001). Since 2009, the decrease in laparoscopic radical nephrectomies paralleled the increase in robotic-assisted radical nephrectomies, while the proportion of open radical nephrectomy cases plateaued. By 2015, robotic-assisted radical nephrectomy was performed more commonly than laparoscopic radical nephrectomy in the United States.

The characteristics before and after propensity weighting are summarized in Table 1. Before the propensity weighting process, the robotic-assisted and laparoscopic radical nephrectomy cohorts differed in several variables, particularly year of surgery, Charlson comorbidity index, and insurance status. After propensity score weighting, similar covariate distributions were achieved between robotic-assisted and laparoscopic radical nephrectomy in the weighted populations (the standardized difference score, <0.2).

Unadjusted and IPTW-adjusted perioperative outcomes are presented in **Table 2**. The unadjusted rate of any (28.2% vs 21.9%; risk difference, 6.3%; 95% CI, 4.9% to 7.6%) or major complications (4.3% vs 3.6%; risk difference, 0.7%; 95% CI, 0.1% to 1.3%), prolonged operating time (43.8% vs 26.2%; risk difference, 17.6%; 95% CI, 16.1% to 19.1%), and blood transfusion (19.5% vs 18.2%; risk difference, 1.4%; 95% CI, 1.4% to 2.6%) for patients receiving robotic-assisted radical nephrectomy were higher than for those who received laparoscopic

Table 1. Baseline Characteristics of Patients Receiving Laparoscopic and Robotic Radical Nephrectomy (2003-2015)

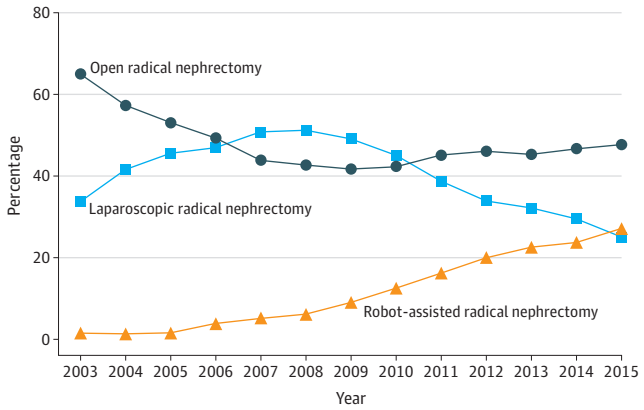
	Before Propensity Weighting				After Propensity Weighting			
	No. (%) of Patients				No. (%) of Patients			
	Laparoscopic (n = 18 573)	Robotic (n = 5180)	Standardized Difference	*P* Value	Laparoscopic (n = 18 573)	Robotic (n = 5180)	Standardized Difference	*P* Value
Age, y								
<55	5313 (28.6)	1472 (28.4)	−0.004	.03	5317 (28.6)	1491 (28.8)	0.003	.92
55-64	4917 (26.5)	1387 (26.8)	0.007		4936 (26.6)	1405 (27.1)	0.013	
65-74	4892 (26.3)	1441 (27.8)	0.033		4936 (26.6)	1345 (26.0)	−0.014	
>74	3451 (18.6)	880 (17.0)	−0.042		3384 (18.2)	1939 (18.1)	−0.002	
Sex								
Men	10 732 (57.8)	3060 (59.1)	0.026	.10	10 781 (58.1)	2998 (57.9)	−0.003	.88
Women	7841 (42.2)	2120 (40.9)			7792 (41.9)	2182 (42.1)		
Race/ethnicity								
White	13 754 (74.1)	3854 (74.4)	0.008	.64	13 756 (74.1)	3873 (74.8)	0.016	.64
Black	1904 (10.2)	540 (10.4)	0.006		1930 (10.4)	587 (11.3)	0.030	
Others[a]	2915 (15.7)	786 (15.2)	−0.014		2887 (15.5)	720 (13.9)	−0.047	
Charlson comorbidity score								
0	10 005 (53.9)	2530 (48.8)	−0.101	<.001	9817 (52.9)	2759 (53.2)	0.008	.93
1	4357 (23.4)	1218 (23.5)	0.001		4346 (23.4)	1195 (23.1)	−0.008	
≥2	4211 (22.7)	1432 (27.7)	0.115		4410 (23.7)	1226 (23.7)	−0.002	
Insurance status								
Medicare	8574 (46.1)	2470 (47.7)	0.030	<.001	8624 (46.4)	2373 (45.8)	−0.012	.73
Medicaid	888 (4.8)	338 (6.5)	0.076		973 (5.2)	303 (5.8)	0.027	
Private	7999 (43.1)	2106 (40.7)	−0.049		7904 (42.6)	2231 (43.1)	0.010	
Others	1112 (6.0)	266 (5.1)	−0.037		1072 (5.8)	273 (5.3)	−0.022	
Teaching hospital								
No	9582 (51.6)	2093 (40.4)	−0.226	<.001	9059 (48.8)	2228 (43.0)	−0.116	.40
Yes	8991 (48.4)	3087 (59.6)			9514 (51.2)	2952 (57.0)		
Hospital bed size								
<300	4668 (25.1)	1098 (21.2)	−0.093	<.001	4469 (24.0)	1044 (20.1)	−0.094	.74
300-500	6817 (36.7)	1707 (32.9)	−0.079		6699 (36.1)	2009 (38.8)	0.056	
>500	7088 (38.2)	2375 (45.9)	0.156		7405 (39.9)	2127 (41.1)	0.024	
Hospital location								
Rural	1517 (8.2)	246 (4.8)	−0.139	<.001	1365 (7.4)	275 (5.3)	−0.084	.25
Urban	17 056 (91.8)	4934 (95.2)			17 208 (92.6)	4905 (94.7)		
Surgery years								
2003-2007	6883 (37.0)	447 (8.6)	−0.720	<.001	5714 (30.7)	1482 (28.6)	−0.047	.83
2008-2011	7087 (38.2)	1681 (32.5)	−0.120		6826 (36.7)	1915 (37.0)	0.004	
2012-2015	4603 (24.8)	3052 (58.9)	0.738		6033 (32.6)	1783 (34.4)	0.041	

[a] Included Hispanic, other, and unknown.

radical nephrectomy. Prolonged length of stay was less frequent in the robotic-assisted vs the laparoscopic radical nephrectomy group (21.2% vs 25.1%; risk difference, −3.9%; 95% CI, −5.2% to −2.7%). However, the IPTW-adjusted rates of any or major complications, blood transfusion, and prolonged length of stay were similar between the robotic-assisted and laparoscopic radical nephrectomy groups. The IPTW-adjusted rate of prolonged operating time for patients undergoing robotic-assisted radical nephrectomy was higher than for patients receiving laparoscopic radical nephrectomy (46.3% vs 25.8%; risk difference, 20.5%; 95% CI, 14.2% to 26.8%).

An unadjusted cost comparison by surgical approach is presented in the eTable 2 in the Supplement. The IPTW-adjusted analysis suggests that robotic-assisted radical nephrectomy was associated with higher mean 90-day direct hospital costs ($19530 vs $16851; difference, $2678; 95% CI, $838 to $4519), likely accounted for by higher operating room ($7217 vs $5378; difference, $1839; 95% CI, $1050 to $2628) and supply costs ($4876 vs $3891; difference, $985, 95% CI, $473 to $1498; **Table 3**). Further analyses were performed to identify the association of the source of cost obtained by the Premier data set (reported vs estimated) and the difference in direct hospital costs between robotic-assisted and

Figure. Trends of Open, Laparoscopic, and Robotic-Assisted Radical Nephrectomy in the United States, 2003 to 2015



Numbers below each year represent the total number of patients receiving radical nephrectomy.

Table 2. Unadjusted and Adjusted Risk Ratios and Absolute Risk Differences for Perioperative Outcomes in Patients Undergoing Laparoscopic and Robotic Radical Nephrectomy, 2003-2015

	No. of Events (%)			
	Laparoscopic (n = 18 573)	Robotic (n = 5180)	Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)
Unadjusted				
Any postoperative complication[a]	4074 (21.9)	1461 (28.2)	6.3 (4.9 to 7.6)	1.29 (1.22 to 1.35)
Major postoperative complications[a]	674 (3.6)	223 (4.3)	0.7 (0.1 to 1.3)	1.19 (1.02 to 1.38)
Operating time (>4 h)	4868 (26.2)	2270 (43.8)	17.6 (16.1 to 19.1)	1.67 (1.61 to 1.74)
Blood transfusion (packed red blood cells)	3373 (18.2)	1011 (19.5)	1.4 (1.4 to 2.6)	1.08 (1.01 to 1.44)
Length of hospital stay (>4 d)	4663 (25.1)	1097 (21.2)	−3.9 (−5.2 to −2.7)	0.84 (0.80 to 0.89)
Adjusted by Inverse Probability of Treatment Weighting[b]				
Any postoperative complication[a]	4347 (23.4)	1149 (22.2)	−1.2 (−5.4 to 3.0)	0.95 (0.78 to 1.15)
Major postoperative complications[a]	709 (3.8)	183 (3.5)	−0.3 (−1.0 to 0.5)	0.93 (0.75 to 1.16)
Operating time (>4 h)	4794 (25.8)	2398 (46.3)	20.5 (14.2 to 26.8)	1.79 (1.52 to 2.11)
Blood transfusion (packed red blood cells)	3310 (17.8)	1098 (21.2)	3.4 (−0.6 to 7.3)	1.19 (0.98 to 1.44)
Length of hospital stay (>4 d)	4593 (24.7)	1253 (24.2)	−0.5 (−3.6 to 2.5)	0.98 (0.86 to 1.11)

[a] Postoperative complications were defined as any (Clavien grades 1-5) or major (Clavien grades 3-5).

[b] Adjusted for age, sex, race, Charlson comorbidity index, insurance status, teaching status, number of beds, hospital location, surgery year, and hospital clustering.

laparoscopic radical nephrectomy (**Table 4**). The 90-day direct hospital ($19 471 vs $16 779; difference, $2692; 95% CI, $787 to $4597), supply ($4905 vs $3999; difference, $906; 95% CI, $289 to $1524), and operating room costs ($7022 vs $5265; difference, $1758; 95% CI, $869 to $2647) were higher for robotic-assisted radical nephrectomy among patients treated at hospitals providing reported costs. Among patients receiving care from hospitals providing estimated costs using MCCR, robotic-assisted radical nephrectomy was associated with higher supply costs ($4728 vs $3474; difference, $1254; 95% CI, $136 to $2373) and operating room costs ($7589 vs $5810; difference, $1779; 95% CI, $227 to $3331) but similar 90-day direct hospital cost compared with laparoscopic radical nephrectomy ($19 187 vs $17 112; difference, $2075; 95% CI, −$1288 to $5439).

Discussion

In this retrospective cohort study evaluating patients undergoing robotic-assisted or laparoscopic radical nephrectomy for renal mass in the United States between 2003 and 2015, use of robotic-assisted surgery increased from 1.5% to 27.0% for the entire radical nephrectomy cohort. Compared with laparoscopic radical nephrectomy, robotic-assisted radical nephrectomy was not associated with an increased risk of any or major postoperative complications but was associated with prolonged operating time and higher hospital costs.

The use of the robotic platform has increased rapidly for curative renal surgery, especially for partial nephrecto-

Table 3. Adjusted Cost Comparison by Surgical Approach, 2003-2015

Services[a]	Costs, Mean (95% CI), US $		Difference (95% CI)	*P* Value
	Laparoscopic (n = 18 573)	Robotic (n = 5180)		
Supply	3891 (3632 to 4150)	4876 (4377 to 5376)	985 (473 to 1498)	<.001
Room and board	4432 (4174 to 4691)	4262 (3691 to 4833)	−170 (−743 to 401)	.56
Pharmacy	1132 (994 to 1270)	1103 (934 to 1272)	−29 (−207 to 150)	.75
Operating room	5378 (5081 to 5676)	7217 (6379 to 8055)	1839 (1050 to 2628)	<.001
90-d Direct hospital	16 851 (16 209 to 17 494)	19 530 (17 617 to 21 443)	2678 (838 to 4519)	.004

[a] Adjusted for age, sex, race, Charlson comorbidity index, insurance status, teaching status, number of beds, hospital location, surgery year, and hospital clustering.

Table 4. Cost Comparison Analysis by the Source of Cost Data, 2003-2015

Services	Costs, Mean (95% CI), US $[a]		Difference (95% CI)	*P* Value
	Laparoscopic (n = 14 679)	Robotic (n = 3958)		
Reported Costs (Procedural)				
Supply	3999 (3694 to 4303)	4905 (4320 to 5491)	906 (289 to 1524)	.004
Room and board	4346 (4053 to 4640)	4290 (3623 to 4957)	−57 (−702 to 589)	.86
Pharmacy	1154 (982 to 1325)	1138 (1016 to 1259)	−16 (−175 to 143)	.85
Operating room	5265 (4921 to 5608)	7022 (6083 to 7961)	1758 (869 to 2647)	<.001
90-d Direct hospital	16 779 (16 042 to 17 516)	19 471 (17 488 to 21 454)	2692 (787 to 4597)	.006
Estimated Costs (MCCR)				
Supply	3474 (3051 to 3896)	4728 (3557 to 5898)	1254 (136 to 2373)	.03
Room and board	4767 (4256 to 5278)	4095 (3491 to 4699)	−672 (−1457 to 113)	.09
Pharmacy	1043 (897 to 1189)	968 (586 to 1351)	−74 (−436 to 287)	.69
Operating room	5810 (5234 to 6387)	7589 (5797 to 9382)	1779 (227 to 3331)	.03
90-d Direct hospital	17 112 (15 891 to 18 333)	19 187 (15 620 to 22 754)	2075 (−1288 to 5439)	.23

Abbreviation: MCCR, Medicare cost-to-charge ratios.

[a] Adjusted for age, sex, race, Charlson comorbidity index, insurance status, teaching status, number of beds, hospital location, surgery year and hospital clustering.

mies. However, little is known about the nationwide use of robotic-assistance for radical nephrectomy in the United States. Some studies have suggested that the proportion of robotic-assisted cases was less than 10% of all radical nephrectomies during the late 2000s.[13,27] In contrast, this study found that the proportion of robotic-assisted radical nephrectomies increased to approximately 30% of all radical nephrectomies by 2015, which is higher than for the laparoscopic approach in the United States. A parallel decrease in the use of laparoscopic radical nephrectomy suggests a shift to robotic surgery from cases that would have been previously treated laparoscopically rather than by open surgery.

It remains unclear why the use of robotic-assistance has increased substantially and has been steadily replacing laparoscopic radical nephrectomies. One possibility is the financial viability of the robotic system in relatively small hospitals. The costs of purchasing and maintaining the robotic system range from $0.5 to $2.5 million and $80 000-$170 000 per year , respectively.[28] Surgeons have to perform at least 100 to 150 procedures annually to offset the upfront and ongoing costs of its acquisition.[29] Another possibility is that the increase in robotic-assisted radical nephrectomies might be associated with the known increase in robotic-assisted partial nephrectomies. The use of robotic-assistance has increased rapidly since 2008 and in some areas has overtaken laparoscopic partial nephrectomy.[27,30] This trend suggests an overall increase in the risk of intraoperative conversion to radical nephrectomy as surgeons attempt to treat larger and more complex tumors using the nephron-sparing approach.[31] Considering that the incidence of intraoperative robotic-assisted partial to radical nephrectomy conversion remains prevalent especially for low-volume hospitals and surgeons in the United States, the increase in unsuccessful robotic-assisted partial nephrectomies may have contributed to the increase in robotic-assisted radical nephrectomy use.[32] As urological training has been focused on robotic surgery driven predominantly by the widespread use of robotic-assisted radical prostatectomy (more than 80% of the total prostatectomies in the United States in 2013), urologists completing their residency or fellowship training may also prefer the robotic platform over laparoscopic surgery due to its ergonomic console and 3-dimensional screen.[6]

Although the use of the robotic platform has been well-received by surgeons performing laparoscopic partial nephrectomy due to ease of tumor resection and renorrhaphy, the evidence supporting the use of robotic-assistance for radical nephrectomy remains somewhat biased. Radical nephrectomy does not require the routine use of intracorporeal suturing, which is a primary advantage of robotic assistance in partial nephrectomy and radical prostatectomy. Furthermore, there are several disadvantages of robotic technology scarcely acknowledged by prior literature. For example, robot arms return minimal tactile feedback to the surgeon. Moreover, the field of view during robotic-assisted radical nephrectomy is relatively narrow. Therefore, special attention is required to prevent unintentional trauma to peripheral organs not felt or visualized by the surgeon.[10]

There is also a significant cost burden attributed to the use of the robotic system. This study shows that the use of the robotic platform for radical nephrectomy increased the total direct hospital cost by nearly $2700, which is more than 15% of the total cost of the laparoscopic approach. This increased expense for robotic-assisted radical nephrectomy was mostly accounted for by increased operating room cost, which is directly correlated with operating time. These findings are consistent with the observations of a study from Maryland that reported a $5111 increase in hospital charges per robotic-assisted radical nephrectomy compared with laparoscopic radical nephrectomy.[33] Hospitals are likely to increase charges for robotic surgery to recoup costs related to the acquisition and maintenance of the robotic system despite not receiving reimbursement for these fixed costs from Medicare and private insurers.[34] Increased hospital charges for robotic surgery influence future reimbursement because the Centers for Medicare & Medicaid Services (CMS) use hospital charges to calculate the relative weight for each diagnosis related group (DRG) annually, which in turn help determine the payment made for inpatient services. The DRG weight is determined by the average resources required to treat cases within the DRG and is multiplied by the average payment rate for a typical case to yield the total reimbursement rate.[35] Thus, hospitals are incentivized to charge payers for the true cost of robot use. A prior study estimates an additional cost to the health care system of $2.5 billion if conventional surgeries were to be fully replaced by robotic surgery.[7]

As for the acquisition, maintenance, and replacement of the robot, the attainment of these costs remains challenging. The true cost of the robot varies based on factors such as the number of robotic cases being performed by each hospital, nonurological use of the robot technology, the type of robotic system being used, specific price negotiations between the hospital and robot company, and likely other variables as well. Thus, the fixed costs of the robot cannot be accurately determined by this database.

Robotic surgery was associated with higher 90-day direct hospital costs (>$2692) for hospitals providing reported costs, though not for hospitals providing MCCR-estimated costs. Although CMS uses hospital charges to estimate the relative cost of treating patients, charges tend to vary among hospitals according to size, location, payer mix, and for-profit status.[36,37] Given the potential for variability using the latter process, hospitals have been encouraged to adopt an internal cost-measurement system.[38] Therefore, the higher costs for robotic surgery observed for patients from hospitals providing reported costs may have greater clinical relevance and accuracy.

Robotic partial nephrectomy does have some advantages over traditional laparoscopic partial nephrectomy, including reduced ischemic time and total operating time. However, this study suggests that the traditional advantages of robotic surgery are not applicable to radical nephrectomy when compared with conventional laparoscopy. Some high-volume surgeons also argue that robotic-assisted radical nephrectomy may be beneficial for treating advanced kidney cancer with vena cava tumor thrombus in a minimally invasive manner.[39] However, that does not adequately explain the rapid increase in robotic-assisted radical nephrectomy within the United States because these advanced kidney cancers have been largely treated by the open approach. Although the initial results of safety and short-term oncological outcomes are promising, further investigation is required to determine the role of robotic surgery for vena cava tumor thrombectomy.

Limitations

This study has several limitations. First, it is subject to potential misclassification bias as billing codes and *ICD-9* procedural codes were used to capture robotic-assisted surgeries. However, previous studies using the same method showed that *ICD-9* coding for robotic-assisted surgery was sufficiently specific.[6,8,17] Second, the Premier Healthcare database does not publish information regarding tumor characteristics. Large or complex renal tumors, such as hilar and endophytic tumors, increase the risk for perioperative complications during laparoscopic surgery, although more notably for partial nephrectomy.[40] The influence of tumor characteristics is likely negligible for both robotic-assisted and laparoscopic radical nephrectomy because they are both minimally invasive and have similar clinical indications. Third, because the rate of conversion to open radical nephrectomy is difficult to evaluate retrospectively, the rates of conversion could not be compared between the 2 approaches using the Premier Healthcare database. Fourth, long-term data are necessary to further compare oncological outcomes and quality of life between robotic-assisted and laparoscopic radical nephrectomy.

Conclusions

Among patients undergoing radical nephrectomy for renal mass between 2003 and 2015, the use of robotic-assisted surgery increased substantially. The use of robotic-assistance was not associated with increased risk of any or major complications but was associated with prolonged operating time and higher hospital costs compared with laparoscopic surgery.

ARTICLE INFORMATION

Accepted for Publication: September 20, 2017.

Author Contributions: Drs Jeong and Chung had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.
Concept and design: Jeong, Han, Chung.
Acquisition, analysis, or interpretation of data: Khandwala, Kim, Han, Li, Wang, Chang.
Drafting of the manuscript: Jeong, Khandwala, Chang.
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Statistical analysis: Jeong, Khandwala, Li, Wang.
Administrative, technical, or material support: Kim, Han.
Supervision: Chung.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Chung reported personal fees from Intuitive Surgical. No other disclosures were reported.

Additional Contributions: We thank Sung-Cheol Yun, PhD, for his assistance with the statistical analysis. He is an associate professor of University of Ulsan College of Medicine, Asan Medical Center (Seoul, Korea) and was not compensated for his work. We also thank Bruce Bowdy, RPh, PhD, vice president of Premier Applied Sciences (Premier, Inc), for his assistance with the study. He was not compensated for his contribution.

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Severe Inflammatory Skin Disease Guideline Revisions

Question: How should the severe inflammatory skin disease guideline be modified to reflect the Pharmacy and Therapeutic Committee's recommendations for treatments for atopic dermatitis?

Question source: P&T staff, HERC staff

Issue: In November 2017, the HERC adopted modifications to the severe inflammatory skin disease guideline for therapies for atopic dermatitis (AD) based on ICD-10 Dermatology reviewer recommendations. However, these therapies do not completely agree with the evidence reviews on medication effectiveness done by the P&T Committee. P&T and HERC staff have worked to propose modifications to the guideline that reflect the evidence reviews done by P&T.

Specific P&T concerns include lack of evidence to support use of cyclosporine, methotrexate or azathioprine in atopic dermatitis. Given the safety risks associated with systemic therapy, it would seem that topical therapies such as tacrolimus or pimecrolimus should be recommended prior to systemic therapy. According to NICE guidelines for AD, systemic immunosuppressants are "treatments of last resort" in AD patients. The cost of tacrolimus and pimecrolimus have come down considerably since the ICD-10 Dermatology review and should no longer be considered prohibitive.

Based on staff and P&T review, removing older language regarding psoriasis was also recommended. P&T review criteria currently match the guideline, but could change in a more nimble fashion if new medications come on the market, costs of medications change, etc.

Note: line 424 is SEVERE INFLAMMATORY SKIN DISEASE.

HERC staff recommendation:

1) Modify GN21 as shown below
    a. Removes wording regarding medications for atopic dermatitis and psoriasis. P&T review criteria will determine coverage

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 424,480,502,530,539,654

Inflammatory skin conditions included in this guideline are:

A) Psoriasis
B) Atopic dermatitis
C) Lichen planus
D) Darier disease
E) Pityriasis rubra pilaris
F) Discoid lupus

The conditions above are included on line 424 if severe, defined as having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND one or more of the following:

A) At least 10% of body surface area involved
B) Hand, foot or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 480, 502, 530, 539 and 654.

~~For severe psoriasis, first line agents include topical agents, phototherapy and methotrexate. Second line agents include other systemic agents and oral retinoids and should be limited to those who fail, or have contraindications to, or do not have access to first line agents. Biologics are included on this line only for the indication of severe plaque psoriasis; after documented failure of first line agents and failure of (or contraindications to) a second line agent.~~

~~For severe atopic dermatitis/eczema, fist line agents include topical corticosteroids, narrowband UVB, cyclosporine, methotrexate, and azathioprine. Second line agents include topical pimecrolimus and topical tacrolimus and should be limited to those who fail or have contraindications to first line agents. Biologic agents are included on this line for atopic dermatitis only after failure of or contraindications to first and second line agents.~~

Ultraviolet Light and
Other Light Therapies

Questions:

1) Should ultraviolet light therapy be paired with mycosis fungoides and similar cutaneous lymphoma diagnoses?
2) Should ultraviolet light therapy be removed from certain lines due to lack of appropriate pairings?
3) Should laser treatment for inflammatory skin disorders be continued? If so, should there be any limitations?
4) Should home light therapy be included on the Prioritized List?
5) Where should home bili-lights for treatment of newborns with hyperbilirubinemia be placed?

Question sources:

1) Dave Pass, MD Providence Medical Director; subsequently other CCO medical directors
2) HERC staff
3) CCO medical directors
4) CCO medical directors, HSD staff
5) HERC staff

Issues:

1) Psoralens and ultraviolet A light (PUVA) treatments and narrow-band UVB phototherapy (NB-UVB) treatments are considered standard of care for mycosis fungoides and other lymphomas involving the skin (See Olsen 2016, https://www.jaad.org/article/S0190-9622(15)02206-9/pdf). Mycosis fungoides is the most common form of cutaneous T-cell lymphoma. It generally affects the skin, but may progress internally over time. Symptoms include rash, tumors, skin lesions, and itchy skin. Other treatments for mycosis fungoides include chemotherapy and radiation therapy.
2) On review, staff found multiple different lines that had PUVA and UVB therapy that did not appear to have any diagnoses that were appropriate for pairing. In addition, PUVA and UVB were missing from lines with some of these appropriate diagnoses. PUVA and UVB are used to treat polycythemia vera, graft-versus-host disease, severe refractory atopic dermatitis, severe psoriasis, severe lichen planus, alopecia areata, vitiligo, localized scleroderma, mastocytosis, severe dermatitis, and severe parapsoriasis.
3) CCO medical directors raised concerns about laser light therapy for inflammatory skin disease. They feel that this therapy is being misused. It is considerably more expensive that traditional light therapy [note: fee schedule information indicates that it is generally in the same cost range], but is being used as first line therapy in many dermatology offices. The CPT codes for laser light therapy (CPT 96920-96922 Laser treatment for inflammatory skin disease (psoriasis)) are on lines 206 SUPERFICIAL ABSCESSES AND CELLULITIS, 424 SEVERE INFLAMMATORY SKIN DISEASE, AND 539 MILD PSORIASIS; DERMATOPHYTOSIS: SCALP, HAND, BODY. Xenon chloride (XeCl) lasers and lamps were developed as targeted NB-UVB treatment devices; they generate monochromatic or very narrow band radiation with a lambda max of 308 nm. Targeted phototherapy devices are directed at specific lesions or affected areas, thus limiting exposure to the surrounding normal tissues. They may therefore allow higher dosages compared to a light box, which could result in fewer treatments to produce clearing. The American Academy of Dermatology guidelines for the treatment of psoriasis state (https://ac.els-cdn.com/S0190962215026146/1-s2.0-S0190962215026146-main.pdf?_tid=1cb1debf-f369-4183-9407-aa978cb7a667&acdnat=1525714939_dc9b3c3e4fe9eba5f2fdfc611beb495d) "Topical

targeted phototherapy (excimer laser) is indicated for adult and pediatric patients with mild, moderate, or severe psoriasis with <10% BSA involvement." Level of Evidence: II Strength of Recommendation: B (Mentor 2010).

4) CCO medical directors requested a review into use of home UVB light boxes for treatment of skin disease. This therapy was felt to be cheaper than biologic medications, but the efficacy of home light therapy was not known by the group. The Ontario Health Technology Assessment (http://www.hqontario.ca/Portals/0/Documents/evidence/reports/rev_uv_photo_20091201.pdf) group reviewed home light therapy in their review of UV light, and found "Effectiveness and safety of home NB-UVB phototherapy was not inferior to NB-UVB phototherapy provided in a clinic to patients with psoriasis referred for phototherapy. Treatment burden was lower and patient satisfaction was higher with home therapy and patients in both groups preferred future phototherapy treatments at home." (OHTA 2009) OHTA based their conclusions on a single high quality study, and noted the literature is very limited on home therapy. They note: "When combined with a telemedicine follow-up, home phototherapy may provide an alternative strategy for improved access to service and follow-up care, particularly for those with geographic or mobility barriers. Safety and effectiveness have, however, so far been evaluated for only one phototherapy home-based delivery model."
    a. No additional high quality trials found of home phototherapy other than the PLUTO trial referenced in the OHTA report
        i. **Koek 2009**, RCT to determine whether ultraviolet B phototherapy at home is equally safe and equally effective as ultraviolet B phototherapy in an outpatient setting for patients with psoriasis [PLUTO trial] (https://www.bmj.com/content/bmj/338/bmj.b1542.full.pdf)
            1. N=196 patients
            2. Results: 82% of the patients treated at home compared with 79% of the patients treated in an outpatient setting reached the SAPASI 50 (difference 2.8%, 95% confidence interval −8.6% to 14.2%), and 70% compared with 73% reached the PASI 50 (−2.3%, −15.7% to 11.1%). For patients treated at home the median SAPASI score decreased 82% (from 6.7 to 1.2) and the median PASI score decreased 74% (from 8.4 to 2.2), compared with 79% (from 7.0 to 1.4) and 70% (from 7.0 to 2.1) for patients treated in an outpatient setting. Treatment effect as defined by the mean decline in PASI and SAPASI scores was significant (P<0.001) and similar across groups (P>0.3). Total cumulative doses of ultraviolet B light were similar (51.5 v 46.1 J/cm2, difference 5.4, 95% confidence interval −5.2 to 16.0), and the occurrence of short term side effects did not differ. The burden of undergoing ultraviolet B phototherapy was significantly lower for patients treated at home (differences 1.23 to 3.01, all P≤0.001). Quality of life increased equally regardless of treatment, but patients treated at home more often rated their experience with the therapy as "excellent" (42%, 38/90) compared with patients treated in the outpatient department (23%, 20/88; P=0.001).
            3. Conclusion Ultraviolet B phototherapy administered at home is equally safe and equally effective, both clinically and for quality of life, as ultraviolet B phototherapy administered in an outpatient setting. Furthermore, ultraviolet B phototherapy at home resulted in a lower burden of treatment and led to greater patients' satisfaction.

ii. **Koek 2010**, economic analysis of PLUTO trial (https://www.bmj.com/content/bmj/340/bmj.c1490.full.pdf)
    1. The average total costs by the end of phototherapy were €800 for home treatment and €752 for outpatient treatment, showing an incremental cost per patient of €48 (95% CI €−77 to €174). The average total costs by one year after the end of phototherapy were €1272 and €1148 respectively (difference €124, 95% CI €−155 to €403).
    2. Cost utility analyses revealed that patients experienced equal health benefits—that is, a gain of 0.296 versus 0.291 QALY (home v outpatient) by the end of phototherapy (difference 0.0052, −0.0244 to 0.0348) and 1.153 versus 1.126 QALY by one year after the end of phototherapy (difference 0.0267, −0.024 to 0.078).
    3. Incremental costs per QALY gained were €9276 and €4646 respectively, both amounts well below the normally accepted standard of €20 000 per QALY.
    4. Conclusions: Home ultraviolet B phototherapy for psoriasis is not more expensive than phototherapy in an outpatient setting and proved to be cost effective. As both treatments are at least equally effective and patients express a preference for home treatment, the authors conclude that home phototherapy should be the primary treatment option for patients who are eligible for phototherapy with ultraviolet B light.

5) HERC staff became aware during this review that home bilirubin lights (HCPCS E0202 Phototherapy (bilirubin) light with photometer) are currently Ancillary. Neonatal jaundice is found on line 102 HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE

Other coverage policies: All major insurers cover PUVA and UVB therapy for mycosis fungoides and related cutaneous lymphomas such as Sezary syndrome. All major insurers also cover UV light therapy for moderate to severe psoriasis, eczema and other inflammatory skin diseases. Most major insurers cover home UVB therapy for qualifying patients.

The American Academy of Dermatology (2017) (https://pdfs.semanticscholar.org/bfb8/2a320b0a0a3547823c088bef7506fe3d728f.pdf) does not include light therapy in their recommendations for treatment of acne, although they note some promising studies for PUVA-type treatments.

Fee Schedule:
CPT 96920-96922 (laser therapy) are paid at $48-168
CPT 96900 (Actinotherapy (ultraviolet light)) is paid at $14
CPT 96910 (Photochemotherapy; tar and ultraviolet B (Goeckerman treatment) or petrolatum and ultraviolet B) is paid at $50
CPT 96912 (Photochemotherapy; psoralens and ultraviolet A (PUVA)) is paid at $64

Ultraviolet Light and
Other Light Therapies

CPT 96913 (Photochemotherapy (Goeckerman and/or PUVA) for severe photoresponsive dermatoses requiring at least 4-8 hours of care under direct supervision of the physician (includes application of medication and dressings)) is paid at $90

Home light therapy units cost:
E0691 - $797.27 (purchase) or $79.73 (monthly rental)
E0692 - $1001.15 (purchase) or $100.11 (monthly rental)
E0693 - $1234.15 (purchase) or $123.42 (monthly rental)
E0694 - $3928.15 (purchase) or $392.82 (monthly rental)
A4633 - $36.41 for each replacement bulb

Claims review: There are paid claims for light therapy for diagnoses such as mycosis fungoides and cutaneous T cell lymphoma. Other paid claims were for psoriasis, severe atopic dermatitis, scleroderma, and lichen sclerosis.

Home light therapy units are currently not allowed in HSD rule. CCOs report little or no use. If home light therapy is added to the Prioritized List, only FDA approved light units would be eligible for reimbursement.

Ultraviolet Light and
Other Light Therapies

Current Prioritized List status:
Mycosis fungoides is on the Non-Hodgkins lymphoma lines (lines 158 [medical therapy], 163 [bone marrow transplant]) which have no ultraviolet light therapy CPT codes.

CPT code	Code description	Current Line(s)
96900	Actinotherapy (ultraviolet light) [used for NB-UVB as well as general UVA and UVB therapy]	56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE 102 HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE 213 BULLOUS DERMATOSES OF THE SKIN 358 BODY INFESTATIONS (E.G., LICE, SCABIES) 373 ACNE CONGLOBATA (SEVERE CYSTIC ACNE) 407 EPIDERMOLYSIS BULLOSA 424 SEVERE INFLAMMATORY SKIN DISEASE 487 DERMATOPHYTOSIS OF NAIL, GROIN, AND FOOT AND OTHER DERMATOMYCOSIS 520 ROSACEA; ACNE 530 MILD ECZEMA 531 CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA 539 MILD PSORIASIS; DERMATOPHYTOSIS: SCALP, HAND, BODY 543 SYMPTOMATIC URTICARIA
96910	Photochemotherapy; tar and ultraviolet B (Goeckerman treatment) or petrolatum and ultraviolet B	56,213,358,373,407,424,487,520, 530, 531, 539, 543
96912	Photochemotherapy; psoralens and ultraviolet A (PUVA)	56,213,358,373,407,424,487,520, 530, 531, 539, 543
96913	Photochemotherapy (Goeckerman and/or PUVA) for severe photoresponsive dermatoses requiring at least 4-8 hours of care under direct supervision of the physician	56,213,358,373,407,424,487,520, 530, 531, 539, 543
A4633 E0691-E0694	Replacement bulb/lamp for ultraviolet light therapy system, each Ultraviolet light therapy system	Ancillary

Ultraviolet Light and
Other Light Therapies

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 424,480,502,530,539,654

Inflammatory skin conditions included in this guideline are:

A) Psoriasis
B) Atopic dermatitis
C) Lichen planus
D) Darier disease
E) Pityriasis rubra pilaris
F) Discoid lupus

The conditions above are included on line 424 if severe, defined as having functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND one or more of the following:

A) At least 10% of body surface area involved
B) Hand, foot or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 480, 502, 530, 539 and 654.

For severe psoriasis, first line agents include topical agents, phototherapy and methotrexate. Second line agents include other systemic agents and oral retinoids and should be limited to those who fail, or have contraindications to, or do not have access to first line agents. Biologics are included on this line only for the indication of severe plaque psoriasis; after documented failure of first line agents and failure of (or contraindications to) a second line agent.

For severe atopic dermatitis/eczema, fist line agents include topical corticosteroids, narrowband UVB, cyclosporine, methotrexate, and azathioprine. Second line agents include topical pimecrolimus and topical tacrolimus and should be limited to those who fail or have contraindications to first line agents. Biologic agents are included on this line for atopic dermatitis only after failure of or contraindications to first and second line agents.

[Note: the last 2 paragraphs of this guideline are proposed for deletion in another topic under consideration at this meeting.]

Ultraviolet Light and
Other Light Therapies

HERC staff summary

1) UVA and UVB light is standard of care for systemic malignancies primarily in the skin, such as mycosis fungoides. Additionally, such therapy is used for graft vs host disease and scleroderma. Light therapy is not recommended for acne by the American Academy of Dermatology.

2) Many of the lines currently containing the CPT codes for UVA and UVB light therapy have no appropriate diagnoses. Other lines with appropriate diagnoses do than have the CPT codes for this therapy.

3) Laser light therapy is only recommended by the American Academy of Dermatology for limited disease (<10% BSE), which by guideline definition limits its placement to the lower inflammatory skin disease line.

4) Home UVB light therapy has been shown by one high quality study to be non-inferior to office based light therapy. It may be easier for patients to comply with light therapy if it is available in the home; cost is similar to office based treatment.

5) Home bili-light therapy should be added to the line containing the diagnosis of neonatal hyperbilirubinemia.

HERC staff recommendations:

1) Add PUVA and UVB therapy for mycosis fungoides
    a. Add CPT 96900, 96910, 96912 and 96913 to line 158 HODGKIN'S LYMPHOMA TX: MEDICAL THERAPY
2) Remove PUVA and UVB therapy (CPT 96900, 96910, 96912 and 96913) from lines with no appropriate diagnoses. Note: few if any claims seen for diagnoses on these lines. Most diagnoses appropriate for ultraviolet light therapy are on line 424
    a. 56 ULCERS, GASTRITIS, DUODENITIS, AND GI HEMORRHAGE
    b. 102 HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE
        i. Bili light therapy has no specific CPT code (it is coded as part of inpatient NICU care). HCPCS E0202 (Phototherapy (bilirubin) light with photometer) is used for the actual lights. CPT 96900, 96912 and 96913 are not appropriate codes for bili lights per coding conventions
    c. 213 BULLOUS DERMATOSES OF THE SKIN
    D. 358 BODY INFESTATIONS (E.G., LICE, SCABIES)
    E. 373 ACNE CONGLOBATA (SEVERE CYSTIC ACNE)
    f. 407 EPIDERMOLYSIS BULLOSA
    g. 487 DERMATOPHYTOSIS OF NAIL, GROIN, AND FOOT AND OTHER DERMATOMYCOSIS
    h. 520 ROSACEA; ACNE
    i. 530 MILD ECZEMA
    j. 543 SYMPTOMATIC URTICARIA
3) Add ultraviolet light therapy (CPT 96900, 96910, 96912 and 96913) to the following lines which contain appropriate diagnoses
    a. 313 DISORDERS INVOLVING THE IMMUNE SYSTEM

        i. To pair with ICD-10 D89.81 (Graft-versus-host disease)
    b. 506 CIRCUMSCRIBED SCLERODERMA
    c. 654 DERMATOLOGICAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
        i. To pair with vitiligo (ICD-10 L80)
4) Remove laser therapy (CPT 96920-96922) from line 206 SUPERFICIAL ABSCESSES AND CELLULITIS [no appropriate diagnoses] and line 424 SEVERE INFLAMMATORY SKIN DISEASE [GN23 excludes <10% of body surface area from line 424 and this is the only indication recommended for laser therapy per the American Academy of Dermatology recommendations]
    a. Will remain on line 539 MILD PSORIASIS; DERMATOPHYTOSIS: SCALP, HAND, BODY
5) Add home light therapy (HCPCS A4633, E0691-E0694) to the following lines and advise HSD to remove HCPCS A4633, E0691-E0694 from the Ancillary list and address its exclusion in OARs
    A. 424 SEVERE INFLAMMATORY SKIN DISEASE
    B. 531 CONTACT DERMATITIS AND NON-INFECTIOUS OTITIS EXTERNA
    C. 539 MILD PSORIASIS; DERMATOPHYTOSIS: SCALP, HAND, BODY
6) Add home bili-light therapy, HCPCS E0202 (Phototherapy (bilirubin) light with photometer) to line 102 HEMOLYTIC DISEASE DUE TO ISOIMMUNIZATION, ANEMIA DUE TO TRANSPLACENTAL HEMORRHAGE, AND FETAL AND NEONATAL JAUNDICE
    A. Advise HSC to remove HCPCS E0202 from the Ancillary List

Section 7.0

Biennial Review

2020 Biennial Review
Severe Acne

Question: Should severe acne other than acne conglobata be included on a covered line on the Prioritized List? If so, what degree of acne severity should qualify for coverage?

Question sources: Julie Dhossche, MD, resident OHSU Dermatology; Darin Vaughan, MD, pediatrician in Bend; several community dermatology providers

Issue: Acne is a common skin disease affecting approximately up to 85% of 11–30 year-olds. Acne is a polymorphic, inflammatory skin disease most commonly affecting the face (99% of cases). Less frequently it also affects the back (60%) and chest (15%).

At the time of the 2012 ICD-10 Dermatology review, no form of acne was covered according to the Prioritized List. During this review, coverage for acne conglobata, the most severe form of cystic acne, was recommended to be added with a new line and guideline, which went into effect on January 1, 2015. Coverage was limited to acne conglobata resulting in recurrent abscesses or communicating sinuses. The new acne conglobata line is Line 373 ACNE CONGLOBATA (SEVERE CYSTIC ACNE). Previously, cystic acne was on line 545 (now line 520), which was renamed ~~CYSTIC ACNE~~ ACNE; ROSACEA with the ICD-10 review. Cystic acne was on a funded line prior to 2003 (with no guideline note) and then no form of acne was on a funded line after that until the appearance of the new acne conglobata line in 2015. Dr. Dhossche and Dr. Vaughan are requesting consideration for coverage for severe cystic acne that does not rise to the severity of recurrent abscesses or communicating sinuses.

Treatment of severe acne may involve oral antibiotics, topical retinoids, benzoyl peroxide, topical antibiotics, oral isotretinoin, and oral contraceptives. Currently, by OHA P&T PA criteria, medications commonly used to treat severe acne, including topical antibiotics, retinoids, and benzoyl peroxide, are all listed as not covered due to acne being an uncovered condition. Oral antibiotics (short course) and oral contraceptives are likely covered as they can be used for other indications which are above the funding line on the Prioritized List.

Current Prioritized List status:

1) Acne conglobata (ICD-10 L70.1) is on line 373 ACNE CONGLOBATA (SEVERE CYSTIC ACNE)
2) All other acne diagnoses (ICD-10 L70.0, L70.2-9) are on line 520 ROSACEA; ACNE

GUIDELINE NOTE 132, ACNE CONGLOBATA

Line 373

Acne conglobata is only included on Line 373 if it involves recurrent abscesses or communicating sinuses.

2020 Biennial Review
Severe Acne

Excerpt from Dr. Dhossche's letter to the HERC (please refer to the entire letter for additional helpful information):

> Given the curative nature and efficacy of isotretinoin in severe and scarring acne, it is the one treatment for acne that should be available to all those at risk for permanent scarring from their disease. Acne disproportionately affects the young population, and it is heartbreaking to see a child's disease cause permanent disfigurement knowing we have the tools to prevent it, but being limited in their treatment course by their insurance coverage and their parents' economic status.
>
> Given the evidence presented above regarding the personal and societal impact of severe and scarring acne on children and adolescents, as well as the excellent and generic treatments available for acne, I propose the following change to the Oregon Health Plan (OHP). Assuming Medicaid coverage is not possible for mild to moderate acne, we advocate for coverage of acne only in cases of scarring disease, particularly in the pediatric population. Currently acne is included with rosacea on line 525, which is not covered by OHP under any conditions. Acne conglobata, which is an uncommon severe eruptive nodulocystic acne, is covered (on line 378) with the proviso that there are communicating sinus tracts as well as recurrent abscesses. As I have discussed, 'acne conglobata' does not encompass all forms of severe and/or scarring acne that require prompt and appropriate treatment. I propose that medical coverage be provided for a diagnosis of 'nodulocystic acne', or 'scarring acne' for those under the age of 21.
>
> This change will make a profound impact in children's lives.

Dr. Dhossche's suggested definition for severe acne:
"[The] presence of persistent or recurrent inflammatory nodules and cysts, ongoing scarring, or recurrent abscesses or communicating sinuses (acne conglobata)."

Suggested alternate definitions:
"The presence of persistent or recurrent inflammatory nodules and cysts **AND** ongoing scarring, or recurrent abscesses or communicating sinuses (acne conglobata)."

"The presence of persistent or recurrent inflammatory nodules and cysts **AND** ongoing scarring, or recurrent abscesses or communicating sinuses."

Information from Dr. Dhossche regarding costs

1) Most acne medications are generic and area available over the counter: generic antibiotics, Differin, benzoyl peroxide
2) Cost analysis of the use of isotretinoin in severe recalcitrant nodular acne in 475 patients in a study done by Neary et al. in 2002 showed an average cost of $1231 for isotretinoin for 141 days, which included office visits and laboratory testing. After isotretinoin therapy, more than 25% of patients had no expenses related to acne for at least the following year, and the mean acne-related expense for remaining patients dropped from $471 to $135 per year.

Information from Dr. Dhossche regarding other state Medicaid coverage:

1) California has on their Medicaid formulary list several generic acne products in each category (topical retinoid, topical antibiotic, oral retinoid), most with a quantity limit per month
2) Certain states, such as Indiana, Mississippi, and Utah, have an age cut-off: they cover in their state Medicaid program a range of generic acne medications, from topical retinoids to oral

retinoid, for patients with a diagnosis of acne who are under the age of 20 (Utah), 21 (Mississippi), or 25 (Indiana)

3) Other states, such as Michigan and Arizona, cover several topical agents ranging from retinoids, topical antibiotics, and benzoyl peroxide, but require a prior authorization when prescribing isotretinoin
4) Colorado requires a prior authorization for all topical products and isotretinoin; the state authorizes payment for these therapies for the diagnoses of cystic acne, disorders of keratinization, and comedonal or acne vulgaris.

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Evidence

1) **Gieler 2015**, review of psychological effects of acne
    a. Significantly lower self-attitude, uselessness feeling, sense of pride and self-worth, body satisfaction, and a higher percentage of patients harbouring suicidal ideation have been observed in the affected population. Left untreated, acne lesions may persist into adulthood, which translates into higher unemployment rates for patients with severe acne compared to adults without acne, implying that acne affects patients' work situations and their ability to obtain employment
    b. Acne patients are characterized by a tremendous impairment of quality of life equal to that reported by patients with other chronic diseases such as asthma, epilepsy, diabetes, back pain or arthritis. Furthermore, surveys indicated that quality of life does not correlate with the physician's assessment of acne severity. Even in mild forms, acne has a detrimental psychological effect on patients
    c. Irrespective of the degree of severity, patients with acne are at increased risk of anxiety and depression compared to the non-affected population
    d. Several studies support the observation that appropriate acne treatment plays a central role in the efforts to enhance patients' quality of life

Expert guidelines

American Academy of Dermatology 2016 guideline on treatment of acne https://ac.els-cdn.com/S0190962215026146/1-s2.0-S0190962215026146-main.pdf?_tid=fd86cfc2-fc10-4e3e-9bf1-8984ca556e33&acdnat=1525190517_15f4dda7deb7d000be0af61c08fefc37:

1) Treatments: lists first line and alternative therapies for mild, moderate or severe acne.
2) Definition of mild, moderate or severe acne:
    a. To date, there is no universally agreed-upon grading system, and systems can differ greatly between studies. In addition, interobserver reliability of these scales varies, but has been poor in some studies.

American Academy of Pediatrics 2013 guideline on treatment of acne http://pediatrics.aappublications.org/content/pediatrics/131/Supplement_3/S163.full.pdf:

1) It has been repeatedly demonstrated that acne can have a significant adverse impact on quality of life, and that the level of distress may not correlate directly with acne severity
2) Defining acne severity:
    a. Acne severity may be classified clinically as mild, moderate, or severe based on the number and type of lesions and the amount of skin involved. Although there are numerous grading systems by which to define acne severity, there is no agreed-upon standard, and interpretation is subjective
    b. Typically, patients' assessments do not correlate well with either those of physicians or published severity scales.
3) Various treatment options are reviewed

European evidence based guidelines for the treatment of acne, 2013 https://www.slideshare.net/UtaiSukviwatsirikul/european-evidencebased-s3-guidelines-for-the-treatment-of-acne:

1) Defining acne severity:

   a. There are inherent difficulties in objectively measuring acne. Over 25 different methods have been described but there is no consensus as to which should be used
2) Evidence for various therapies reviewed. For nodular/conglobate acne, a high strength of recommendation was given to oral isotretinoin; a medium strength of recommendation was given to systemic antibiotics in combination with azelaic acid. Low strength of recommendation was given or oral anti-androgens in combination with oral antibiotics, and to systemic antibiotics in combination with adapalene and/or benzoyl peroxide

Consensus conference on acne classification 1990

1) Severe acne was defined as having numerous and/or extensive papules and pustules with many nodules
2) "The clinical diagnosis of severe acne should be based on the presence of any of the following characteristics: persistent or recurrent inflammatory nodules, extensive papulopustular disease, ongoing scarring, persistent purulent and/or serosanguinous drainage from lesions, or the presence of sinus tracks."

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Similar conditions on the Prioritized List

Skin conditions which only appear on a funded line include severe, life threatening conditions like scalded skin syndrome as well as conditions with systemic effects such as epidermolysis bullosa or pemphigus vulgaris.

Conditions similar to acne affecting facial skin that appear on both a funded and an unfunded line depending on severity include psoriasis, atopic dermatitis and discoid lupus. There is a guideline indicating that these conditions are only on line 424 SEVERE INFLAMMATORY SKIN DISEASE if the condition results in functional impairment (e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND one or more of the following: 1) at least 10% of body surface area involved and /or 2) hand, foot or mucous membrane involvement. Similarly, hemangiomas of the face are included on a funded line only when ulcerated, infected, recurrently hemorrhaging, or function-threatening (e.g. eyelid hemangioma); otherwise, they are on an unfunded line.

Similar conditions which are only on unfunded lines include contact dermatitis, tinea (ring worm), diaper rash, localized scleroderma, pityriasis, rosacea, and vitiligo. These conditions are either self-limited, do not affect overall health, are treated with inexpensive over the counter medications, and/or have no effective treatment.

HERC staff summary:

Severe acne can have significant impact on quality of life; however, there appears to be no agreed upon definition of severe acne. Evidence also does not support that the severity of acne correlates with the degree of impact on quality of life. There is evidence that treatment of acne (of any severity) improves measures of quality of life for patients.

Similar conditions such as psoriasis and eczema have been placed on funded lines for severe forms of the condition. Other similar conditions remain on unfunded lines only.

If coverage were adopted for severe acne, the following issues would need to be addressed:

1) Defining severe acne vs mild/moderate disease. There is no agreed upon definition. Staff has worked with Dr. Dhossche to develop a definition used in the proposal below only as a starting point for discussion.
2) The increased need for and cost of dermatology consultation to determine if a patient has severe acne, rather than mild or moderate disease.
3) The increased cost of medications to treat severe acne, such as isotretinoin or topical retinoids. Additionally, most recommended treatment algorithms include medications which could be used to treat mild or moderate acne, such as benzoyl peroxide or topical antibiotics. If these medications were opened for use, P&T would need to develop PA criteria to ensure only severe disease is treated, and the cost and resource utilization involved in managing such a PA process would need to be considered.

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HERC staff recommendation:

1) Consider coverage for severe cystic acne.
    a. **Option 1**: change line 373 ACNE CONGLOBATA (SEVERE CYSTIC ACNE) to a line for severe cystic acne.
        i. Add the entire ICD-10 L70 series to line 373 and keep on line 520 ROSACEA; ACNE
        ii. Change the line titles for line 373 ~~ACNE CONGLOBATA (~~SEVERE CYSTIC ACNE~~)~~ and 520 ROSACEA; MILD/MODERATE ACNE
        iii. Modify GN132 as shown below.
        iv. Make such a change effective January 1, 2020 to allow for evaluation of cost impacts and development of PA criteria by P&T

GUIDELINE NOTE 132, ~~ACNE CONGLOBATA~~ SEVERE CYSTIC ACNE

Line 373,520

Acne ~~conglobata~~ is only included on Line 373 if it ~~involves recurrent abscesses or communicating sinuses.~~ is severe, defined as the presence of: persistent or recurrent inflammatory nodules and cysts AND ongoing scarring, or recurrent abscesses or communicating sinuses. Otherwise, acne diagnoses are included on line 520.

    b. **Option 2**: Creation of a new line for severe cystic acne.
        i. Change line title for line 373 ACNE CONGLOBATA ~~(SEVERE CYSTIC ACNE)~~
        ii. Create a new line and guideline as shown below
        iii. Score this new line as shown below

New line

Line XXX SEVERE CYSTIC ACNE

Treatment: MEDICAL AND SURGICAL TREATMENT

    a. ICD-10 codes: L70 (acne)
    b. CPT/HCPCS codes: all included on line 373 ACNE CONGLOBATA (SEVERE CYSTIC ACNE)

GUIDELINE NOTE XXX SEVERE CYSTIC ACNE

Line XXX,520

Acne is only included on Line XXX if it is severe, defined as the presence of the following characteristics: persistent or recurrent inflammatory nodules and cysts AND ongoing scarring, or recurrent abscesses or communicating sinuses. Otherwise, acne diagnoses are included on line 520.

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Line scoring

Current scoring in parentheses for lines 373 ACNE CONGLOBATA (SEVERE CYSTIC ACNE)/530 ROSACEA; ACNE

Category 7 (7,7)
Impact on Healthy Life Years 1 (2,1)
Impact on Pain and Suffering 3 (3,2)
Population effects 0 (0)
Vulnerable populations 0 (0)
Tertiary prevention 0 (2,0)
Effectiveness 4 (4,4)
Need for treatment 0.8 (1,0.5)
Net cost 3 (3,3)

SCORE 256, PUTS ON LINE 451

Introduction:
Acne vulgaris is one of the most prevalent skin diseases in children and adolescents. It is typically considered a disease of older youth, affecting up to 85% of adolescents [1,2]; however, acne can occur in neonates, infants, and younger children as well [3]. Acne is a multifactorial skin disease that affects the pilosebaceous unit, leading to clinical findings that range from scattered comedones to widespread inflammatory lesions that form nodules and cysts [1]. Inflammation can be severe and cause permanent scarring and disfigurement [4]. The degree of scarring is related to the severity and duration of acne prior to treatment [5,6]. Early, appropriate treatment is critical in the prevention of lifelong disfigurement in patients with severe acne [1]. Multiple recent studies have demonstrated the negative impact that acne scarring has on self-esteem, quality of life, and risk for depression and suicidality [7]. This document will focus on the pediatric population and review current literature on the mental health effects of acne on patients, as well as the current treatment guidelines for acne, especially scarring acne. Severe, nodulocystic, or scarring acne poses a substantial burden on the mental health of teenagers and young adults. Successful and cost-effective treatments are widely available and should be covered for children on the Oregon Health Plan.

Current Treatment Guidelines:
In 2015, evidence-based clinical practice guidelines and algorithms for the treatment of acne vulgaris were published by Zaenglein et al, with the approval of the American Academy of Dermatology [8]. Evidence-based recommendations issued by the American Acne and Rosacea Society in 2013 provide a step-wise therapy approach to pediatric acne, based on the type and severity of the acne [3]. These guidelines are endorsed by the American Academy of Pediatrics, the advocacy organization committed to the health of infants, children, adolescents, and young adults [9]. The treatment of acne in each age group—neonatal acne, infantile acne, mid-childhood acne, and pre-adolescent acne—is comparable to the treatment of acne in adolescents and adults, as many of the medications have been shown to be safe for use in children younger than 12 years [3].

For mild acne, which may feature comedones and scattered superficial pustules or inflammatory papules, the first line is a benzoyl peroxide product or topical retinoid, or a combination of these. A topical antibiotic agent may be added in combination with benzoyl peroxide (e.g. clindamycin-benzoyl peroxide); monotherapy with a topical antibiotic (except dapsone) is discouraged given widespread resistance. For moderate acne, which typically features a marked number of inflammatory lesions with some comedones, topical combination treatment may be first line (benzoyl peroxide with topical antibiotic and topical retinoid), though oral antibiotics may be warranted (in the pediatric population under 8 years old, tetracycline, doxycycline and minocycline are avoided in favor of erythromycin, azithromycin and trimethoprim/sulfamethoxazole). If there is inadequate response, hormonal therapy should be considered for pubertal females, and isotretinoin should be considered. For severe acne, which features inflammatory and/or nodular lesions as well as scarring, treatment may consist of an oral antibiotic, a topical retinoid, and benzoyl peroxide with or without a topical antibiotic; however, oral isotretinoin and hormonal therapy in pubertal females should be considered given that prompt, appropriate treatment is crucial to achieve control of the inflammation and prevent permanent scarring [3,8].

Psychiatric Effects of Undertreated Acne:
Acne overwhelmingly affects children and adolescents in the crucial years of identity and social development, and it is no surprise that psychiatric and psychosocial effects of skin disease in the pediatric population have been increasingly studied [2]. Acne adversely affects the self-image and confidence of many patients suffering from the disease [2,10-15]. The association of acne with psychiatric disorders such as social phobia, anxiety, and depression has been well established [12, 15-22]. Multiple studies have shown a strong association between acne and depression: one large retrospective study found clinical depression to be two to three times more prevalent in acne patients than general population [16]. Suicidal ideation and suicide attempts are also two times more common in those affected with acne. Acne is significantly associated with suicidal ideation in adolescents; adolescent dermatology patients have been reported to be more likely to express suicidal ideation than those with other skin conditions [17,18, 20]. In a recent study of patients with acne, over 95% of the respondents said they had reduced quality of life due to acne, and 12.9% had suicidal thoughts due to acne [22].

Stigmatization:
The disfigurement caused by acne scarring not only affects behavior and self-esteem, but also impacts social relationships. Discrimination is often experienced by those with severe acne and acne scarring. In a study by Timms et al, when compared to photographs of a male and female with clear skin, photographs of a male and female with moderate acne were on first impression judged as younger, less mature, and significantly less attractive, and given lower potential friendship and overall personality scores [10]. It has been reported that the social disadvantage of having acne translates itself into disadvantage in obtaining work [11]. The condition of skin has certainly been described as a limiting factor in employment: in an interview-based study by Jowett and Ryan examining the impact of eczema, psoriasis, and acne on various aspects of life, 45% of those with acne reported experiencing interpersonal difficulty, and the appearance of skin was a limiting factor for a young man wanting to work in a fashion store, and a young woman wanting to work as a hairdresser [23].

Treatment considerations:
Isotretinoin has been shown in multiple controlled studies to improve testing parameters and patient symptoms of anxiety and depression, as well as quality of life, during and after therapy [24-29]. In fact, compared to groups with topical treatments only, in which there were higher drop-out rates, patients in the isotretinoin group had significantly reduced rates of depression after 4 months of treatment [29].

Isotretinoin became available in the early 1980s, and since that time has transformed the treatment for acne vulgaris [30]. This vitamin A analogue remains the most efficacious treatment for severe acne as well as moderate acne that is unresponsive to topical and/or oral antibiotics. In randomized double-blinded clinical studies isotretinoin has been clearly shown to be effective in the treatment of acne by reducing acne lesions and reducing scarring [25-27,31]. The efficacy of isotretinoin in the treatment of severe nodular acne and scarring acne is well documented throughout the literature, and the current guidelines for acne treatment recommend use of isotretinoin in severe forms of acne, including cystic acne or acne refractory to other treatments, as well as acne with marked inflammation and tendency to early scarring [3,8,32-36].

Factors to consider in the assessment of severity of disease and necessity of isotretinoin should include the impact of the disease on the patient and the presence or potential for scarring [25,32].

Isotretinoin is the only drug available that targets the four main factors of pathogenesis of acne, as it decreases sebum production and sebaceous gland size by decreasing basal sebocyte proliferation and terminal sebocyte differentiation, thereby resulting in an altered microenvironment which decreases Propionibacterium presence and decreases its potential for causing inflammation [36]. Isotretinoin is usually prescribed as a 4-6 month treatment course, with the intent to be a curative. Relapses do occur, most often among patients with severe acne on lower doses of isotretinoin [5,36]. However, with a repeat course of therapy, the acne remains equally responsive to the drug [37]. A course of isotretinoin is essentially considered a cure for acne.

Cost Considerations:
Studies regarding the cost-effectiveness of acne treatments are limited. However, most acne treatments are available as generics, and benzoyl peroxide and differin, which are effective for mild to moderate acne, are even over the counter. The step-wise treatment approach assures safe, individualized, and targeted treatment [3,8]. Isotretinoin has the highest initial cost of the acne treatments, but given its efficacy and limited course duration, is very cost-effective [38,39]. A 4-6 month course of isotretinoin has been shown to more effective long-term than a 3-year combination course of oral antibiotics and topical treatments: upon reassessment 3-5 years after treatment, only the patients treated with isotretinoin had complete clearance of their acne [5]. Cost analysis of the use of isotretinoin in severe recalcitrant nodular acne in 475 patients in a study done by Neary et al. in 2002 showed an average cost of $1231 for isotretinoin for 141 days, which included office visits and laboratory testing. After isotretinoin therapy, more than 25% of patients had no expenses related to acne for at least the following year, and the mean acne-related expense for remaining patients dropped from $471 to $135 per year. Recent studies are now showing that increased laboratory monitoring is not necessarily beneficial in determining course of treatment given that severe adverse effects are rare and most likely occur early in the treatment course; this change will likely decrease costs more [40].

Conclusions:
Given the curative nature and efficacy of isotretinoin in severe and scarring acne, it is the one treatment for acne that should be available to all those at risk for permanent scarring from their disease. Acne disproportionately affects the young population, and it is heartbreaking to see a child's disease cause permanent disfigurement knowing we have the tools to prevent it, but being limited in their treatment course by their insurance coverage and their parents' economic status.

Given the evidence presented above regarding the personal and societal impact of severe and scarring acne on children and adolescents, as well as the excellent and generic treatments available for acne, I propose the following change to the Oregon Health Plan (OHP). Assuming Medicaid coverage is not possible for mild to moderate acne, we advocate for coverage of acne only in cases of scarring disease, particularly in the pediatric population.
Currently acne is included with rosacea on line 525, which is not covered by OHP under any conditions. Acne conglobata, which is an uncommon severe eruptive nodulocystic acne, is covered (on line 378) with the proviso that there are communicating sinus tracts as well as

recurrent abscesses. As I have discussed, ‘acne conglobata’ does not encompass all forms of severe and/or scarring acne that require prompt and appropriate treatment. I propose that medical coverage be provided for a diagnosis of ‘nodulocystic acne’, or ‘scarring acne’ for those under the age of 21.

This change will make a profound impact in children’s lives.

Of note, I have listed here a few examples of individual states and how their Medicaid program covers acne. California has on their Medicaid formulary list several generic acne products in each category (topical retinoid, topical antibiotic, oral retinoid), most with a quantity limit per month [41]. Certain states, such as Indiana, Mississippi, and Utah, have an age cut-off: they cover in their state Medicaid program a range of generic acne medications, from topical retinoids to oral retinoid, for patients with a diagnosis of acne who are under the age of 20 (Utah), 21 (Mississippi), or 25 (Indiana) [42-44]. Utah requires a prior authorization for acne treatment in patients over 20 [44]. Other states, such as Michigan and Arizona, cover several topical agents ranging from retinoids, topical antibiotics, and benzoyl peroxide, but require a prior authorization when prescribing isotretinoin [45-46]. Michigan also has a quantity limit of isotretinoin per month [45]. Colorado requires a prior authorization for all topical products and isotretinoin; the state authorizes payment for these therapies for the diagnoses of cystic acne, disorders of keratinization, and comedonal or acne vulgaris. For the diagnoses of cystic acne or comedonal acne they do not require previous trials and therapy failure with other anti-acne products regardless of age [47].

These are only a handful of examples.

Please do the right thing for the children of Oregon.

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SUPPLEMENT ARTICLE

Acne and quality of life – impact and management

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Abstract

Acne is a common skin disease with a high prevalence in adolescents and young adults. In addition to physical effects such as permanent scarring and disfigurement, acne has long-lasting psychosocial effects that affect the patient's quality of life. Depression, social isolation and suicidal ideation are frequent comorbidities of acne that should not be neglected in the therapy of acne patients. Research evidence suggests that the impairment of quality of life can be alleviated by appropriate topical acne treatment.

Received: 16 April 2015; Accepted: 16 April 2015

Conflict of Interest

Prof Gieler has participated in acne-related clinical and experimental studies, symposia and advisory boards of Galderma Laboratorium GmbH, GSK-Stiefel GmbH and Bayer AG. T. Gieler and JP Kupfer have no conflict of interest.

Introduction

Acne is a common skin disease affecting approximately up to 85% of 11–30 year-olds.[1] Frequently, acne affects the face, is difficult to hide and may produce scars that can persist for years or for life. Although acne is known to be the primary reason for consulting a dermatologist,[2] the psychological consequences of the disease have often been underestimated. In the classical view, the disease was dismissed as purely physiological or even discussed as a non-medical symptom.[3] Meanwhile, experts agree that adequate acne management entails far more than treatment of pimples. Adolescence is a time of important physical, emotional and social development. With its high prevalence particularly in the adolescent population,[4] facial acne has a considerable psychosocial impact on these patients by causing significant negative effects on self-image leading to feelings of isolation and loneliness.[5–7] A significantly lower self-attitude, uselessness feeling, sense of pride and self-worth, body satisfaction,[8] and a higher percentage of patients harbouring suicidal ideation have been observed in the affected population.[9] Left untreated, acne lesions may persist into adulthood, which translates into higher unemployment rates for patients with severe acne compared to adults without acne, implying that acne affects patients' work situations and their ability to obtain employment.[10] Consistently, lower social status has been associated with greater acne severity.[11]

Acne and impaired quality of life

In order to improve the understanding of the disease from the patient's point of view, assessing the quality of life has become a standard outcome measure in most studies. Since acne can adversely affect patient's quality of life in many ways, a variety of methods has been described to assess quality of life including dermatology-specific measures such as the Dermatology Life Quality Index (DLQI), the Dermatology Quality of Life Scales (DQOLS), the Dermatology Specific Quality of Life (DSQL), the Acne Disability Index (ADI)[12] and Skindex.[13–15] These quality of life instruments can advance the physician–patient relationship by giving clinicians accurate knowledge of how patients live with their disease.[16]

Unsurprisingly, acne patients are characterized by a tremendous impairment of quality of life equal to that reported by patients with other chronic diseases such as asthma, epilepsy, diabetes, back pain or arthritis.[17] Furthermore, surveys indicated that quality of life does not correlate with the physician's assessment of acne severity.[16,18] Even in mild forms, acne has a detrimental psychological effect on patients.[19] Several studies analysed the effect of acne on quality of life in detail.[20] A greater impact on quality of life was associated with older age, female gender and longer acne duration (>5 years).[21,22] The way in which patients perceive their skin to be evaluated by others has implications for self-perception and may act as a barrier to participation in public sports and exercise.[23] Irrespective of the degree of severity, patients with acne are at increased risk of anxiety and depression compared to the non-affected population. The greater the impairment of quality of life due to acne, the higher the level of anxiety and depression.[24,25] Also, the tendency to experience emotions of anger at regular intervals might be

partly responsible for patients' poor global and skin-related quality of life and dissatisfaction with treatments.[26] Given the psycho-social ramifications of acne, it is important to identify and treat the affected teenagers at an early stage in order to alleviate the individual impairment of quality of life and, as a result, reduce the future socio-economic burden of their acne.[4]

Management of quality of life problems in acne patients

Several studies support the observation that appropriate acne treatment plays a central role in the efforts to enhance patients' quality of life.[27] For instance, oral treatment with roxithromycin had a therapeutic effect on inflammatory acne and led to improvement in quality of life.[28] Similarly, acne grading and acne-related quality of life, along with severity of depression, improved after 8 weeks of oral isotretinoin treatment, whereby improvement in depression was found to be directly related to acne-related quality of life improvements rather than to improvement in the acne grade.[29] A small study compared the effect of oral isotretinoin and topical antibiotics or retinoids on quality of life, and on symptoms of depression and anxiety. Results revealed that successful treatment in general improved both symptoms of depression and anxiety as well as quality of life.[30] The impact of topical acne treatment on quality of life was further investigated in a prospective randomized case–control study with 382 patients. Patients were randomized (115:130) to receive topical clindamycin/benzoyl peroxide or adapalene/benzoyl peroxide (adapalene-BPO). Improvement in quality of life from baseline to week 12 was observed in both treatment groups. Quality of life increased more in those patients with a successful treatment. There was a higher impairment of quality of life in patients with more side-effects, and females had a lower quality of life than men. Patients with higher impairment of quality of life at baseline had a greater benefit from the treatment than those with an acceptable quality of life at baseline [data on file]. Moreover, in the long-term treatment of patients with predominantly moderate inflammatory facial acne using adapalene-BPO alone or in combination with other drugs, application of the gel over a 9-month period led to a marked increase in quality of life at all grades of acne severity.[31] Another case–control study compared 32 acne patients with 32 healthy individuals. At baseline, the acne group showed a significantly increased grade of disgust on the Skin Satisfaction Questionnaire, lower ratings in attractiveness and self-confidence according to a questionnaire evaluating their own body, and a significant reduction in social functioning in the SF-36 questionnaire. Treatment produced highly significant improvements of Investigator's Global Assessment and total face lesion count. Simultaneously, impairment of quality of life measured by the Cardiff Acne Disability Index (CADI) declined significantly as well. Women with acne had been significantly more affected in their quality of life than their male counterparts. However, they showed a greater decrease in the percentage of acne lesions.[32] A marked beneficial effect of acne treatment on quality of life was also demonstrated in two sequential double-blind randomized studies, in which patients received either adapalene-BPO or vehicle, in combination with doxycycline for 12 weeks. Patients having obtained at least a good improvement according to investigator global assessment were re-randomized for a 24-week therapy with adapalene-BPO or vehicle. Quality of life assessed by the Acne-QoL was improved at week 12 in all domains with a significant difference for the acne-symptoms domain in favour of the adapalene-BPO regimen. Additional 24-week adapalene-BPO treatment showed a sustained improvement, significant for all domains except for acne symptoms. In the vehicle arm, quality of life significantly worsened for all domains.[33] In accordance, a phase IV, prospective, 12-week, open-label trial with 544 patients showed significant improvement on the Acne Quality of Life Index scale 12 weeks after switching from a previous dissatisfactory acne regimen to tretinoin dispensed from a pump.[34]

Comment

The studies summarized above underline the necessity of appropriate acne treatment in an approach that includes the overall morbidity associated with acne. In this context, medical adherence to acne treatment has become a prerequisite to avoid treatment failure. Although there have been relatively few formal studies of adherence in acne, data suggest it is poor overall, especially in young adults and adolescent patients.[35,36] The leading factors that contribute to poor adherence may be reduced with enhanced patient consultation, reminder systems, education, as well as ease of application, for instance using formulations for once-daily administration.[37–39] Adherence to treatment is also linked to better quality of life[40]: Adherence to topical acne therapy has been shown to increase with impact on quality of life, while increasing acne severity led to a decrease in adherence.[41] Vice versa, quality of life was rated significantly better in adherent patients compared to those with poor adherence.[31] Although secondary emotional impairment due to disfigurement by acne is undisputed, psychological aspects are often neglected in the therapy of acne patients, which may result in poor adherence and discontent with treatment. Therefore, it is imperial to consider acne as more than a mere cosmetic problem and to include psychosocial aspects in the management of acne.

In conclusion, acne has a considerable impact on quality of life. Especially in the group of adolescent patients, the effect on psychosocial stress should be given more attention. The impairment of quality of life can be alleviated by appropriate topical acne treatment.

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From the Academy

This report reflects the best data available at the time the report was prepared, but caution should be exercised in interpreting the data. The results of future studies may require alteration of the conclusions or recommendations set forth in this report.

Report of the Consensus Conference on Acne Classification

Washington, D.C., March 24 and 25, 1990

Planning Committee Members: Peter E. Pochi, MD, Chairman; Alan R. Shalita, MD, John S. Strauss, MD, and Stephen B. Webster, MD

Other Consensus Panel members: William J. Cunliffe, MD, H. Irving Katz, MD, Albert M. Kligman, MD, James J. Leyden, MD, Donald P. Lookingbill, MD, Gerd Plewig, MD, Ronald M. Reisner, MD, Orlando G. Rodman, Jr., MD, Maria L. Turner, MD, and Guy F. Webster, MD, PhD

A number of systems have been described for the classification of acne vulgaris, but there is no universally accepted method for assessing gradations of acne severity. As a result, determining whether a patient has severe acne or not becomes a subjective assessment. Furthermore, this lack of uniformity from one classification system to another has made it difficult to compare therapeutic efficacy among different studies.

To address the issue of acne classification, the American Academy of Dermatology convened a Consensus Conference on Acne Classification in Washington, D.C., on March 24 and 25, 1990, in which a group of 14 expert clinicians and specialists interested in acne participated. In addition, representatives from the pharmaceutical industry were invited to attend as observers and were asked to offer their opinions. After lengthy discussion on the complex issues concerning the clinical rating of acne severity, two broad focus questions were addressed. Why is a suitable acne classification difficult to establish unequivocally? What elements should be considered in establishing ratings of severity and how are these modified by other considerations?

Question 1: What are the difficulties in establishing a standardized and reproducible system of classifying acne vulgaris?

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The central problem is that acne vulgaris is a highly pleomorphic disorder in which (1) there may be an admixture of both inflammatory and noninflammatory lesions involving multiple skin sites; (2) the inflammatory lesions vary in size, density, and severity of inflammation within localized sites of involvement in the same person, as well as among persons; and (3) there is considerable variability in the natural evolution and healing of lesions, and in the response to therapy.[1]

To the members of the Consensus Conference, it seemed obvious from the outset that one of the more frequently used classification systems, dividing acne into four grades of severity,[2-4] is overly simplistic. Other classifications have attempted to measure the number and extent of inflamed and noninflamed lesions.[5-9] These semiquantitative classifications require special training for the user and seem better suited for the evaluation of new therapies in the investigative arena rather than for use in the clinical setting. Some methods have relied on standardized photographs to establish baseline observations and to document lesion types.[9-12] Although photographs provide a permanent record, they may not accurately reflect disease activity. Photographs do not discriminate between macular and elevated lesions; in addition, small comedones may not be fully visualized, which result in their being underrecorded.

Question 2: Should a standardized system of classification be based on lesion type, lesion count, global evaluation, or a combination thereof, and should the presence of scarring be considered in a

Burn Line "Vital Site" Definition

Question: Should "vital site" in the burn line titles be defined?

Question source: Kaiser Permanente

Issue: Since their creation, two of the burns lines reference "vital site" in their line titles. This designation determines which line a burn would be included on. There is no definition of what is meant by vital site on these lines or anywhere on the Prioritized List. No mention was found of such a definition in a search of old minutes.

There are currently 4 burn lines and 1 line for other types of burns:
57 BURN, FULL THICKNESS GREATER THAN 10% OF BODY SURFACE Treatment: FREE SKIN GRAFT, MEDICAL THERAPY
72 BURN, PARTIAL THICKNESS GREATER THAN 30% OF BODY SURFACE OR WITH VITAL SITE; FULL THICKNESS, LESS THAN 10% OF BODY SURFACE Treatment: FREE SKIN GRAFT, MEDICAL THERAPY
181 CONDITIONS INVOLVING EXPOSURE TO NATURAL ELEMENTS (E.G., LIGHTNING STRIKE, HEATSTROKE) Treatment: MEDICAL THERAPY, BURN TREATMENT
197 BURN, PARTIAL THICKNESS WITHOUT VITAL SITE REQUIRING GRAFTING, UP TO 30% OF BODY SURFACE Treatment: FREE SKIN GRAFT, MEDICAL THERAPY
602 MINOR BURNS Treatment: MEDICAL THERAPY

On review, HERC staff found that line 57 included all third degree burn diagnoses and multiple treatment codes not found on other burn lines, mostly involving amputations. Lines 72 and 197 had essentially the same treatment CPT codes. The ICD-10 diagnoses codes that differed between lines 72 and 197 mainly appeared to be regarding burns to the face, neck, genitals, foot and palm (on line 72). Most other second degree burn diagnoses appear on both lines 72 and 197. Line 602 had many similar diagnoses to lines 72 and 197, as well as first degree burn diagnoses.

Standard references for defining burn severity state:

> Major burn injury is defined as partial-thickness burns involving more than 25% of total body surface area (TBSA) in adults or 20% of TBSA in children younger than 10 years or adults older than 50 years; full-thickness burns involving more than 10% of TBSA; burns involving the face, eyes, ears, hands, feet, or perineum that may result in functional or cosmetic impairment; burns caused by caustic chemical agents; high-voltage electrical injury; burns complicated by inhalation injury or major trauma; or burns sustained by high-risk patients (those with underlying debilitating diseases).

HERC staff recommendations:

1) For October 1, 2018: Add a new guideline to lines 72 and 197 as shown below

GUIDELINE NOTE XXX VITAL SITE DEFINITION FOR BURN LINES

Lines 72, 197

A burn to a "vital site" is defined as a burn involving the face, eyes, ears, hands, feet, or perineum that may result in functional impairment.

2) For January 1, 2020, consider merging the three upper burn lines (lines 57, 72 and 197) into a single line for "severe burns." The current division of these lines does not correlate well with current definitions of severe burns. There is very little differences between these lines, other than amputations on the most severe burn line. Prioritize this new line at line 57. Delete the guideline adopted above and add the new guideline shown below.

Line: 57

Condition:	SEVERE BURNS (See Guideline Notes 6,64,65,XXX)
Treatment:	FREE SKIN GRAFT, MEDICAL THERAPY
ICD-10:	Any appearing on line 57, 72, or 197
CPT:	Any appearing on line 57, 72, or 197
HCPCS:	Any appearing on line 57, 72, or 197

GUIDELINE NOTE XXX SEVERE BURNS

Lines 57, 602

Severe burns are defined as partial-thickness burns involving more than 25% of total body surface area (TBSA) in adults or 20% of TBSA in children younger than 10 years or adults older than 50 years; full-thickness burns involving more than 10% of TBSA; burns involving the face, eyes, ears, hands, feet, or perineum that may result in functional impairment; burns caused by caustic chemical agents; burns complicated by inhalation injury or major trauma; or burns sustained by high-risk patients (those with underlying debilitating diseases).

Section 8.0

Coverage Guidances

Prostatic Urethral Lift for Treatment of Benign Prostatic Hypertrophy

Draft Coverage Guidance for VbBS Consideration

May 17, 2018

Oregon Health Authority

OREGON HEALTH & SCIENCE UNIVERSITY

Center For Evidence-based Policy

Background

- Benign prostatic hyperplasia (BPH) is the nonmalignant growth of the prostate
- BPH typically starts at approximately 40 years of age and increases as men age
- Many men with histologic BPH never consult a health care provider or receive treatment
- Most frequent manifestation is lower urinary tract symptoms, caused by the prostate putting pressure on the bladder or urethra and interfering with urine flow

Background

- Lower urinary tract symptoms caused by BPH are among the most common reasons for urologic consultation in clinical practice
- Urinary symptoms include hesitancy, straining, weak flow, prolonged voiding, partial or complete urinary retention, nocturia, incontinence, and painful urination
- In the U.S., estimated $6 billion dollars spent annually on management of lower urinary tract symptoms due to BPH
- Treatments for BPH include conservative approaches, pharmacological options, and various surgical procedures

International Prostate Symptom Score (I-PSS)

- Scoring system includes 7 items, such as:
  - Urgency: How often have you found it difficult to postpone urination?
  - Weak stream: How often have you had a weak urinary stream?
  - Straining: How often have you had to strain to start urination?
  - Intermittency: How often have you found you stopped and started again several times when you urinated?
- Each item scored from 0 to 5:

  0–Not at all

  1–Less than 1 in 5 times

  2–Less than half the time

  3–About half the time

  4–More than half the time

  5–Almost always

Background

- Most frequent form of surgery is monopolar or bipolar transurethral resection of the prostate (TURP)
  - Uses transurethral electrosurgery to remove prostate tissue during irrigation
  - May cause complications including ejaculatory dysfunction (65%), erectile dysfunction (10%), urethral strictures (7%), urinary tract infection (4%), bleeding requiring transfusion (2%), urinary incontinence (2%)
  - TURP has a retreatment rate of 6%
- A more recent surgical intervention is prostatic urethral lift (PUL), sold under the trade name of UroLift®

Prostatic Urethral Lift

- PUL implantation can be performed in an outpatient or inpatient setting and under general or local anesthesia
- Delivery device is used to compress one lateral lobe of the prostate toward the prostatic capsule, and a needle is used to deploy the implant
- One end of the implant is anchored in the urethra and the other on the outer surface of the prostatic capsule, retracting the prostatic lobe away from the urethral lumen

Prostatic Urethral Lift

- The UroLift® System (PUL) received De Novo approval from U.S. Food and Drug Administration (FDA) in 2013
- The UroLift® System is indicated for urinary outflow obstruction due to BPH in men 50 years of age or older
- Contraindications include:
  - Prostate volume > 80 cc
  - Obstructive or protruding median lobe of the prostate
  - Urinary tract infection
  - Urethra conditions that could prevent insertion of delivery system into bladder
  - Urinary incontinence
  - Current gross hematuria

Scope Statement

- Populations
  - Men with BPH and lower urinary tract symptoms
- Interventions
  - PUL procedure

Scope Statement

- Comparators
  - Medical management (alpha blockers, 5-alpha reductase inhibitors)
  - Transurethral resection of the prostate (TURP)
  - Bipolar TURP
  - Transurethral incision of the prostate (TUIP)
  - Photoselective vaporization of the prostate (PVP)
  - Holmium laser enucleation of the prostate (HoLEP)
  - Transurethral needle ablation of the prostate (TUNA)
  - Transurethral microwave thermotherapy (TUMT)
  - Bipolar transurethral electrovaporization of the prostate (TUVP)
  - Thulium laser vaporization/resection of the prostate

Scope Statement

- Critical Outcomes
  - Quality of life
- Important Outcomes
  - Need for reoperation
  - Procedural complications
  - Long-term harms (e.g., urinary incontinence, erectile dysfunction)
  - Symptom improvement
    - International Prostate Symptom Score [IPSS]
    - American Urological Association Symptom Index [AUASI] scores

Scope Statement

Key Questions

1. What is the comparative effectiveness of PUL for men with lower urinary tract symptoms from BPH?
   a. Does comparative effectiveness vary by baseline symptom severity?
   b. Does the age of the patient or duration of symptoms affect the comparative effectiveness?
2. What are the comparative harms of PUL for men with lower urinary tract symptoms from BPH?

Contextual Questions

1. In what settings (outpatient, ambulatory surgical center, inpatient) and with what types of anesthesia or analgesia can PUL be safely performed?

Evidence Sources

- Perera et al., 2016
  - Fair-quality systematic review of 6 studies of PUL
- Roehrborn et al., 2017
  - Fair-quality study of 5-year outcomes from a prospective, randomized, sham-controlled, double-blind trial
- Gratzke et al., 2017
  - Fair-quality RCT comparing PUL to TURP conducted at 10 centers in 3 European countries

Evidence Review

- Perera et al. 2016 systematic review
  - Review includes 1 sham-controlled RCT, 1 observational cohort that followed crossover patients from that RCT, 2 prospective cohorts, and 2 retrospective cohorts; n = 680
  - Most patients:
    - Between ages 65 and 75
    - IPSS > 12
    - Prostate volumes between 20 and 100 ml
  - Patients were excluded if they had obstructive median prostate lobes, urinary infections, acute urinary retention, or PSA levels greater than 10 ng/ml

Evidence Review

- Perera et al. 2016 systematic review
  - Meta-analytic results at the 12-month follow-up
    - Standard mean gain in health-related quality of life was -2.2 (95% CI -2.4 to -2.1)
    - Standard mean gain in prostate symptom scores was -1.5 (95% CI -1.6 to -1.3)
    - Standard mean gain in male sexual health scores was 0.3 (95% CI 0.2 to 0.4)

Evidence Review

- Roehrborn et al. 2017 RCT
  - Study was performed at 19 centers in the U.S., Canada, and Australia
  - 206 patients were randomized (2:1) to PUL or cystoscopy with sham procedure
  - Eligible patients:
    - Age 40 or older
    - IPSS ≥ 13
    - Peak urinary flow rate ≤ 12 ml/s
    - Prostate volume between 30 cc and 80 cc
    - No obstructive median lobe or active urinary infection

Evidence Review

- Roehrborn et al. 2017 RCT
  - Patients and outcomes assessors were blinded for 3 months
  - Comparison between groups at 3 months:
    - Greater improvement in quality of life in the PUL group (2.2 ± 1.8) than in the sham control group (1.0 ± 1.5) ($p < 0.001$)
    - Greater improvement in IPSS in the PUL group (-11.1 ± 7.7) than in the sham control group (-5.9 ± 7.7) ($p = 0.003$)
  - Adverse effects were uncommon and most likely to occur in the first 3 months
    - Pelvic pain, dysuria, hematuria, and urge incontinence were the most common adverse events, occurring in 3% to 9% of patients
    - Other adverse effects occurred in less than 1% of patients

Evidence Review

- Roehrborn et al. 2017 RCT
  - At 5 years of follow-up, data were available for 104 of the original 140 patients (74.3%) in the PUL arm
    - Rate of surgical retreatment at 5 years was 13.6%: 6 patients received additional PUL procedures and 13 patients received TURP
    - Intention-to-treat outcomes for the PUL arm (compared to baseline) at 5 years were calculated using the last observation carried forward
      - Mean change in IPSS at 5 years was -7.85, which reflects a 35% improvement from baseline
      - Mean change in quality of life at 5 years was -2.08, which reflects a 45% improvement from baseline
      - No significant change in sexual function compared to baseline

Evidence Review

- Gratzke et al., 2017 RCT
  - Conducted at 10 centers in 3 European countries
  - 90 patients were randomized to undergo either PUL or TURP and followed for 2 years
  - Eligible patients:
    - Over age 50
    - Candidate for TURP
    - IPSS > 12
    - PSA < 10 ng/l
    - Maximum urinary flow rate of 15 ml/s
    - Prostate volume < 60 cc by ultrasound
    - No active urinary infection or obstructive median lobe
    - No previous TURP or laser ablation

Evidence Review

- Gratzke et al. 2017 RCT
  - Change in IPSS was smaller in the PUL arm than the TURP arm (-9.2 vs. -15.3, p = 0.004)
  - Change in IPSS health-related quality of life was similar between the PUL arm and the TURP arm (-3.3 vs. -2.5, p = 0.066)
  - Incontinence was more likely in the TURP arm at 2 weeks and 3 months of follow-up, but did not significantly differ between the groups at 12 or 24 months of follow-up

Evidence Review

- Gratzke et al. 2017 RCT
  - Erectile function was similar in both arms: 98% of PUL patients and 94% of TURP patients met the erectile function criterion at 2 years
    - Ejaculatory function at 2 years was preserved in 100% of PUL patients compared to 34% of TURP patients
  - Clavien-Dindo grade 1 adverse events occurred in 68% of PUL patients and 74% of TURP patients (p = 0.6)
  - Clavien-Dindo grade 2 or 3 adverse events occurred in 16% of PUL patients and 22% of TURP patients
  - Reintervention within 1 year occurred in 3 patients in PUL arm (7%) and 5 patients in TURP arm (14%) (p = 0.5)

Evidence Summary

- Moderate-quality evidence that PUL results in improvements in quality of life and prostate symptom scores and that those improvements persist up to 5 years of follow-up

Evidence Summary

- In a single small trial that directly compared PUL to TURP:
  - Symptom scores at 2 years were slightly better for TURP
  - Quality of life outcomes were similar in both groups
  - PUL did not appear to result in significant changes in sexual function or continence, and reduced the likelihood of ejaculatory dysfunction when compared to TURP
  - Adverse events (including pelvic pain, hematuria, dysuria, and transient urinary retention) were commonly reported, but generally limited to the first 3 months after the procedure and were similar to the rates with TURP
  - Reintervention rates at 1 year were lower for PUL compared to TURP, but the differences were not statistically significant

GRADE Table

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
Quality of life (Critical outcome)	PUL is associated with a standard mean gain in health-related quality of life of -2.2 (95% CI -2.4 to -2.1) (negative values represent improvement) ●●●○ *(Moderate confidence, based on 6 studies with 680 patients)* *Extended follow-up (5 years) of patients in an RCT of PUL found these improvements to be durable*
Need for reoperation (Important outcome)	1.5% to 16% of patients will undergo TURP within 12 months of the PUL procedure ●●○○ *(Low confidence, based on 6 studies with 680 patients)*

GRADE Table

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
Procedural complications (Important outcome)	For the direct comparison of PUL and TURP, Clavien-Dindo grade 1 adverse events occurred in 68% of PUL patients and 74% of TURP patients (p = 0.6); Clavien-Dindo grade 2 or 3 adverse events occurred in 16% and 22% of patients respectively ●○○○ *(Very low confidence, based on 1 RCT with 80 patients)*

GRADE Table

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
Long-term harms (Important outcome)	For the direct comparison of PUL and TURP, erectile function was similar at 2 years in both arms: 98% of PUL patients and 94% of TURP patients met the erectile function criterion; ejaculatory function at 2 years was preserved in 100% of PUL patients compared to 34% of the TURP patients For the direct comparison of PUL and TURP, urinary incontinence was more likely in the TURP arm at 2 weeks and 3 months of follow-up, but did not significantly differ between the groups at 12 or 24 months follow-up ●○○○ *(Very low confidence, based on 1 RCT with 80 patients)*

GRADE Table

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
Change in prostate symptom scores (Important outcome)	PUL is associated with a standard mean gain in prostate symptom scores of -1.5 (95% CI -1.6 to -1.3) (negative changes represent improvement) ●●●◌ *(Moderate confidence, based on 6 studies with 680 patients)* *Extended follow-up (5 years) of patients in an RCT of PUL found these improvements to be durable*

Payer Policies

- Washington State Medicaid Program
  - No Washington Medicaid coverage policy was found for PUL
- Medicare
  - No National Coverage Determinations identified for PUL
  - 3 Local Coverage Determinations (LCDs), covering 18 states, were found for PUL
    - These 3 LCDs provide coverage for PUL under certain conditions

Payer Policies

- All 3 LCDs include these restrictions, among others:
  - At least 50 years old
  - Documented voiding symptoms consistent with prostatic hypertrophy
  - Peak urine flow rate (Qmax) ≤ (12 or 15) cc/sec on a voided volume that is greater than 125 cc
  - Prostatic volume ≤ 80 cc
  - No obstructive median lobe
  - No active urinary infection
  - Refractory to or intolerant of usual BPH medication

Payer Policies

- Private payers
  - Aetna, Cigna, and Regence provide coverage for PUL
    No coverage policy on PUL found for Moda
  - Cigna and Regence include coverage criteria:
    - Age 50 and older
    - Prostate volume (< 80 cc; < 100 cc)
    - No obstructive median lobe
  - Cigna also requires failure, contraindication, or intolerance to at least 3 months of conventional medical therapy for BPH (e.g., alpha blocker, PDE5 Inhibitor, finasteride/dutasteride)

Guidelines

- 2 guidelines that include recommendations on the use of PUL
  - European Association of Urology (2016)
    - PUL leads to objective and subjective short- and medium-term improvements in symptoms
    - High-quality studies are needed to compare the efficacy, safety, and durability between PUL and other established invasive treatments
  - National Institute for Health and Care Excellence (NICE) medical technology guidance (2016)
    - Recommend that PUL be considered for use in men with lower urinary tract symptoms of BPH who are aged 50 years and older and have a prostate of less than 100 cm^3
    - Cost-modeling studies showed that PUL is cost saving compared to TURP if it is used in a day surgery unit

Public Comment

- Public comment submitted by Jackie Madison, MS, COC, Sr. Manager, Strategic Reimbursement Access, Interventional Urology, NeoTract |Teleflex
  - Comment: Coverage criteria should be men 45 years or older, and include coverage for obstruction caused by both lateral and median lobes
    - Response: Coverage criteria are based on the most common inclusion and exclusion criteria from the relevant trials

Appointed Expert

- Input from appointed expert Nicholas Boncher, urologist
  - Recommended removing PSA score because this high of a score would be investigated separately
  - Recommended changing recommendation to strong
    - Response: Subcommittee accepted both recommendations

Discussion

Values and Preferences

Most men with symptomatic BPH would value surgical intervention that is less invasive and less costly than TURP, if the alternative procedure has similar effectiveness and a similar or lower rate of procedural complications. We would expect low variability in this preference, although some men would still prefer TURP as a more definitive and better established procedure.

Discussion

Resource Allocation

When PUL is performed as an outpatient procedure under local anesthesia, cost savings are significant compared to TURP (given that procedural complication rates are similar or lower). PUL cost savings are moderated by the low but significant rate of subsequent requirement for TURP, however.

Cost-modeling studies performed for NICE showed that PUL is cost saving compared to TURP (if used in a day surgery unit).

Discussion

Balance of Benefits and Harms

Fair-quality RCTs utilizing PUL demonstrated small but consistent improvements in health-related quality of life and prostate symptom scores, findings in which we have moderate confidence. Symptomatic improvements have been shown to be durable in a 5-year RCT. Compared with TURP, PUL has similar procedural complication rates, but PUL appears to be much better in preservation of ejaculatory function at 2 years post-procedure. The balance of benefits and harms weighs in favor of PUL, but benefits are moderated by a subsequent need for TURP in 1.5% to 16% of patients within 1 year of PUL.

Discussion

Rationale

Our recommendation for coverage of PUL is based on consistent results in critical and important outcomes, demonstrating symptomatic improvement in lower urinary tract symptoms caused by BPH. Values and preferences, as well as resource allocation, weigh in favor of PUL as the less invasive, less costly outpatient procedure (compared with TURP). Our recommendation is strong because of the moderate strength of the evidence and positive balance of benefits and harms.

Discussion

The Prostatic Urethral Lift procedure is recommended for coverage (*strong recommendation*) for treatment of men with symptomatic benign prostatic hypertrophy when the following criteria are met:

- Age 50 or older
- Estimated prostate volume < 80 cc
- IPSS score ≥ 13
- No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure
- Failure, contraindication, or intolerance to at least 3 months of conventional medication therapy for benign prostatic hypertrophy

Health Evidence Review Commission (HERC)

Coverage Guidance:

Prostatic Urethral Lift for

Treatment of Benign Prostatic Hypertrophy

DRAFT for VbBS/HERC meeting materials 5/17/2018

HERC Coverage Guidance

The Prostatic Urethral Lift procedure is recommended for coverage *(strong recommendation)* for treatment of men with symptomatic benign prostatic hypertrophy when the following criteria are met:

- Age 50 or older
- Estimated prostate volume < 80 cc
- IPSS score ≥ 13
- No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure
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Note: Definitions for strength of recommendation are in Appendix A. *GRADE Informed Framework Element Description*.

Table of Contents

Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patient experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on clinical interventions and modes of care, evidence is evaluated using an adaptation of the GRADE methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness may be dependent on the environment in which the intervention is implemented.

GRADE-Informed Framework

HERC develops recommendations by using the concepts of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by HERC based on the assessment of two independent reviewers from the Center for Evidence-based Policy (CEbP).

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from CEbP. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of HERC.

Should prostatic urethral lift be recommended for coverage for benign prostatic hypertrophy with lower urinary tract symptoms?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Quality of life *(Critical outcome)*	PUL is associated with a standard mean gain in health-related quality of life of -2.2 (95% CI -2.4 to -2.1) (negative values represent improvement). ●●●○ *(Moderate confidence, based on 6 studies with 680 patients)* *Extended follow-up (5 years) of patients in an RCT of PUL found these improvements to be durable.*	When PUL is performed as an outpatient procedure under local anesthesia, cost savings are significant as compared with TURP (given that procedural complication rates are similar or lower).	Most men with symptomatic BPH would value surgical intervention that is less invasive and less costly than TURP, if the alternative procedure has similar effectiveness and a similar or	
Need for re-operation *(Important outcome)*	1.5% to 16% of patients will undergo TURP within 12 months of the PUL procedure. ●●○○ *(Low confidence, based on 6 studies with 680 patients)*			

Should prostatic urethral lift be recommended for coverage for benign prostatic hypertrophy with lower urinary tract symptoms?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Procedural complications *(Important outcome)*	For the direct comparison of PUL and TURP, Clavien-Dindo grade 1 adverse events occurred in 68% of PUL patients and 74% of TURP patients (p = 0.6); Clavien-Dindo grade 2 or 3 adverse events occurred in 16% and 22% of patients respectively. ●○○○ *(Very low confidence, based on 1 RCT with 80 patients)*	PUL cost savings are moderated by the low but significant rate of subsequent requirement for TURP, however. Cost modeling studies performed for NICE showed that PUL is cost saving compared with TURP (if used in a day surgery unit).	lower rate of procedural complications. We would expect low variability in this preference, although some men would still prefer TURP as a more definitive and better established procedure.	
Long-term harms *(Important outcome)*	For the direct comparison of PUL and TURP, erectile function was similar at 2 years in both arms: 98% of PUL patients and 94% of TURP patients met the erectile function criterion; ejaculatory function at 2 years was preserved in 100% of PUL patients compared to 34% of the TURP patients. For the direct comparison of PUL and TURP, urinary incontinence was more likely in the TURP arm at 2 weeks and 3 months of follow-up, but did not significantly differ between the groups at 12 or 24 months follow-up. ●○○○ *(Very low confidence, based on 1 RCT with 80 patients)*			
Change in prostate symptom scores *(Important outcome)*	PUL is associated with a standard mean gain in prostate symptom scores of -1.5 (95% CI -1.6 to -1.3) (negative changes represent improvement). ●●●○ *(Moderate confidence, based on 6 studies with 680 patients)* *Extended follow-up (5 years) of patients in an RCT of PUL found these improvements to be durable.*			

Should prostatic urethral lift be recommended for coverage for benign prostatic hypertrophy with lower urinary tract symptoms?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Balance of benefits and harms: Fair-quality RCTs utilizing PUL demonstrate small but consistent improvements in health-related quality of life and prostate symptom scores, findings in which we have moderate confidence. Symptomatic improvements have been shown to be durable in a 5-year RCT. Compared with TURP, PUL has similar procedural complication rates, but PUL appears to be much better in preservation of ejaculatory function at two years post-procedure. The balance of benefits and harms weighs in favor of PUL, but benefits are moderated by a subsequent need for TURP in 1.5% to 16% of patients within one year of PUL.				
Rationale: Our recommendation for coverage of PUL is based on consistent results in critical and important outcomes, demonstrating symptomatic improvement in lower urinary tract symptoms caused by BPH. Values and preferences, as well as resource allocation, weigh in favor of PUL as the less invasive, less costly outpatient procedure (compared with TURP). Our recommendation is strong because of the moderate strength of the evidence and positive balance of benefits and harms.				
Recommendation: The Prostatic Urethral Lift procedure is recommended for coverage *(strong recommendation)* for treatment of men with symptomatic benign prostatic hypertrophy when the following criteria are met: • Age 50 or older • Estimated prostate volume < 80 cc • IPSS score ≥ 13 • No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure • Failure, contraindication, or intolerance to at least three months of conventional medication therapy for benign prostatic hypertrophy				

Note: GRADE-informed framework elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Background

Benign prostatic hyperplasia (BPH) is the nonmalignant growth of the prostate and typically starts at approximately 40 years of age and increases as men age (Roehrborn, 2005). Many men with histologic BPH will never consult a healthcare provider or receive treatment for the condition (Roehrborn, 2005). The most frequent manifestation of BPH is lower urinary tract symptoms, caused by the prostate putting pressure on the bladder or urethra and thus interfering with urine flow. Urinary symptoms include hesitancy, straining, weak flow, prolonged voiding, partial or complete urinary retention, nocturia, incontinence, and painful urination (Roehrborn, 2005).

The chart below shows the calculations to create the International Prostate Symptom Score (I-PSS). A score of 1 to 7 is categorized as Mild, 8 to 19 is Moderate, and 20 to 35 is Severe.

In the past month:	Not at all	Less than 1 in 5 times	Less than half the time	About half the time	More than half the time	Almost always	Score
1. Incomplete Emptying – How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency – How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency – How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency – How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream – How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining – How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times	
7. Nocturia – How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Lower urinary tract symptoms caused by BPH are among the most common reasons for urologic consultation in clinical practice (Magistro et al., 2017). In the U.S., the annual expenditures on the management of lower urinary tract symptoms due to BPH are estimated at approximately $6 billion dollars (Magistro et al., 2017).

Treatments for BPH include conservative approaches, pharmacological options, and various surgical procedures. Side effects of pharmacological treatments can include postural hypotension, dizziness, asthenia, and compromised sexual function (Magistro et al., 2017). The most frequent form of surgery is monopolar or bipolar transurethral resection of the prostate (TURP), which uses transurethral electrosurgery to remove prostate tissue during irrigation (Ray et al., 2015). Refinements of the technique have improved the safety profile of TURP over time; however, the procedure causes considerable long-term complications including ejaculatory dysfunction (65%), erectile dysfunction (10%), urethral strictures (7%), urinary tract infection (4%), bleeding requiring transfusion (2%), urinary incontinence (2%), and the procedure has a retreatment rate of 6% (Magistro et al., 2017).

A more recent surgical intervention is prostatic urethral lift (PUL), sold under the trade name of UroLift®. The PUL system lifts and holds the enlarged prostate tissue to create a continuous anterior channel through the prostatic lumen extending from the bladder neck to the verumontanum (Magistro, 2017). The UroLift® System (PUL) received De Novo approval from the U.S. Food and Drug Administration (FDA) in 2013 (NeoTract, 2017).

Indications

The UroLift® System (PUL) is indicated for the treatment of symptoms due to urinary outflow obstruction secondary to BPH in men 50 years of age or older. The contraindications include:

- Prostate volume of > 80 cc
- Obstructive or protruding median lobe of the prostate
- Urinary tract infection
- Urethra conditions that could prevent insertion of delivery system into bladder
- Urinary incontinence
- Current gross hematuria (NeoTract, 2017).

Technology Description

The PUL implantation procedure can be performed in an outpatient or inpatient setting and under general or local anesthesia, and the attending urologist completes comprehensive training prior to using the PUL system (NeoTract, 2017). The delivery device is used to compress one lateral lobe of the prostate toward the prostatic capsule. Then, a needle is used to deploy the implant, with one end of the implant anchored in the urethra and the other on the outer surface of the prostatic capsule, retracting the prostatic lobe away from the urethral lumen (Ray, 2015).

The permanent PUL implant is composed of a nitinol capsular tab (diameter: 0.6 mm, length: 8 mm), an adjustable polyethylene teraphtalate nonabsorbable monofilament (diameter: 0.4 mm), and a stainless steel urethral end piece (8 mm x 1mm x 0.5 mm). In most cases, no postinterventional catheterization is required (Magistro, 2017). Typically, four implants are placed (NeoTract, 2017).

Evidence Review

Perera et al., 2016

This is a fair-quality systematic review of six studies of PUL. The review includes one sham-controlled randomized controlled trial (RCT), one observational cohort that followed crossover patients from that RCT, two prospective cohorts, and two retrospective cohorts. These studies involved 680 patients. Results for most of the outcome measures were reported as standardized mean gains (which the authors noted can be interpreted as similar to Cohen's *d* statistic). In most of the included studies, patients were eligible if they were over age 50, had an IPSS greater than 12, and had prostate volumes estimated between 20 and 100 ml. Patients were excluded if they had obstructive median prostate lobes, urinary infections, acute urinary retention, or prostate-specific antigen (PSA) levels greater than 10 ng/ml. Most of the enrolled patients were between age 65 and 75, and the mean baseline IPSS was in the low to mid-20s. For meta-analytic results at the 12-month follow-up, the standard mean gain in health-related quality of life was -2.2 (95% CI -2.4 to -2.1), where negative scores reflect improvement; the standard mean gain in prostate symptom scores was -1.5 (95% CI -1.6 to -1.3); and the standard mean gain in male sexual health scores was 0.3 (95% CI 0.2 to 0.4). These effects on health-related quality of life and prostate symptom scores are conventionally regarded as large effect sizes. Among the included studies, the rate of insufficient improvement and progression to TURP ranged from 1.5% to 16% of patients at 12 months. Nearly all of the procedures were performed under local anesthesia. The most commonly reported complications in the first three months after the procedure were hematuria (16% to 75% of patients), dysuria (25% to 53% of patients), pelvic pain (3.7% to 19.3% of patients), urinary tract infection (3.2% to 10% of patients), and transient urinary incontinence (1.9% to 16% of patients). Overall, the authors concluded that the procedure is well tolerated with few periprocedural complications and is effective for improving quality of life, prostate symptom scores, and sexual function scores at up to 12 months.

Roehrborn et al., 2017

This is a fair-quality study of five-year outcomes from the prospective, randomized, sham-controlled, double-blind trial of the PUL. The study was performed at 19 centers in the United States, Canada, and Australia. Patients were eligible to enroll if they were age 40 or older, had IPSS ≥ 13, peak urinary flow rate ≤ 12 ml/s, and prostate volume between 30 cc and 80 cc as assessed by transrectal ultrasound. Patients were excluded if they had an obstructive median lobe or active urinary infection. Patients treated with alpha blockers or 5-alpha reductase inhibitors were required to stop these medications during a washout period (two weeks and three months, respectively). Ultimately, 206 patients were randomized (2:1) to PUL or cystoscopy with sham procedure. The groups had similar characteristics at baseline. Planned follow-up for the randomized access portion of the trial was three months, and patients and outcomes assessors were blinded during this period. After three months, patients in the sham control arm were unblinded and allowed to cross over to PUL (80% of sham control patients did so). About one-third of the patients experienced voiding dysfunction after the procedure and required a catheter for a mean duration of 0.9 days.

For the randomized comparison between groups at three months, there was greater improvement in quality of life in the PUL group (2.2 ± 1.8) than in the sham control group (1.0 ± 1.5) ($p < 0.001$). Similarly, there was greater improvement in IPSS in the PUL group (-11.1 ± 7.7) than in the sham control group (-5.9 ± 7.7) ($p = 0.003$).

At five years of follow-up, data were available for 104 of the original 140 patients (74.3%) in the PUL arm (of the 36 patients for whom data were incomplete, 18 were lost to follow-up, nine died, five sought treatment for cancer, and four underwent TURP or laser ablation). The overall rate of surgical retreatment at five years was 13.6%: six patients received additional PUL procedures and 13 patients received TURP. Intention-to-treat outcomes for the PUL arm (compared to baseline) at five years were calculated using the last observation carried forward. The mean change in IPSS at five years was -7.85, which reflects a 35% improvement from baseline. The mean change in quality of life at five years was -2.08, which reflects a 45% improvement from baseline. There was no significant change in sexual function compared to baseline in the per-protocol five-year follow-up among patients in the PUL arm.

Adverse effects were uncommon and most likely to occur in the first three months. Pelvic pain, dysuria, hematuria, and urge incontinence were the most common adverse events, occurring in 3% to 9% of patients. Other adverse effects occurred in less than 1% of patients.

CEbP staff noted that the study was limited by the absence of blinded, randomized follow-up beyond three months, the moderate loss to follow-up at five years, and the attendant use of last observation carried forward to estimate the durability of effects. Three of the authors disclosed conflicts of interest with NeoTract, the maker of the PUL system. This study was rated fair quality for these reasons.

Gratzke et al., 2017

This is a fair-quality RCT comparing PUL to TURP that was conducted at 10 centers in three European countries. Patients were eligible for inclusion if they were over age 50; were a candidate for TURP; and had IPSS > 12, a maximum urinary flow rate of 15 ml/s, and prostate volume < 60 cc by ultrasound. Patients were excluded if they had active urinary infection, had obstructive median lobe, had previously undergone TURP or laser ablation, or had a PSA >10 ng/l. Ninety patients were randomized (1:1) to undergo either PUL or TURP. Ten patients randomized to TURP declined treatment, and one patient randomized to PUL declined treatment; ultimately there were 35 patients in the TURP group and 45 patients in the PUL group. Patients were followed for two years. A variety of prostate symptom-specific measures and general quality of life measures were assessed. Baseline patient characteristics were not reported. The groups were generally similar at baseline, the mean age was approximately 64 years, and the mean IPSS was approximately 22.

At two years follow-up, IPSS and IPSS health-related quality of life had improved compared to baseline in both treatment arms. The change in IPSS was smaller in the PUL arm than the TURP arm (-9.2 vs. -15.3, p = 0.004). The change in IPSS health-related quality of life was similar between the PUL arm and the TURP arm (-3.3 vs. -2.5, p = 0.066). The proportion of patients achieving a minimal clinically important difference in quality of life as measured by the SF-6D utility score was similar at two years (47% in the PUL arm vs. 37.5% in the TURP arm, p = 0.43). Erectile function was similar at two years in both arms: 98% of PUL patients and 94% of TURP patients met the erectile function criterion. However, ejaculatory function at two years was preserved in 100% of PUL patients compared to 34% of the TURP patients. Incontinence was more likely in the TURP arm at two weeks and three months of follow-up, but did not significantly differ between the groups at 12 or 24 months of follow-up. The rates of serious adverse events and reintervention between the two groups at 12 months were reported in a previous study (Sonksen et al., 2015). Overall, Clavien-Dindo grade 1 adverse events occurred in 68% of PUL patients and 74% of TURP patients (p = 0.6); Clavien-Dindo grade 2 or 3 adverse events occurred in 16%

and 22% of patients respectively. Reintervention within one year occurred in three patients in the PUL arm (7%) and five patients in the TURP arm (14%) (p = 0.5).

CEbP researchers noted that the study was limited by the differential drop-out of patients randomized to the TURP arm. Five of the authors disclosed conflicts of interest with NeoTract, the maker of the PUL system.

Evidence Summary

There is moderate-quality evidence that PUL results in improvements in quality of life and prostate symptom scores and that those improvements persist at up to five years of follow-up. In a single small trial that directly compared PUL to TURP, symptom scores at two years were slightly better for TURP, and quality of life outcomes were similar in both groups. PUL did not appear to result in significant changes in sexual function or continence, and reduced the likelihood of ejaculatory dysfunction when compared to TURP. Adverse events (including pelvic pain, hematuria, dysuria, and transient urinary retention) were commonly reported, but generally limited to the first three months after the procedure and were similar to the rates observed with TURP. Reintervention rates at one year were numerically lower for PUL compared to TURP, but the differences were not statistically significant.

Policy Landscape

Payer Coverage Policies

Medicaid

No Washington Medicaid coverage policy was found for PUL.

Medicare

Three Local Coverage Determinations (LCDs), covering 18 states, were found for PUL: L36109, L36601, and L36775. The manufacturer's website for UroLift® states that all Medicare carriers provide benefits for PUL when medically necessary (NeoTract, 2017).

L36109 provides coverage for an initial implant and up to five additional implants, although implants in excess of six may be reconsidered on appeal. L36775 provides coverage for the PUL procedure once in a lifetime per beneficiary with a maximum of six implants. L36601 provides coverage for the surgical intervention with up to a total of six implants, although implants in excess of six may be reconsidered on an exception basis with a formal redetermination.

L36601 and L36775 provide coverage for PUL to treat BPH when all these conditions are met:

- Beneficiary is at least 50 years old with well-documented voiding symptoms consistent with prostatic hypertrophy
- AUA symptom index (AUASI) score ≥ 13
- Peak urine flow rate (Qmax) ≤ 12 cc/sec on a voided volume that is greater than 125 cc
- The beneficiary has had an adequate trial of, but is refractory to or intolerant of, usual BPH medication
- Prostate volume ≤ 80 cc without an obstructive median lobe
- There are no signs, symptoms, or diagnostic evidence of an active urinary infection and no history of bacterial prostatitis in the past three months
- The beneficiary is a poor candidate for other surgical interventions for BPH due to underlying disease (e.g., cardiac disease, pulmonary disease, etc.), or at high risk of bleeding, or the

beneficiary has opted for PUL based on likelihood of preserving erectile function, or there is another documented clinical reason for opting for PUL.

L36109 provides coverage for PUL for the treatment of symptomatic benign prostatic hyperplasia in men who are at least 50 years old when all these criteria are met:

- Moderate to severe BPH, defined as an AUA symptom score above 7 including signs of obstruction, such as increased voiding symptoms or decreased peak urinary flow rate (i.e., individual has a peak urine flow rate (Qmax) < 15 cc/sec on a voided volume that is greater than 125 cc
- Refractory to or intolerant of usual BPH medication
- Enlarged lateral lobes without an obstructive median lobe
- Prostatic volume ≤ 80 cc
- No active urinary infection
- Normal renal function

Private Payers

Coverage policies were searched for Aetna, Cigna, Moda, and Regence. No coverage policy on PUL was found for Moda.

The Aetna policy on BPH treatments (last reviewed 7/17/2017) provides coverage for PUL. The Cigna policy (effective 10/15/2017) states that PUL is considered medically necessary for the treatment of symptomatic BPH when all these criteria are met:

- Age 50 or above
- Estimated prostate volume < 80 cc
- No obstructive median lobe of the prostate identified on cystoscopy
- Failure, contraindication, or intolerance to at least three months of conventional medical therapy for BPH (e.g., alpha blocker, PDE5 Inhibitor, finasteride/dutasteride)

The Regence Clinical Position Statement on PUL (last reviewed 6/22/2017) states that PUL may be considered as an alternative to current surgical procedures for men aged 50 years and older with lower urinary tract symptoms of benign prostatic hyperplasia, who have a prostate of less than 100 ml without an obstructing middle lobe.

Recommendations from Others

Two guidelines were found that include recommendations on the use of PUL. The 2016 guidelines from the European Association of Urology conclude that PUL leads to objective and subjective short- and mid-term improvements in symptoms. However, according to the guideline authors, high-quality studies are needed to compare the efficacy, safety, and durability between PUL and other established invasive treatments (Gratzke et al., 2015).

A 2016 medical technology guidance from the National Institute for Health and Care Excellence (NICE) concludes that using PUL to treat symptoms of BPH is supported by the evidence if it is used in a day surgery unit. The NICE guidelines recommend that PUL be considered for use in men with lower urinary tract symptoms of BPH who are aged 50 years and older and who have a prostate of less than 100 cm^3. Cost modeling studies showed that PUL is cost saving compared with TURP (Ray et al., 2016).

Quality Measures

No quality measures were identified when searching the National Quality Measures Clearinghouse for prostatic urethral lift or BPH.

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (CEbP). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

CEbP is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of CEbP. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Suggested citation: Obley, A., Mosbaek, C., King, V., & Shaffer, W. (2018). *Coverage guidance: Prostatic urethral lift for treatment of benign prostatic hypertrophy*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University

Appendix A. GRADE-Informed Framework Element Descriptions

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors., but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical

sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Appendix B. GRADE Evidence Profile

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Quality of life							
6	Mix of observational studies and 1 RCT	Moderate	Not serious	Not serious	Not serious	Large effect size	Moderate ●●●○
Need for reoperation							
6	Mix of observational studies and 1 RCT	Moderate	Not serious	Not serious	Serious		Low ●●○○
Procedural complications							
1	RCT	Moderate	Not estimable	Not serious	Serious		Very low ●○○○
Long-term harms							
1	RCT	Moderate	Not estimable	Not serious	Serious		Very low ●○○○
Change in prostate symptom scores							
6	Mix of observational studies and 1 RCT	Moderate	Not serious	Not serious	Not serious	Large effect size	Moderate ●●●○

Appendix C. Methods

Scope Statement

Populations

Men with benign prostatic hypertrophy (BPH) and lower urinary tract symptoms (LUTS)

Population scoping notes: None

Interventions

Prostatic urethral lift (PUL) procedure

Intervention exclusions: None

Comparators

Medical management (alpha blockers, 5-alpha reductase inhibitors), transurethral resection of the prostate (TURP), bipolar TURP, photoselective vaporization of the prostate (PVP), holmium laser enucleation of the prostate (HoLEP), transurethral incision of the prostate (TUIP), transurethral needle ablation of the prostate (TUNA), transurethral microwave thermotherapy (TUMT), bipolar transurethral electrovaporization of the prostate (TUVP), thulium laser vaporization/resection of the prostate

Outcomes

Critical: Quality of life

Important: Need for reoperation, procedural complications, long-term harms (e.g., urinary incontinence, erectile dysfunction), symptom improvement (e.g., International Prostate Symptom Score [IPSS], American Urological Association Symptom Index [AUASI] scores)

Considered but not selected for the GRADE table: Flow rate, post-void residual, post-procedural catheterization time, urinary retention

Key Questions

KQ1: What is the comparative effectiveness of PUL for men with lower urinary tract symptoms from BPH?

a. Does comparative effectiveness vary by baseline symptom severity?
b. Does the age of the patient or duration of symptoms affect the comparative effectiveness?

KQ2: What are the comparative harms of PUL for men with lower urinary tract symptoms from BPH?

Contextual Questions

CQ1: In what settings (outpatient, ambulatory surgical center, inpatient) and with what types of anesthesia or analgesia can PUL be safely performed?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2012.

The core sources searched included:

- Agency for Healthcare Research and Quality (AHRQ)
- Blue Cross/Blue Shield Center for Clinical Effectiveness
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Online Library)
- Institute for Clinical and Economic Review (ICER)
- Medicaid Evidence-based Decisions Project (MED)
- National Institute for Health and Care Excellence (NICE)
- Tufts Cost-effectiveness Analysis Registry
- Veterans Administration Evidence-based Synthesis Program (ESP)
- Washington State Health Technology Assessment Program

A MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search term prostatic urethral lift or Urolift. The search was limited to publications in English published since 2012. In addition, a MEDLINE® search was conducted for randomized controlled trials published after the search dates of the 2015 systematic review by Perera and colleagues.

Searches for clinical practice guidelines were limited to those published since 2012. A search for relevant clinical practice guidelines was also conducted using MEDLINE® and the following sources:

- Australian Government National Health and Medical Research Council (NHMRC)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Centers for Disease Control and Prevention (CDC) – Community Preventive Services
- National Guidelines Clearinghouse
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense (VA/DOD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, randomized controlled trials, or clinical practice guidelines.

Appendix D. Applicable Codes

CODES	DESCRIPTION
CPT Codes	
52441	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; single implant
52442	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; each additional permanent adjustable transprostatic implant (List separately in addition to code for primary procedure)
HCPCS Codes	
C9739	Cystourethroscopy, with insertion of transprostatic implant; 1 to 3 implants
C9740	Cystourethroscopy, with insertion of transprostatic implant; 4 or more implants

Note: Inclusion on this list does not guarantee coverage.

Prostatic urethral Lift for Benign Prostatic Hypertrophy

Question: How should the draft Coverage Guidance **Prostatic Urethral Lift for Treatment of Benign Prostatic Hypertrophy** be applied to the Prioritized List?

Question source: HERC Staff, HTAS

Issue: The HTAS approved the following draft "box language":

The Prostatic Urethral Lift procedure is recommended for coverage *(strong recommendation)* for treatment of men with symptomatic benign prostatic hypertrophy when the following criteria are met:

- Age 50 or older
- Estimated prostate volume < 80 cc
- IPSS score ≥ 13
- No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure
- Failure, contraindication, or intolerance to at least three months of conventional medication therapy for benign prostatic hypertrophy

Rationale for Recommendations

The prostatic urethral lift (PUL) implantation procedure can be performed in an outpatient or inpatient setting and under general or local anesthesia. The PUL delivery device is used to compress a lateral lobe of the prostate toward the prostatic capsule, and then the implant is deployed, with one end of the implant anchored in the urethra and the other on the outer surface of the prostatic capsule, retracting the prostatic lobe away from the urethral lumen. Typically, four implants are placed.

Fair-quality RCTs utilizing PUL demonstrate small but consistent improvements in health-related quality of life and prostate symptom scores, and symptomatic improvements have been shown to be durable in a 5-year RCT. Compared with Transurethral Resection of the Prostate (TURP), PUL has similar procedural complication rates, but PUL appears to be much better in preservation of ejaculatory function. The balance of benefits and harms weighs in favor of PUL, although benefits are moderated by a subsequent need for TURP in 1.5% to 16% of patients within one year of PUL.

Our recommendation for coverage of PUL is based on consistent evidence demonstrating symptomatic improvement in lower urinary tract symptoms caused by BPH. Values and preferences, as well as resource allocation, weigh in favor of PUL as the less invasive, less costly outpatient procedure (compared with TURP).

Current Prioritized List Status: Codes

The CPT codes used for prostatic urethral lift procedures (52441, 52442) appear on Guideline Note 173/line 660 and HCPCS codes (C9739, C9740) are currently on the defunct Services Recommended for Non-Coverage Table.

Current Prioritized List Guidelines:

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

Procedure Code	Intervention Description	Rationale	Last Review
….			
52441-52442	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant	No evidence of effectiveness	March, 2015 Coverage Guidance
….			

GUIDELINE NOTE 145, TREATMENTS FOR BENIGN PROSTATE ENLARGEMENT WITH LOWER URINARY TRACT SYMPTOMS

Line 327

For men with lower urinary tract symptoms (LUTS) due to benign prostate enlargement, coverage of surgical procedures is recommended only if symptoms are severe, and if drug treatment and conservative management options have been unsuccessful or are not appropriate.

The following interventions for benign prostate enlargement are not included on Line 327 due to lack of evidence of effectiveness:

- Botulinum toxin
- HIFU (High Intensity Focused Ultrasound)
- TEAP (Transurethral Ethanol Ablation of the Prostate)
- Prostatic urethral lifts
- Laser coagulation (for example, VLAP/ILC)
- Prostatic artery embolization

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

HERC Staff Recommendations:

1) Add the following codes to Line 327, FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION; MEDICAL AND SURGICAL TREATMENT

CPT Codes	
52441	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; single implant
52442	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; each additional permanent adjustable transprostatic implant (List separately in addition to code for primary procedure)
HCPCS Codes	
C9739	Cystourethroscopy, with insertion of transprostatic implant; 1 to 3 implants
C9740	Cystourethroscopy, with insertion of transprostatic implant; 4 or more implants

2) Revise Guideline Note 145, as follows:

GUIDELINE NOTE 145, TREATMENTS FOR BENIGN PROSTATE ENLARGEMENT WITH LOWER URINARY TRACT SYMPTOMS

Line 327

For men with lower urinary tract symptoms (LUTS) due to benign prostate enlargement, ~~coverage of~~ surgical procedures ~~is recommended~~ are included on these lines only if symptoms are severe, and if drug treatment and conservative management options have been unsuccessful or are not appropriate.

Prostatic urethral lift procedures (CPT 52441, 52442, HCPCS C9739, C9740) are included on Line 327 when the following criteria are met:

- Age 50 or older
- Estimated prostate volume < 80 cc
- International Prostate Symptom Score (IPSS) ≥ 13
- No obstructive median lobe of the prostate identified on cystoscopy at the time of the procedure

The following interventions for benign prostate enlargement are not included on Line 327 due to lack of evidence of effectiveness:

• Botulinum toxin
• HIFU (High Intensity Focused Ultrasound)
• TEAP (Transurethral Ethanol Ablation of the Prostate)
~~• Prostatic urethral lifts~~
• Laser coagulation (for example, VLAP/ILC)
• Prostatic artery embolization

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

3) Remove the entry on Prostatic Urethral Lifts from Guideline Note 173 and remove CPT 52441 and 52442 from line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS

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

Procedure Code	Intervention Description	Rationale	Last Review
….			
~~52441-52442~~	~~Cystourethroscopy, with insertion of permanent adjustable transprostatic implant~~	~~No evidence of effectiveness~~	~~March, 2015~~ ~~Coverage Guidance~~
….			

HERC Coverage Guidance: Prostatic Urethral Lift for Treatment of Benign Prostatic Hypertrophy
Disposition of Public Comments

Table of Contents

Commenters

Identification	Stakeholder
A	Jackie Madison, MS, COC, Sr. Manager, Strategic Reimbursement Access, Interventional Urology, NeoTract |Teleflex *[Submitted March 27, 2018]*

Public Comments

ID/#	Comment	Disposition
A1	Please accept these comments on your draft coverage guidance for Urolift prostatic urethral lift. I work for the manufacturer of Urolift, NeoTract, now owned by Teleflex, but as one intimately familiar with our data and coding I hope you will take these comments into consideration. In light of the robust clinical portfolio of peer-reviewed published data available for Urolift and coverage from other plans in the state, including Regence, Premera, Providence, UnitedHealthcare, Cigna, Aetna, and of course, Medicare, the coverage guidance is very timely. As you have outlined in your draft guidance, Urolift offers a minimally invasive option for men who have failed medical therapy, who are unable to take medications, who may be interested in preserving sexual function, and/or who are not willing to undergo an invasive treatment option with known risks of sexual dysfunction, incontinence, or bleeding. Not to mention, Urolift results in a more rapid relief of symptoms and a faster return	*Thank you for your comments.*

ID/#	Comment	Disposition
	to work and preoperative activities than interventions using prostate destruction techniques. There are only a few comments I would offer about your draft guidance:	
A2	There is a coverage criterion stating that patients should be 50 or older to be eligible for Urolift. The FDA recently updated the indication for Urolift to include men that are 45 years of age or older based on a white paper. The updated indication also includes coverage for obstruction caused by both lateral and median lobes based on clinical data. I've attached both the white paper and the FDA's summary of safety and effectiveness with the updated indication and supporting data.	*The current coverage criteria are based on the most common inclusion and exclusion criteria from the relevant trials that established the benefits of the procedure. Unpublished data are generally excluded from HERC's deliberations.*
A3	HERC indicated that the coverage recommendation was "weak" based on the fact the future studies could change the understanding of the procedure. However, all studies have been remarkably consistent. The repeatable, reliable improvement has been achieved across randomized controlled studies, open label studies, across different centers and even countries, and from first cases (i.e., each physicians' first patients are included in the LIFT study) to cases after any learning curve (i.e., LOCAL study). This consistency, and the ability to observe the deobstruction accomplished during the procedure, is a hallmark of the Urolift procedure. Most recently, a retrospective registry was presented at the European Association of Urology meeting in Copenhagen just last week, vastly increasing the number of patients studied. The registry that shows in the 'real world' and outside the rigor of a clinical trial, Urolift reliably performs in the method reported in the prospective studies. The presented poster is attached.	*We believe the weak recommendation is warranted because the major randomized trial data are limited by unblinding and the high rate of crossover at three months. Additional data could change the estimate of effect, particularly data from a high-quality randomized trial in which group assignment and blinding are maintained beyond three months to establish the procedure's longer-term effectiveness. Similarly, additional data on adverse events or the need for reoperation or progression to TURP would alter the balance of benefits and harms.*
A4	I am confused at the retreatment rate of up to 16% in the first year listed in the coverage guidance. In the prospective studies there is no such retreatment rate that high. The LIFT study shows retreatment of 13.6% at five years. Even the BPH-6 study, slightly higher, shows 11% retreatment at two years.	*The reported range for progression to TURP is derived from the systematic review by Perera et al. (2016, p. 709).*

HERC Coverage Guidance: Prostatic Urethral Lift for Treatment of Benign Prostatic Hypertrophy
Disposition of Public Comments

ID/#	Comment	Disposition
A5	Lastly, I would mention that the procedure codes used by hospitals and surgery centers to bill for Urolift are excluded from the policy. While 52441 and 52442 are the physician codes, in 2014 CMS issued HCPCS codes that allowed hospitals and surgery centers to bill for Urolift. They elected to assign these codes, C9739 and C9740, to permanent APCs. Now hospitals and surgery centers cannot bill the CPT codes to Medicare and must bill either C9739 or C9740 to Medicare for the procedure. Because of the structure of these codes, C9739 used for cases using 1 to 3 implants and C9740 used for cases using 4 or more implants), they also work as cost containment codes in the facility setting. I've attached CMS's original memo demonstrating that these particular C-codes are procedure codes and not device codes. I've also attached the current year ASC procedures list showing that the C-codes show as billable to Medicare and the CPT codes 52441 and 52442 do not.	*Thank you for your comments and for providing this information on coding and billing for the procedure. C9739 and C9740 have been added to the list of codes in the draft coverage guidance.*
A6	I respectfully request that implementation of this coverage guidance is not delayed to ensure that beneficiaries under the care of OHA have the same access to minimally invasive, effective, and durable care as members under the care of other health plans. If you have any additional questions or need any additional studies, please don't hesitate to reach out to me. Thank you again for the development of this robust and comprehensive guidance.	*Thank you for your comments.*

Genome Expression Profiling for Breast Cancer

Draft Coverage Guidance for VbBS Consideration

May 17, 2018

Oregon Health Authority

Oregon Health & Science University

Center For Evidence-based Policy

Background

- Approximately 1 in 8 women (12.5%) in the U.S. develop invasive breast cancer during their lifetime
- Treatments for breast cancer include surgery, chemotherapy, hormonal therapy, biological therapy using the immune system, and radiation therapy
- Web-based tools (e.g., Adjuvant! Online, PREDICT) are used to predict cancer prognosis and aid decision making
  - These tools use patient and tumor characteristics (tumor size and grade, number of positive axillary nodes, hormone receptor status)

Background

- Genome expression profiling tests can also be used to predict a cancer's aggressiveness, and thereby inform decision making on treatments
  - Tests analyze cancer tissue to assess the activity level of certain genes, which may indicate the likelihood of the cancer spreading
  - Tests for women with early-stage invasive breast cancer:
    - Oncotype DX Breast Recurrence Score
    - EndoPredict
    - MammaPrint
    - Prosigna
    - Breast Cancer Index (BCI)
  - Test for women with ductal carcinoma in situ (DCIS)
    - Oncotype DX Breast DCIS Score

Scope Statement

- Populations
  - Women diagnosed with early-stage breast cancer
- Interventions
  - Genome expression profiling on cancer tissue
- Comparators
  - Usual care, immunohistochemical assays, genome expression profiling tests compared to each other

Scope Statement

- Critical Outcomes
  - Breast cancer morbidity
  - Breast cancer mortality
- Important Outcomes
  - Quality of life
  - Harms
  - Change in management of breast cancer

Considered but not selected for the GRADE table: analytic validity, clinical validity

Scope Statement

Key Questions

1. What is the comparative effectiveness of genome expression profiling in early-stage breast cancer?
2. How does the comparative effectiveness of genome expression profiling vary by:
   a. Age
   b. Race or ethnicity
   c. Patient and family history
   d. Cancer characteristics (e.g., tumor size, tumor grade, type of tumor, nodal status, hormone receptor status, HER2 status, proliferation rate, cancer stage)
   e. Menopausal status
3. What are the harms of genome expression profiling for breast cancer?

Evidence Review: Oncotype DX Breast Recurrence Score

Systematic Review:

- Scope et al., 2017
  - Good-quality narrative systematic review, undertaken to inform National Institute for Health and Care Excellence (NICE)
  - 41 observational studies on the use of Oncotype DX breast recurrence score, MammaPrint, Mammostrat, and IHC4 testing in adjuvant chemotherapy decisions
    - 5 studies based on a prospective analysis using archived tissue specimens from an adjuvant chemotherapy RCT, judged to be at moderate risk of bias
    - Remaining studies were mainly limited by small size, retrospective designs, and incomplete reporting of patient characteristics
  - High levels of clinical heterogeneity among the studies

Evidence Review: Oncotype DX Breast Recurrence Score

- Scope et al., 2017
  - 3 studies examined the ability of Oncotype DX breast recurrence score to predict adjuvant chemotherapy benefit for women with ER-positive, lymph node-negative breast cancer
    - High-risk recurrence score was correlated with chemotherapy benefit
  - 28 studies of the effect of Oncotype DX on clinical decisions
    - Reported changes in adjuvant chemotherapy recommendations or receipt ranged from 21% to 74% of the patients who were tested
    - All but one of the studies found overall decreases in the recommendations for or receipt of adjuvant chemotherapy; decreases ranged from 6% to 51%
    - The authors noted difficulty in ascertaining the effects of the testing on actual treatments rendered

Evidence Review: Oncotype DX Breast Recurrence Score

Additional trials summary

- Bear et al. RCT of neoadjuvant hormonal treatment (NHT) vs. neoadjuvant systemic chemotherapy (NCT) among patients with recurrence score 11-25
  - In the RS 11-25 group, 18 patients received NHT and 11 patients received NCT (some patients assigned to NCT refused treatment and 2 crossed to the NHT group)
  - Patients who received NCT were more likely to have a clinical response (72.7% vs. 50%, p = 0.049)
  - There was no statistically significant difference in the rate of successful breast-conserving surgery (63.6% vs. 72.2%, p = NS)
- 11 observational trials, generally consistent with the findings from the Scope et al. systematic review

Evidence Review: MammaPrint

Scope et al. systematic review

- 6 studies of how MammaPrint influenced clinical decisions
  - These studies reported overall changes in adjuvant chemotherapy recommendations or receipt in 18% to 40% of the patients who were tested
  - The studies found that overall, 2% to 32% of patients would have recommendations changed from adjuvant chemotherapy to no chemotherapy
  - The authors noted difficulty in ascertaining the effects of the testing on actual treatments rendered

Evidence Review: MammaPrint

Randomized Controlled Trial:

- Cardoso et al., 2016 (MINDACT)
  - Fair-quality prospective RCT of the clinical utility of MammaPrint for early-stage breast cancer, as part of the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) study
  - Between 2007 and 2011, 6,693 patients were enrolled at 112 centers in 9 European countries
  - Patients had early-stage breast cancer (defined as T1 or T2 disease or operable T3 disease) and were 18 to 70 years old

Evidence Review: MammaPrint

- Cardoso et al., 2016 (MINDACT)
  - Patients were classified as clinically low risk or high risk using Adjuvant! Online
  - MammaPrint testing of frozen tumor tissue to classify as genomically low or high risk
    - Patients with low clinical and low genomic risk were advised against receiving adjuvant chemotherapy (41% of patients)
    - Patients with high clinical and high genomic risk were advised to receive adjuvant chemotherapy (27% of patients)
    - Patients with discordance between their clinical and genomic risk classification were randomized to adjuvant chemotherapy or no adjuvant chemotherapy (32% of patients)

Evidence Review: MammaPrint

- Cardoso et al., 2016 (MINDACT)
  - Patients with high clinical and low genomic risk
    - Patients randomized to receive chemotherapy had a rate of distant metastasis-free survival of 95.9% at 5 years, compared to 94.4% among those randomized to not receive chemotherapy (HR 0.78, 95% CI 0.50 to 1.21)
    - From these results, the authors observed that use of MammaPrint would have led to an overall reduction in adjuvant chemotherapy in 46.2% of patients with high clinical risk
    - The study findings suggest that patients deemed to be at high clinical risk may avoid the use of adjuvant chemotherapy when they are classified as low genomic risk by MammaPrint without a statistically significant increase in distant metastasis or death at 5 years

Evidence Review: MammaPrint

- Cardoso et al., 2016 (MINDACT)
  - Patients with low clinical risk and high genomic risk
    - Patients randomized to chemotherapy had a rate of distant metastasis-free survival of 95.8% at 5 years compared to 95.0% for those randomized to no chemotherapy (HR 1.17, 95% CI 0.59 to 2.28)
    - The study findings suggest that in patients with low clinical risk, there is no advantage to offering chemotherapy to patients with high genomic risk

Evidence Review: MammaPrint

5 additional observational trials:

- Kuijer et al., 2017, Prospective case series with decision impact analysis
- Kuijer et al., 2016(a), Cross-sectional study using the Netherlands Cancer Registry
- Kuijer et al., 2016(b), Retrospective historically controlled cohort
- Pohl et al., 2016, Retrospective case series with decision impact analysis
- Tsai et al., 2017, Prospective case series with decision impact analysis

Results generally consistent with the Scope et al. systematic review

Evidence Review: Prosigna (PAM50)

Two observational trials:

- Hequet et al., 2017
  - Prospective consecutive case series with decision impact analysis
  - 210 postmenopausal women with Stage I-II, ER-positive, HER2-negative, lymph node-negative breast cancer
  - Prosigna results led to change in adjuvant treatment recommendation in 34 patients (18%)
    - 25 patients changed from a recommendation of no adjuvant chemotherapy to a recommendation for chemotherapy
    - 9 recommendations for adjuvant chemotherapy were changed to no chemotherapy

Evidence Review: Prosigna (PAM50)

- Wuerstlein et al., 2016
  - Prospective consecutive case series with decision impact analysis
  - 198 postmenopausal women with ER-positive, HER2-negative, lymph node-negative early-stage breast cancer
  - Prior to Prosigna results, adjuvant chemotherapy was recommended for 45 patients (22.7%)
  - Prosigna results led to a change in adjuvant chemotherapy recommendation in 27 cases
    - Higher number of recommendations for adjuvant chemotherapy (20) among patients with high- or intermediate-risk scores

Evidence Review: EndoPredict

One observational trial:

- Ettl et al., 2017
  - Prospective consecutive case series comparing treatment decisions with and without information from EndoPredict EPclin and/or protein marker uPA/PAI-1
  - EPclin results were obtained for all 395 patients and uPA/PAI-1 results were obtained for 190 patients
  - Among the patients with results for both EPclin and uPA/PAI-1, when assessed independently:
    - EPclin led to treatment recommendation change in 87 patients (46%)
    - uPA/PAI-1 led to treatment recommendation change in 46 patients (24%)

Evidence Review: Breast Cancer Index

One observational trial:

- Sanft et al., 2015
  - Prospective case series with decision impact analysis
  - Pre- and post-BCI treatment recommendations were available for 96 patients
  - Before BCI results, extended endocrine therapy was recommended for 71 women (74%)
  - After BCI results, treatment recommendations changed for 25 patients and extended endocrine therapy was recommended for 52 patients (54%)

Evidence Review: Oncotype DX Breast DCIS Score

One observational trial:

- Manders et al., 2016
  - Prospective case series with a decision impact analysis
  - 127 patients with histologically confirmed pure DCIS who were candidates for breast-conserving surgery and radiotherapy naïve
  - Before the DCIS score results, 72% of recommendations were to receive radiotherapy
  - Overall, 26.4% of treatment recommendations changed after the DCIS score:
    - 15% of recommendations changed from radiotherapy to no radiotherapy
    - 11% of recommendations changed from no radiotherapy to radiotherapy

Evidence Summary

- A growing number of observational clinical utility studies have found that genome expression testing for patients with early-stage breast cancer results in changes to adjuvant treatment recommendations and can help identify low-risk patient groups that are unlikely to benefit from adjuvant chemotherapy
- There is no evidence that directly compares different genome expression profiling tests with respect to clinical utility
- Although there is a growing body of evidence for the use of these tests in lymph node-positive patients, there is still uncertainty about the effects of these tests on treatment decisions and clinical outcomes in this population
  - An evidence-based clinical practice guideline from the American Society of Clinical Oncology in 2016 recommends against their use in lymph node-positive patients.

Evidence Summary

- There are only small, single studies regarding the clinical utility of gene expression profiling for neoadjuvant treatment decisions or for determining the use of radiotherapy after surgery for DCIS, and these studies have not reported on long-term clinical outcomes
- On the basis of a single RCT, patients (including those with 1-3 positive nodes, representing about 20% of the overall study population) who were considered high risk by clinical classification but low risk by genomic classification utilizing MammaPrint can forgo adjuvant chemotherapy without a statistically significant reduction in the likelihood of distant metastasis-free survival at 5-year follow-up

GRADE Table

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
Breast cancer mortality (Critical outcome)	Use of the 70-gene signature (MammaPrint) to determine recommendations for the use of adjuvant chemotherapy when there is a discordance between clinical and genomic risk classification does not result in statistically significant differences in the likelihood of 5-year distant metastasis-free survival. ●●●○ (Moderate confidence, based on 1 RCT) In the per-protocol analysis of the same trial (which excluded patients who were ineligible, had a change in risk status, or did not adhere to the treatment assignment), patients with high clinical risk and low genomic risk who were treated based on their clinical risk (i.e., received adjuvant chemotherapy) had a higher rate of disease-free survival (93.3% vs. 90.3%, HR 0.63, 95% CI 0.43 to 0.95, p = 0.03), but survival without distant metastasis and overall survival did not significantly differ. ●●○○ (Low confidence, based on per-protocol analysis of 1 RCT)

GRADE Table

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
Breast cancer morbidity (Critical outcome)	See above (the reported 5-year distant metastasis-free survival and disease-free survival outcomes encompass morbidity and mortality).
Change in management (Important outcome)	Use of genome expression profile tests (Oncotype DX Breast Recurrence Score, MammaPrint, EndoPredict, Prosigna) results in changes to treatments recommended or received (mainly for lymph node-negative patients) and contributes to the identification of patients who are likely or unlikely to benefit from adjuvant systemic chemotherapy. ●●●◌ (Moderate confidence, based on 56 observational studies and 1 RCT)

GRADE Table

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate
Quality of Life (Important outcome)	Insufficient data
Harms (Important outcome)	Insufficient data

Payer Policies

- Washington Medicaid
  - No coverage policy found for MammaPrint, Prosigna, Breast Cancer Index, or Oncotype DX Breast DCIS
  - Coverage for Oncotype DX breast Recurrence Score and EndoPredict when:
    - Test is performed within 6 months of the diagnosis
    - Node negative (micrometastases less than 2mm in size are considered node negative)
    - Hormone receptor positive
    - Tumor size 0.6 to 1.0 cm with moderate/poor differentiation or unfavorable features (i.e., angiolymphatic invasion, high nuclear grade, high histologic grade) OR tumor size >1 cm
    - Unilateral disease
    - HER2 negative
    - Patient will be treated with adjuvant endocrine therapy
    - The test result will help the patient make decisions about chemotherapy when chemotherapy is a therapeutic option

Payer Policies

- Medicare
  - No National Coverage Determinations
  - No Local Coverage Determinations for Oncotype DX Breast Recurrence Score or MammaPrint
  - Local Coverage Determinations provide coverage for EndoPredict, Prosigna, and Breast Cancer Index generally with these restrictions:
    - Patient is postmenopausal
    - ER positive
    - HER2 negative
    - Lymph node negative (or sometimes 1 to 3 positive lymph nodes)
    - Test result will be used to determine treatment decisions
  - Local Coverage Determinations provide coverage for Oncotype DX Breast DCIS with restrictions

Payer Policies

Private Payer Coverage

	Aetna	Cigna	Moda	Regence
Oncotype DX breast recurrence score	X	X	X	X
EndoPredict	X			X
MammaPrint	X	X		
Prosigna	X	X		
Breast Cancer Index	X			X
Oncotype DX Breast DCIS				

The restrictions on the covered tests vary by payer and by test, but generally restrictions include ER positive, HER2 negative, lymph node negative (or sometimes 1 to 3 positive nodes), and results will inform treatment decisions

Guidelines

- The NCCN guidelines include discussion of Oncotype DX breast recurrence score, MammaPrint, and Prosigna
  - Oncotype DX assay is to be considered with pT1, pT2, or pT3, and pN0 or pN1mi, and the tumor is greater than 0.5 cm
  - The guidelines state that the Oncotype DX assay is the best validated breast cancer assay
- National Institute for Health Care Excellence guidelines recommend Oncotype DX breast recurrence score as an option for guiding adjuvant chemotherapy decisions for people with ER-positive, node-negative, and HER2-negative early-stage breast cancer when the patient is assessed as being at intermediate risk
  - MammaPrint and Mammostrat are only recommended for use in research

Guidelines

- American Society of Clinical Oncology Clinical Practice Guideline includes recommendations for when to use Oncotype DX breast recurrence score, EndoPredict, MammaPrint, Prosigna, and Breast Cancer Index
  - Generally, requirements include:
    - ER/PR positive
    - HER2 negative
    - Lymph node negative
  - Patients with 1 to 3 positive nodes may use the MammaPrint assay if they are at high clinical risk per MINDACT categorization, however, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with more than 1 involved lymph node
    - Otherwise, patients with node-positive cancer should not use these tests

Public Comment

- Public comments submitted by
  - Jay Andersen, MD
  - David B. Page, MD
  - Karen Heller, MS, CGC, Medical Policy Manager, Myriad Genetics, Inc.
  - Calvin Chao, MD, Vice President of Global Medical Affairs, Genomic Health
- Some commenters requested the inclusion of clinical validity studies, and the subcommittee directed that a discussion of clinical validity be added to the coverage guidance
- Other comments focused on adding coverage for node-positive patients based on guidelines, clinical validity data, registry studies, and a single small decision impact analysis – HTAS voted to add coverage for patients with 1-3 positive nodes

Discussion

Values and Preferences

Most women with early-stage breast cancer would highly value the additional information on treatment options informed by genome expression profile testing. Many (but not all) women classified as low risk would value the reassurance that chemotherapy would provide little or no benefit, and that the risks and side effects of treatment can be safely avoided. Similarly, women whose testing confirms high-risk status would value the knowledge that chemotherapy is necessary and likely beneficial.

The value attributed to test results would be more variable in women who are clinically high risk, but for whom testing indicates low-risk status, and even less relied upon by women with lymph node involvement who are deemed low risk by genomic profiling.

Discussion

Resource Allocation

Coverage of genome expression profile testing would add significant cost, given the prevalence of breast cancer in the U.S. population and the price range of these tests.

In cases that can be newly classified or convincingly confirmed as low risk based on these tests, there will be offsetting savings in chemotherapy avoided.

Potentially, there could also be treatment savings in cases deemed as high risk by genome expression profiling, if earlier interventions result in more effective initial treatment.

Discussion

Balance of Benefits and Harms

The clinical utility evidence base available to determine the balance of population benefits and harms is mainly limited to observational studies, but use of genome expression profile tests appears to consistently result in management decision changes that allow avoidance of adjuvant chemotherapy when scores indicating low risk are identified. Retrospective analysis of a prospective randomized adjuvant chemotherapy trial has validated the use of Oncotype DX Breast Recurrence Score in predicting chemotherapy benefit among women with estrogen receptor-positive, lymph node-negative breast cancer. One RCT utilizing MammaPrint demonstrated no significant difference in 5-year metastasis-free survival and overall survival in the high clinical risk group. No safety concerns or direct harms are associated with use of these genomic tests.

Discussion

Rationale

We have moderate confidence that genome expression profile testing on patients with early-stage breast cancer results in changes to treatment recommendations and can help identify low-risk patient groups that are unlikely to benefit from adjuvant chemotherapy. Values and preferences weigh in favor of additional testing, which provides reassurance that the risks, side effects, and cost of chemotherapy can be safely avoided.

There is preliminary evidence from decision impact studies to support coverage of genome expression profile testing in early-stage breast cancer with positive lymph nodes, although values and preferences for reliance on such testing will be more variable among patients with lymph node involvement. Despite the weak evidence, we recommend coverage based on potential benefits of reducing the use of chemotherapy.

Discussion

Rationale *(continued)*

Evidence of clinical utility is insufficient at present (small, single studies) to recommend coverage of Oncotype DX Breast DCIS Score to determine the use of radiotherapy after surgery for DCIS, and insufficient to recommend coverage of Breast Cancer Index to predict the likelihood of benefit from extended (greater than 5 years) endocrine therapy.

The recommendation for coverage of Oncotype DX Breast Recurrence Score for patients who are lymph node negative is strong because the ability of that profile test to predict adjuvant chemotherapy benefit has the largest and best-established evidence base. The other coverage recommendations are weak because additional studies might better establish clinical utility and predictive value.

Coverage Guidance

The following breast cancer genome profile tests (1 test per primary breast cancer) are recommended for coverage in patients with early-stage breast cancer when the patient is willing to use the results of this testing in a shared decision-making process regarding adjuvant chemotherapy, and when the listed criteria are met (lymph nodes with micrometastases less than 2 mm in size are considered node negative):

- Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative (*strong recommendation*).
- Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative, with 1-3 positive nodes (*weak recommendation*).
- EndoPredict (12 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative (*weak recommendation*).
- Prosigna (50 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative (*weak recommendation*).
- MammaPrint (70 gene) 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 (*weak recommendation*).

Coverage Guidance

EndoPredict, Prosigna, and MammaPrint are not recommended for coverage in early-stage breast cancer with involved axillary lymph nodes (weak recommendation).

Oncotype DX Breast DCIS Score is not recommended for coverage (weak recommendation).

Breast Cancer Index is not recommended for coverage (weak recommendation).

Health Evidence Review Commission (HERC)

Coverage Guidance:

Genome Expression Profiling for Breast Cancer

DRAFT for VbBS/HERC meeting materials 5/17/2018

HERC Coverage Guidance

The following breast cancer genome profile tests (one test per primary breast cancer) are recommended for coverage in patients with early-stage breast cancer when the patient is willing to use the results of this testing in a shared decision-making process regarding adjuvant chemotherapy, and when the listed criteria are met (lymph nodes with micrometastases less than 2 mm in size are considered node negative):

- Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative *(strong recommendation*).
- Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative, ~~is also recommended for coverage in patients~~ with 1-3 positive nodes *(weak recommendation).*
- EndoPredict (12 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative *(weak recommendation).*
- Prosigna (50 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative *(weak recommendation).*
- MammaPrint (70 gene) 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 *(weak recommendation)*.

~~Oncotype DX Breast Recurrence Score,~~ EndoPredict, Prosigna, and MammaPrint are not recommended for coverage in early-stage breast cancer with involved axillary lymph nodes *(weak recommendation).*

Oncotype DX Breast DCIS Score is not recommended for coverage *(weak recommendation).*

Breast Cancer Index is not recommended for coverage *(weak recommendation).*

Note: Definitions for strength of recommendations are in Appendix A. *GRADE Informed Framework Element Description*.

Table of Contents

Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patient experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on clinical interventions and modes of care, evidence is evaluated using an adaptation of the GRADE methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness may be dependent on the environment in which the intervention is implemented.

GRADE-Informed Framework

HERC develops recommendations by using the concepts of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by HERC based on the assessment of two independent reviewers from the Center for Evidence-based Policy.

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of HERC.

Should genome expression profiling be recommended for coverage for early-stage breast cancer?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Breast cancer mortality *(Critical outcome)*	Use of the 70-gene signature (MammaPrint) to determine recommendations for the use of adjuvant chemotherapy when there is a discordance between clinical and genomic risk classification does not result in statistically significant differences in the likelihood of five-year distant metastasis-free survival. ●●●○ *(Moderate confidence, based on 1 RCT)* In the per-protocol analysis of the same trial (which excluded patients who were ineligible, had a change in risk status, or did not adhere to the treatment assignment), patients with high clinical risk and low genomic risk who were treated based on their clinical risk (i.e., received adjuvant chemotherapy) had a higher rate of disease-free survival (93.3% vs. 90.3%, HR 0.63, 95% CI 0.43 to 0.95, p=0.03), but survival without distant metastasis and overall survival did not significantly differ. ●●○○ *(Low confidence, based on per-protocol analysis of 1 RCT)*	Coverage of genome expression profile testing would add significant cost, given the prevalence of breast cancer in the U.S. population and the price range of these tests. In cases that can be newly classified or convincingly confirmed as low risk based on these tests, there will be offsetting savings in chemotherapy avoided. Potentially, there could also be treatment savings in cases deemed as high risk by genome expression profiling, if earlier interventions result in more effective initial treatment.	Most women with early-stage breast cancer would highly value the additional information on treatment options informed by genome expression profile testing. Many (but not all) women classified as low risk would value the reassurance that chemotherapy would provide little or no benefit, and that the risks and side effects of treatment can be safely avoided. Similarly, women whose testing confirms high-risk status would value the knowledge that chemotherapy is	
Breast cancer morbidity *(Critical outcome)*	See above (the reported five-year distant metastasis-free survival and disease-free survival outcomes encompass morbidity as well as mortality).			

Should genome expression profiling be recommended for coverage for early-stage breast cancer?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Change in management *(Important outcome)*	Use of genome expression profile tests (Oncotype DX Breast Recurrence Score, MammaPrint, EndoPredict, Prosigna) results in changes to treatments recommended or received (mainly for lymph node-negative patients) and contributes to the identification of patients who are likely or unlikely to benefit from adjuvant systemic chemotherapy. ●●●○ *(Moderate confidence, based on 56 observational studies and 1 RCT)*		necessary and likely beneficial. The value attributed to test results would be more variable in women who are clinically high risk, but for whom testing indicates low-risk status, and even less relied upon by women with lymph node involvement who are deemed low risk by genomic profiling.	
Quality of Life *(Important outcome)*	Insufficient data			
Harms *(Important outcome)*	Insufficient data			

Balance of benefits and harms: The clinical utility evidence base available to determine the balance of population benefits and harms is mainly limited to observational studies, but use of genome expression profile tests appears to consistently result in management decision changes that allow avoidance of adjuvant chemotherapy when scores indicating low risk are identified. Retrospective analysis of a prospective randomized adjuvant chemotherapy trial has validated the use of Oncotype DX Breast Recurrence Score in predicting chemotherapy benefit among women with estrogen receptor-positive, lymph node-negative breast cancer. One RCT utilizing MammaPrint demonstrated no significant difference in five-year metastasis-free survival and overall survival in the high clinical risk group. No safety concerns or direct harms are associated with use of these genomic tests.

Should genome expression profiling be recommended for coverage for early-stage breast cancer?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Rationale: We have moderate confidence that genome expression profile testing on patients with early-stage breast cancer results in changes to treatment recommendations and can help identify low-risk patient groups that are unlikely to benefit from adjuvant chemotherapy. Values and preferences weigh in favor of additional testing, which provides reassurance that the risks, side effects, and cost of chemotherapy can be safely avoided. There is preliminary evidence from decision impact studies to support coverage of genome expression profile testing in early-stage breast cancer with positive lymph nodes, ~~and~~ although values and preferences for reliance on such testing will be more variable among patients with lymph node involvement. Despite the weak evidence, we recommend coverage based on ~~the variability in values and preferences and~~ potential benefits of reducing the use of chemotherapy. Evidence of clinical utility is insufficient at present (small, single studies) to recommend coverage of Oncotype DX Breast DCIS Score to determine the use of radiotherapy after surgery for ductal carcinoma in situ, and insufficient to recommend coverage of Breast Cancer Index to predict the likelihood of benefit from extended (greater than five years) endocrine therapy. The recommendation for coverage of Oncotype DX Breast Recurrence Score for patients who are lymph node negative is strong because the ability of that profile test to predict adjuvant chemotherapy benefit has the largest and best-established evidence base. The other coverage recommendations are weak because additional studies might better establish clinical utility and predictive value.				

Should genome expression profiling be recommended for coverage for early-stage breast cancer?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations

Recommendation:

The following breast cancer genome profile tests (one test per primary breast cancer) are recommended for coverage in patients with early-stage breast cancer when the patient is willing to use the results of this testing in a shared-decision making process regarding adjuvant chemotherapy, and when the listed criteria are met (lymph nodes with micrometastases less than 2 mm in size are considered node negative):

- Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative *(strong recommendation).*
- Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative ~~x is also recommended for coverage in patients~~ with 1-3 positive nodes (*weak recommendation*).
- EndoPredict (12 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative *(weak recommendation).*
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- MammaPrint (70 gene) 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 *(weak recommendation)*.

~~Oncotype DX Breast Recurrence Score,~~ EndoPredict, Prosigna, and MammaPrint are not recommended for coverage in early-stage breast cancer with involved axillary lymph nodes *(weak recommendation).*

Oncotype DX Breast DCIS Score is not recommended for coverage *(weak recommendation).*

Breast Cancer Index is not recommended for coverage *(weak recommendation).*

Note: GRADE-informed framework elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Background

Approximately 1 in 8 women (12%) in the United States develop invasive breast cancer during their lifetime, making breast cancer the second most common cancer (following skin cancer) in American women (American Cancer Society [ACS], 2017). In 2014, there were 236,968 breast cancer diagnoses and 41,211 breast cancer deaths in women in the United States. In men, breast cancer is relatively rare, accounting for an additional 2,141 breast cancer diagnoses and 465 breast cancer deaths in 2014 (Centers for Disease Control and Prevention [CDC], 2017a).

Treatments for breast cancer include surgery, chemotherapy, hormonal therapy, biological therapy using the immune system, and radiation therapy (CDC 2017b). Genome expression profiling tests can be used to predict a cancer's aggressiveness, and thereby inform decision making on treatments. These tests analyze a sample of a cancer tissue to assess the activity level of certain genes, which may indicate the likelihood of the cancer growing and spreading. Other methods to predict cancer prognosis and aid in decision-making include web-based tools such as Adjuvant! Online and PREDICT. Using patient and tumor characteristics (e.g., tumor size and grade, number of positive axillary nodes, hormone receptor status), these tools estimate the risk of cancer-related mortality or relapse without systemic adjuvant therapy, and then estimate the reduction of these risks if various therapy options are implemented.

Indications

The breast cancer genome expression profile tests Oncotype DX Breast Recurrence Score, EndoPredict, MammaPrint, Prosigna, and Breast Cancer Index (BCI) are indicated for women with early-stage, invasive breast cancer. Each of these tests can be used for estrogen receptor-positive (ER-positive) or hormone receptor-positive cancers. MammaPrint can also be used with ER-negative cancers. Oncotype DX and EndoPredict can only be used with cancers that are negative for human epidermal growth factor receptor 2 (HER2). The Oncotype DX Breast DCIS Score is indicated for women diagnosed with ductal carcinoma in situ. More detailed descriptions of the indications are provide in the technology description below.

Technology Description

The Oncotype DX Breast Recurrence Score test is used to predict the likely benefit of chemotherapy and the risk of distant recurrence among patients newly diagnosed with early-stage ER-positive, HER2-negative invasive breast cancer, both lymph node negative and lymph node positive. The Oncotype DX breast cancer assay uses reverse transcription polymerase chain reaction (RT-PCR) to measure the expression of 21 genes, including 16 cancer-related genes and five reference genes. The Oncotype DX Breast Recurrence Score ranges from zero to 100: higher numbers indicate a higher risk for distant recurrence and higher likelihood of chemotherapy benefit for that patient. The Oncotype DX report also provides a quantitative ER score by RT-PCR to help assess the magnitude of hormonal therapy benefit (Genomic Health, 2017a).

The Oncotype DX Breast DCIS Score is an assessment of 12 cancer-related genes that is performed on a tumor sample (after a biopsy or surgery) from a woman with DCIS. The Oncotype DX Breast DCIS Score results predict the 10-year risk of any local recurrence (DCIS or invasive carcinoma) or an invasive local recurrence, establish a baseline for consideration of the absolute risk reduction from radiation therapy, and provide quantitative ER and progesterone receptor (PR) single gene expression values (Genomic Health, 2017b).

The EndoPredict test is used to estimate the 10-year risk of distant recurrence of early-stage ER-positive, HER2-negative invasive breast cancer, both lymph node negative and lymph node positive. The EPclin risk score algorithm integrates a 12-gene molecular score, tumor size, and nodal status. The 12-gene molecular score uses quantitative RT-PCR on eight signature genes, three normalization genes, and one control gene. The EPclin score ranges from 1.0 to 6.0, and the test report includes the likelihood of distant metastasis if the patient receives five years of endocrine therapy alone (Myriad Genetic Laboratories, 2017).

The MammaPrint breast cancer recurrence assay is used to assess the likelihood of breast cancer recurrence among women with Stage I or Stage II invasive breast cancer, with a tumor size ≤5.0 cm, that is lymph node negative, ER positive or negative, and HER2 negative or positive. The assay assesses 70 genes using formalin-fixed paraffin-embedded tissue or fresh tissue for microarray analysis. MammaPrint uses an algorithm to classify patients as being at high or low risk of breast cancer recurrence (Agendia, 2017).

The Prosigna breast cancer gene signature assay is based on the PAM50 gene signature, which measures the expression of 50 genes to classify tumors into four intrinsic subtypes: luminal A, luminal B, HER2-negative enriched, and basal-like. Prosigna is indicated for use in postmenopausal women with hormone receptor-positive, lymph node-negative or lymph node-positive, Stages I, II, or IIIA breast cancer to be treated with adjuvant endocrine therapy. The Prosigna algorithm uses the PAM50 gene signature, intrinsic subtype, tumor size, nodal status, and proliferation score. The risk of recurrence score (ROR) is on a zero to 100 scale, which correlates with the probability of distant recurrence in a 10-year period (NanoString Technologies, 2017).

BCI predicts the likelihood of benefit from extended endocrine therapy among women with ER-positive, lymph node-negative or lymph node-positive (with one to three positive nodes), early-stage, invasive breast cancer. BCI provides an assessment of the likelihood of both late (post-five years) and overall (zero to 10 years) distant recurrence after an initial five years of endocrine therapy in lymph node-negative patients or five years of endocrine therapy plus adjuvant chemotherapy in lymph node-positive patients. BCI also predicts the likelihood of benefit from extended (>5 years) endocrine therapy (Biotheranostics, 2017).

Evidence Review

Systematic Reviews

Scope et al., 2017

This is a good-quality narrative systematic review of the use of genome expression profiling (GEP) and immunohistochemical (IHC) tests in adjuvant chemotherapy decisions for patients with breast cancer. The review was undertaken to inform the United Kingdom's National Institute for Health and Care Excellence (NICE) and was funded by the National Institute for Health Research. The authors reported no conflicts of interest. It includes 41 studies regarding MammaPrint, Oncotype DX, Mammostrat, and IHC4 testing published between 2002 and May 2016.

All of the included studies were observational, although five studies were based on a prospective analysis using archived tissue specimens from a larger adjuvant chemotherapy randomized controlled trial (RCT). These five studies were judged to be at moderate risk of bias. The remaining studies described changes in treatment recommendations or decisions based on GEP or IHC results and were

mainly limited by their small size, retrospective designs and incomplete reporting of patient characteristics. The authors also noted high levels of clinical heterogeneity among the studies.

Three of the included studies examined the ability of Oncotype DX breast cancer assay to predict adjuvant chemotherapy benefit among women with ER-positive, lymph node-negative breast cancer. The studies were based on archived tissue specimens from RCTs that compared endocrine therapy to endocrine therapy plus chemotherapy. In these studies, a high-risk 21-gene recurrence score was correlated with chemotherapy benefit defined by 10-year distant recurrence-free survival or disease-free survival. One of the three studies suggested that high-risk recurrence scores predicted benefit for chemotherapy among lymph node-positive patients and might be useful for avoiding adjuvant chemotherapy for patients with low recurrence score and positive nodes. The fourth study concluded that recurrence score offered the best predictive information about adjuvant chemotherapy benefit in ER-positive, lymph node-negative breast cancer. The authors noted that three of the four studies included data derived from National Surgical Adjuvant Breast and Bowel Project (NSABP) cohorts, which raises the possibility of double-counting in the systematic review.

The authors identified 28 studies of the effect of Oncotype DX on clinical decisions. These studies reported changes in adjuvant chemotherapy recommendations or receipt in 21% to 74% of the patients who were tested. All but one of the studies found overall decreases in the recommendation for or receipt of adjuvant chemotherapy; decreases ranged from 6% to 51%. The authors noted that in many studies it was not possible to determine whether the findings reported changes to the actual treatments received.

The authors identified six studies of how MammaPrint influenced clinical decisions. These studies reported overall changes in adjuvant chemotherapy recommendations or receipt in 18% to 40% of the patients who were tested. The studies found that overall, 2% to 32% of patients would have recommendations changed from adjuvant chemotherapy to no chemotherapy. The authors again noted difficulty in ascertaining the effects of the testing on actual treatments rendered. Two additional studies based on a prospective observational cohort in the Netherlands found that the use of MammaPrint would have increased recommendations for adjuvant chemotherapy from 48% (based on the Dutch Institute for Health Care Improvement guideline alone) to 62%, though MammaPrint would have lowered the rate of adjuvant chemotherapy recommendations compared to recommendations based on other guidelines (St Gallen, Nottingham Prognostic Index, and Adjuvant! Online). In the five-year follow-up study, 15% of low-risk patients by MammaPrint had received chemotherapy and the overall distant recurrence-free survival was 97%; among high-risk patients by MammaPrint, 81% received chemotherapy with a distant recurrence-free survival rate of 91.7%.

Overall, the authors concluded that Oncotype DX was “furthest along the validation pathway” and has “a reasonably large evidence base” with “some methodological weaknesses” (Scope et al., 2017, p. 42). The authors stated that new studies showed “MammaPrint is a strong independent prognostic factor” (Scope et al., 2017, p. 43), but noted that the populations in these studies were small. They also observed that the limited evidence and clinical heterogeneity made comparisons between tests difficult.

Harris et al., 2016

This is a clinical practice guideline from the American Society of Clinical Oncology on the use of biomarkers for adjuvant systemic chemotherapy decisions in women with early-stage breast cancer. The recommendations are apparently based on a systematic review of the clinical utility literature for these

tests, but the evidence findings are not described in sufficient detail to allow inclusion as part of this evidence review. The recommendations resulting from this review are discussed in the guideline section below.

Randomized Trials

Cardoso et al., 2016 (MINDACT)

This is a fair-quality prospective RCT of the clinical utility of the 70-gene signature (MammaPrint) test for early-stage breast cancer, as part of the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) study. Between 2007 and 2011, 6,693 patients were enrolled at 112 centers in nine European countries. Patients were eligible for enrollment if they were between the ages of 18 and 70 years old and had early-stage breast cancer (defined as T1 or T2 disease, or operable T3 disease). The study initially only enrolled patients without nodal involvement, but a protocol amendment in 2009 allowed patients with one to three positive axillary lymph nodes to enroll. Unlike most other studies of genome expression tests, patients with hormone receptor-negative and/or HER2-positive disease were included.

All patients were classified as clinically low risk or high risk using the Adjuvant! Online tool. Patients were considered clinically high risk if their 10-year probability of breast cancer-specific survival without adjuvant chemotherapy was less than 88% for ER-positive patients and 92% for ER-negative patients. All patients had genome expression testing on frozen tumor tissue using the 70-gene signature (70-GS) assay to classify them as genomically low or high risk. Patients with low clinical and genomic risk were advised against receiving adjuvant chemotherapy; patients with high clinical and genomic risk were advised to receive adjuvant chemotherapy. Patients with discordance between their clinical and genomic risk classification were randomized to adjuvant chemotherapy or no adjuvant chemotherapy. Randomization was stratified by institution, hormone receptor status, HER2 status, age, nodal status, and type of initial surgical resection. Patients were followed for a median of five years.

Overall, 41% of patients were classified as low clinical and genomic risk and 27% of patients were classified as high clinical and genomic risk. There were 690 patients with low clinical risk and high genomic risk (592 patients after correction, 8.8%). There were 1,497 patients classified as high clinical risk and low genomic risk (1,550 after correction, 23.2%). Within each of the discordant groups, patients were randomly assigned (1:1) to receive adjuvant treatment recommendations on the basis of their clinical or genomic risk classification. Overall adherence to the adjuvant chemotherapy recommendation was 86%.

In the intention-to-treat analysis, patients with high clinical and low genomic risk who were randomized to treatment based on their clinical risk assessment (i.e., recommended to receive chemotherapy) had a rate of distant metastasis-free survival of 95.9% at five years, compared to 94.4% among those randomized to treatment on the basis of their genomic risk assessment (i.e., recommended not to receive chemotherapy) (Hazard Ratio [HR] 0.78, 95% confidence interval [CI] 0.50 to 1.21). On the basis of these results, the authors observed that the use of the 70-GS would have led to an overall reduction in adjuvant chemotherapy in 46.2% of patients with high clinical risk. It should be noted that in the per-protocol analysis, five year disease-free survival was higher in the group treated with chemotherapy based on high clinical risk (93.3%) compared to those treated without chemotherapy based on low genomic risk (90.3%) (HR 0.64, 95% CI 0.43 to 0.95). Five-year overall survival and survival without distant metastases did not differ significantly between the treated arms in the per-protocol analysis. In a

subgroup analysis based on nodal status among patients with high clinical risk and low genomic risk, five-year survival without distant metastases was 95.7% and 93.2% for lymph node-negative patients randomized to chemotherapy or no chemotherapy respectively, and 96.3% and 95.6% for lymph node-positive patients randomized to chemotherapy or no chemotherapy respectively. It should be noted that lymph node-positive patients represented only about 20% of the overall study population.

In the intention-to-treat analysis of the group with low clinical risk and high genomic risk, patients randomized to chemotherapy on the basis of their high genomic risk had a rate of distant metastasis-free survival of 95.8% at five years compared to 95.0% for those randomized to no chemotherapy on the basis of their low clinical risk (HR 1.17, 95% CI 0.59 to 2.28). Thus, in the population of patients with low clinical risk, there is no advantage to offering chemotherapy to patients with high genomic risk. Similarly, five-year survival without distant metastases, disease-free survival, and overall survival did not vary based on the treatment received in the per-protocol analysis for this group, although there was greater imprecision in the estimates of effect.

Potential sources of bias in this trial include the use of multiple regimens among those randomized to systemic chemotherapy and the use of different hormonal therapies among women with ER-positive disease. There was also a protocol revision in 2010 to address a misclassification of high genomic risk in 162 patients stemming from a change in the RNA-extraction solution. An additional 113 patients had their clinical or genomic risk reclassified after enrollment. The study was funded by several research foundations, some of which accept donations from industry. Additional data are being collected to determine outcomes beyond five years.

The findings of this study suggest that patients deemed to be at high clinical risk may avoid the use of adjuvant chemotherapy when they are classified as low genomic risk by the 70-GS without a statistically significant increase in distant metastasis or death at five years of follow-up.

Ongoing Trials

In addition to the longer-term outcomes of the MINDACT study, the randomized portion of two studies (TAILORx and RxPONDER) involving the Oncotype DX 21-RS score and a UK National Health Service study comparing genome expression test-guided treatments for early-stage breast cancer (OPTIMA) are ongoing.

Additional Observational Studies

Additional observational studies published after the dates of the search conducted by Scope and colleagues (2017) are briefly summarized in Table 1.

Table 1: Additional recent observational trials

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Sanft et al., 2015 **Breast Cancer Index** Funding source not disclosed Three authors reported conflicts of interest related to employment, shareholding, or honoraria from the maker of BCI	Prospective case series with decision impact analysis Single center Connecticut 2014	N = 153 ER-positive, Stage I-III breast cancer patients receiving adjuvant endocrine therapy for at least 3.5 years	Pre- and post-BCI treatment recommendations were available for 96 patients. Before BCI results, 49% were assessed as low risk for recurrence after 5 years (defined as <5% risk), 38% were assessed as intermediate risk (6% to 15% risk of recurrence after 5 years), and 13% were assessed as high risk (>15% risk of recurrence after 5 years). Overall, before BCI results, extended endocrine therapy was recommended for 71 women (74%); after BCI results, treatment recommendations changed for 25 patients and extended endocrine therapy was recommended for 52 patients (54%); most of the changes in treatment recommendation occurred in patients classified as low risk by BCI; 29% fewer patients reported that they planned to pursue extended endocrine therapy after testing. BCI was also associated with more accurate risk perception, reduced decisional conflict, and reduced anxiety.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Ettl et al., 2017 **EndoPredict (11-gene expression assay) and Protein marker uPA/PAI-1** No specific funding reported Two authors reported past employment, patents, or honoraria from the maker of EndoPredict	Prospective consecutive case series comparing treatment decisions with and without information from EndoPredict EPclin and/or protein marker uPA/PAI-1 (a protein marker test commonly used in Germany) Single center Germany 2012-2015	N = 395 Invasive, intermediate risk, ER-positive, HER2-negative breast cancer (Intermediate risk as classified by the Interdisciplinary S3-Guideline)	EPclin results were obtained for all 395 patients, among whom 250 patients were classified as low risk and 145 as high risk. uPA/PAI-1 results were obtained for 190 patients, among whom 46% were classified as low risk and 54% as high risk. Overall, the tests showed concordant risk stratification in 59% of patients. In the analysis of all patients, the results of EPclin (with uPA/PAI-1 results when available) did not affect treatment recommendation in 225 patients (57%), led to a recommendation of adjuvant chemotherapy in 20 patients (5%), and led to a recommendation against adjuvant chemotherapy in 150 patients (38%). Among the patients with results for both EPclin and uPA/PAI-1, when assessed independently, EPclin results led to changes in treatment recommendation in 87 patients (46%); uPA/PAI-1 led to changes in treatment recommendations in 46 patients (24%).

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Kuijer et al., 2017 **MammaPrint (70-gene expression assay)** Funded by Agendia NV One of the authors reported conflicts of interest	Prospective case series with decision impact analysis Multi-center Netherlands 2013-2015	N = 698 patients with early-stage, ER-positive, HER2-negative, pN0-N1 breast cancer	Pre-GEP treatment decisions were for adjuvant chemotherapy in 41% of patients and against adjuvant chemotherapy in 16% of patients; in the remaining cases, clinicians preferred to wait for the GEP before making a recommendation. Among patients for whom a pre-GEP treatment recommendation was rendered, that recommendation changed after the GEP results in 51% of patients. Overall, the rate of actual adherence to the treatment recommendation was 91% and was similar whether the recommendation was for or against adjuvant chemotherapy.
Kuijer et al., 2016(a) **MammaPrint (70-gene expression assay)** Funded by the Dutch Cancer Society Authors reported no conflicts of interest	Cross-sectional study using the Netherlands Cancer Registry Population-based Netherlands 2011-2013	N = 2,043 women under age 70 with ER-positive, HER2-negative, pN0-pN1mi, grade I-II invasive breast cancer	Overall, 298 eligible patients (15%) received 70-GS testing; 70-GS testing was more likely in younger women with smaller tumors and more limited axillary lymph node involvement. After adjustment for measured confounders, the 70-GS was associated with 9.5% reduction in the absolute risk of receiving adjuvant chemotherapy in the linear mixed-effects model; the observed reduction in the rate of chemotherapy use was statistically significant only among women under age 50.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Pohl et al., 2016 **MammaPrint (70-gene expression assay)** Funded by the South African Medical Research Council One author reported a conflict of interest	Retrospective case series with decision impact analysis Multi-center South Africa 2007-2014	N = 107 patients with hormone receptor-positive, HER2-negative, 0-3 positive nodes, invasive breast cancer and available 70-gene expression assay results	Overall, 60 patients were considered clinically high risk and 47 were clinically low risk; 56 patients had treatment changes based on 70-GS results. Among clinically high-risk patients, 37 (62%) with low-risk 70-GS results did not receive chemotherapy. Among clinically low-risk patients, 19 (40%) with high-risk 70-GS results received chemotherapy
Tsai et al., 2017 **MammaPrint (70-gene expression assay)** Funded by Agendia Eight authors reported various conflicts of interest	Prospective case series with decision impact analysis Multi-center United States 2012-2015	N = 840 patients with ER-positive, HER2-negative, 0-3 positive nodes and an intermediate risk (RS 18-30) by 21-gene expression assay testing	Overall, the initial treatment recommendations (after 21-gene assay but before 70-GS) were for adjuvant chemotherapy in 45.5% of patients; recommendations for adjuvant chemotherapy were more likely as the recurrence score increased. Among 374 patients with a low-risk 70-GS, 108 (28.9%) had chemotherapy omitted from their treatment recommendation; among the 466 patients with a high-risk 70-GS 171 (36.7%) had chemotherapy added to their treatment recommendation.
Kuijer et al., 2016(b) **MammaPrint (70-gene expression assay) or Oncotype DX Breast Recurrence score (21-gene expression assay)** Funded by the Dutch Cancer Society Conflicts of interest were not reported	Retrospective historically controlled cohort Population-based Netherlands 2004-2006 2012-2014	N = 3,864 women with ER-positive, HER2-negative, pN0-N1mi, grade I-II invasive breast cancer	A guideline change between the historical and contemporary cohorts resulted in an overall increase in the use of adjuvant chemotherapy (9% to 40%), but use of GEP was associated with a smaller and nonsignificant increase in the use of chemotherapy between the two cohorts (21% to 28%, p = 0.191). Adherence to the treatment recommendations based on GEP results were similar for the 70-GS (91%) and the 21-RS (89%) in the contemporary cohort.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Bear et al., 2017 **Oncotype DX Breast Recurrence Score (21-gene expression assay) on core needle biopsy specimen** Funded by Genomic Health Inc. and an NCI grant One author reported speaking advisory board honoraria from Genomic Health Inc.	RCT of neoadjuvant hormonal treatment vs. neoadjuvant systemic chemotherapy among patients with recurrence score (RS) 11-25 Multi-center United States and Canada	N = 64 cN0, cN1a or CN2a; hormone receptor positive, HER2 negative, with tumors >2cm desiring breast-conserving surgery Patients with RS <11 received neoadjuvant hormonal therapy (NHT) Patients with RS 11-25 were randomized to NHT or neoadjuvant chemotherapy (NCT) Patients with RS >25 received NCT	Among 55 patients with complete follow-up, the overall distribution of recurrence scores was: • RS <11 = 12 • RS 11-25 = 29 • RS >25 = 14 In the RS 11-25 group, 18 patients received NHT and 11 patients received NCT (some patients assigned to NCT refused treatment and 2 crossed to the NHT group) In as-treated analysis, patients with RS 11-25 who received NCT were more likely to have a clinical response (72.7% vs. 50%, p = 0.049), but there was no statistically significant difference in the rate of successful breast-conserving surgery (63.6% vs. 72.2%, p = NS), which was the primary outcome for the study.
Barcenas et al., 2017 **Oncotype DX Breast Recurrence Score (21-gene expression assay)** Funded by an NCI grant One author reported serving on a scientific advisory board for MammaPrint	Retrospective descriptive analysis Single center Texas 2005-2011	N = 1,424 Stage I-II, hormone receptor-positive HER2 negative, lymph node negative	Rate of adjuvant chemotherapy by risk score: • RS <11 = 1.7% • RS 11-25 = 15% • RS >25 = 73.4% Among those with RS 11-25, overall invasive disease-free survival at 5 years was 92.6% (95% CI 89.6 to 94.7) and there were no statistically significant differences between those who received adjuvant chemotherapy and those who did not with respect to invasive disease-free survival (HR 1.64, 95% CI 0.73 to 3.71), relapse-free survival (HR 1.46, 95% CI 0.41 to 5.23), or overall survival (HR 2.19 95% CI 0.44 to 11).

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Dzimitrowicz et al., 2017 **Oncotype DX Breast Recurrence Score (21-gene expression assay)** Funding not reported Seven authors reported various potential financial conflicts	Retrospective historically controlled cohort investigating early ordering of RS (before or at the time of surgery rather than the time of the postoperative visit) Single center Connecticut July-December 2015 (Historical controls January-June 2015)	N = 90 in the early RS testing group (N = 76 in the historical control group) Patients under age 80 years with invasive breast cancer, tumor size >0.5 cm to <5 cm ER positive, HER2 negative, lymph node negative (clinically or pathologically)	In the early RS group, 82 of 90 eligible patients had an RS ordered (91%) compared to 58 of 76 patients (76%) in the control group. Overall, 21% of patients received adjuvant chemotherapy. Median time to chemotherapy decision was 20 days in the early RS group compared to 32 days in the control group ($p < 0.001$), but there were no differences between the groups in rate of chemotherapy use, time to chemotherapy start, or the average costs of testing plus planned treatment. Most (80%) of the medical oncologists surveyed reported that the early RS results were useful.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Friese et al., 2017 **Oncotype DX Breast Recurrence Score (21-gene expression assay)** Funding by NCI, CDC, and the California Department of Public Health One author reported research funding from multiple sources including Genomic Health Inc. and Myriad Genetics Laboratories Inc.	Cross-sectional survey using SEER and Genomic Health Inc. registries Population-based study in Los Angeles County and Georgia 2013-2014	N = 1,527 Early-stage breast cancer survey respondents	Overall, 60% of the sample had received RS testing; the rate of RS testing varied by risk group: 62.6% for lymph node negative with favorable disease, 24.3% for lymph node negative with less favorable disease, and 13% for lymph node-positive disease. There were no statistically significant differences in the likelihood of RS testing based on educational attainment, income, or race; women with 2 or more comorbidities were less likely to receive RS testing than those with no comorbidities (OR 0.5, 95% CI 0.3 to 0.7). Compared with no RS testing, RS testing was associated with a lower likelihood of receiving adjuvant chemotherapy in the low RS group (OR 0.1, 95% CI 0.1 to 0.2) and a higher likelihood of receiving adjuvant chemotherapy in the intermediate RS (OR 1.4, 95% CI 1.1 to 1.7) and high RS (OR 2.8, 95% CI 2.8 to 4) groups. Patients reported high levels of satisfaction with RS testing and 64% rated it as very or extremely helpful in their decision making.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Gluz et al., 2016 **Oncotype DX Breast Recurrence Score (21-gene expression assay)** Funding support from Genomic Health Inc., Sanofi Aventis, and Amgen Inc. Ten of the authors reported varied conflicts of interest including honoraria, consulting, employment, or ownership	Prospective cohort derived from a larger RCT of adjuvant chemotherapy; trial was amended to recommend endocrine therapy only in patients with RS <11 Multi-center Germany 2009-2011	N = 2,274 Mainly pN0-N1 (94%) Hormone receptor positive, HER2 negative	Overall, 404 patients had RS <11 with 86% adherence to the recommendation for endocrine therapy only; 1,397 patients had RS 12-25 with 78.6% adherence to recommendation for chemotherapy; 473 patients had RS >25 with 89.7% adherence to recommendation for chemotherapy. In the analysis of treatment adherers, 3-year disease-free survival was 98.4% in the RS <11 group, 97.5% in the RS 12-25 group, and 94.9% in the RS >25 group. In a multivariate analysis of predictors of disease-free survival, RS, nodal status, and tumor grade were independent prognostic factors.
Jasem et al., 2017 **Oncotype DX Breast Recurrence Score (21-gene expression assay)** Funding source not reported Authors reported no conflicts of interest	Retrospective cohort using the National Cancer Database Population-based study in the US 2010-2012	N = 10,434 patients with pT1-T2, pN1 (1-3 nodes involved), hormone receptor-positive, HER2-negative breast cancer who had a known RS assay ordered compared to 21,991 women with similar disease profile and no RS score	After adjustment for other factors that predict likelihood of adjuvant chemotherapy, patients exposed to RS testing were less likely to receive chemotherapy than those who did not receive RS testing (aOR 0.21, 95% CI 0.20 to 0.22); compared to a low-risk RS (<18) referent, intermediate (18-30) and high-risk (>30) RS were associated with a greater likelihood of receiving adjuvant chemotherapy (aOR of 4.5 and 20, respectively). RS testing was less likely to be performed in Black patients, those treated at community medical centers, uninsured or governmentally insured patients, and those with poorer prognostic features; Black patients who were tested were more likely to have high-risk RS scores.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Kozick et al., 2017 **Oncotype DX Breast Recurrence Score (21-gene expression assay)** Funding source not reported Authors reported no conflicts of interest	Cross-sectional study using the National Cancer Database Population-based study in the US 2010-2012	N = 158,235 women with ER-positive, HER2-negative, lymph node-negative breast cancer, tumor size >0.5 cm, who had received partial or total mastectomy and who had no evidence of metastatic disease	Overall, 56,323 patients (35.6%) received RS testing. Factors that predicted greater odds of RS testing were younger age, white race/ethnicity, residence in a higher income area, treatment at an academic medical center, and private insurance. Larger tumor size, total mastectomy, and higher comorbidity score were associated with lower odds of RS testing. Among 30,011 patients classified as low risk by RS score, 95% adhered to the guideline-based recommendation to omit adjuvant chemotherapy. Among 4,278 patients classified as high risk, 89.6% adhered to the guideline-based recommendation to receive adjuvant chemotherapy. 44% of patients in the intermediate-risk group received adjuvant chemotherapy; younger age, larger tumor size, and higher RS score were associated with greater odds of receiving chemotherapy in this group.
Leung et al., 2016 **Oncotype DX Breast Recurrence Score (21-gene expression assay)** Funded by Genomic Health Inc. Two authors reported conflicts of interest related to employment	Prospective case series with impact decision analysis Six centers Hong Kong	N = 146 patients with early-stage breast cancer, ER positive, HER2 negative, pN0-pN1mi	Overall, 34 (23.3%) pre-RS-score treatment recommendations changed after the RS-score was made available to clinicians; in 28 cases there was a decrease in recommended treatment intensity, and in 7 cases there was an increase in recommended treatment intensity.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Pestalozzi et al., 2017 **Oncotype DX Breast Recurrence Score (21-gene expression assay)** Funded in part by the Swiss State Secretariat for Education, Research, and Innovation One author reported lecture fees from Genomic Health Inc.	Prospective case series with decision impact analysis Multicenter Switzerland 2013-2014	N = 222 patients with ER-positive, HER2-negative, pN0-pN1a	Overall, 154 patients were considered low risk and 68 were considered non-low risk prior to RS score results. In the low-risk group, RS score led to changes in treatment recommendations for 23 patients (15%); recommendations for 5 patients changed to include chemotherapy and recommendations for 18 patients changed to omit chemotherapy. In the non-low risk group, RS score led to changes in treatment recommendations for 22 patients (32%); recommendations for 3 patients changed to include chemotherapy while recommendations for 19 patients changed to omit chemotherapy.
Stemmer et al., 2017 **Oncotype DX Breast Recurrence Score (21-gene expression assay)** Funded by Teva Pharmaceuticals Nine authors reported various conflicts of interest	Retrospective registry analysis Single center Israel 2006-2010	N = 1,801 patient with ER-positive, HER2-negative, lymph node-negative invasive breast cancer	Overall, 880 patients (48.9%) had RS <18, 733 patients (40.7%) had RS 18-30, and 188 (10.4%) had RS >30. 1.4% of patients with RS <18, 23.7% of patients with RS 18-30, and 87.2% of patients with RS >30 received adjuvant chemotherapy. At median follow-up of 6.2 years, distant recurrence was observed in 0.8% of patients with RS <18, 3.0% of patients with RS 18-30, and 8.6% of patients with RS >30; within the intermediate risk group, there was no difference in the 5-year distant recurrence risk or time to distant recurrence between the adjuvant chemotherapy and untreated groups.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Loncaster et al., 2017 **Oncotype DX Breast Recurrence Score (21-gene expression assay)** Funded in part by Genomic Health Inc. Three authors reported conflicts of interest	Prospective case series with decision impact analysis Multi-center Manchester, England 2012-2015	N = 210 patients with ER-positive, HER2-negative, intermediate clinical risk invasive breast cancer (Note: 1/3 of women were postmenopausal and node positive)	All patients had an initial recommendation for adjuvant chemotherapy; after RS results, 37% underwent chemotherapy and 63% received endocrine therapy only. Among patients with a low-risk RS (<18), 4.7% of patients received chemotherapy; 54% of patients with intermediate-risk RS (18-30) received chemotherapy with a greater likelihood among those with a higher RS; 85% of patients with RS >30 received chemotherapy. A budget impact analysis based on this study suggested that the avoidance of chemotherapy afforded by use of the GEP made the test cost saving (under an assumption that all patients initially recommended for chemotherapy would receive it.
Manders et al., 2016 **Oncotype DX DCIS (12-gene expression assay for DCIS)** Funded by Genomic Health Inc. Twelve of the authors reported conflicts of interest	Prospective case series with a decision impact analysis Thirteen sites United States 2014-2015	N = 127 patients with histologically confirmed pure DCIS who were candidates for breast-conserving surgery and were radiotherapy naive	Before the DCIS score results, 72% of recommendations were to receive radiotherapy. Most patients (66%) had low DCIS scores, 20% had intermediate scores, and 14% had high scores. Overall, 26.4% of treatment recommendations changed after the DCIS score; 15% of recommendations changed from radiotherapy to no radiotherapy and 11.4% were from no radiotherapy to radiotherapy; surgeons were more likely than radiation oncologists to recommend against radiotherapy in the low DCIS score group . Among a small number of patients with completed questionnaires, use of the DCIS score was associated with reduced decisional conflict and anxiety.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Hequet et al., 2017 **Prosigna (50-gene expression assay)** Funded by NanoString Technologies Inc. Four of the authors reported employment conflicts of interest	Prospective consecutive case series with decision impact analysis Multi-center France 2015-2016	N = 210 Postmenopausal women with Stage I-II, ER-positive, HER2-negative, lymph node-negative breast cancer	Compared to pre-GEP treatment recommendations, knowledge of the genome expression assay results led to change in adjuvant treatment recommendation in 34 patients (18%); 25 patients changed from a recommendation of no adjuvant to chemotherapy to a recommendation for chemotherapy, and 9 recommendations for adjuvant chemotherapy were changed to no chemotherapy. 75% of physicians agreed or strongly agreed that the GEP provided valuable information. There were statistically significant differences in patient-reported anxiety, decisional conflict, and emotional wellbeing (Note: There was significant loss to follow-up for collection of patient-reported outcomes measures).
Wuerstlein et al., 2016 **Prosigna (50-gene expression assay)** Funded by NanoString Technologies Inc. Seven authors reported various conflicts of interest	Prospective consecutive case series with decision impact analysis 11 centers Germany 2013-2014	N = 198 postmenopausal women with ER-positive, HER2-negative, lymph node-negative early-stage breast cancer	Prior to GEP results, adjuvant chemotherapy was recommended for 45 patients (22.7%). Overall, 50-gene expression assay results led to a change in recommendation about adjuvant chemotherapy in 27 cases; this was mainly due to a greater number of recommendations for adjuvant chemotherapy (20) among patients with high- or intermediate-risk 50-gene expression assay scores.

Clinical Validity

The following section was added at the request of the subcommittee to address questions about whether the tests had equivalent clinical validity and to provide more in depth information on the Albain study of patients with lymph node positive disease.

Blok et al., 2017

A recent systematic review by Blok et al. (2018) summarized the available clinical validity studies of breast cancer genome expression tests. The authors identified 50 clinical validation studies including 21 studies of MammaPrint, 20 studies of Oncotype DX, five studies of Prosigna, and four studies of EndoPredict. The authors cautioned that differences in the patient populations and clinical outcome measures across the studies made it difficult to compare the tests. Meta-analysis was not performed, but the authors observed that the tests were generally able to distinguish between high and low genomic risk and that those classifications were correlated with various prognostic measures (e.g., distant metastasis-free survival, recurrence-free survival, loco-regional recurrence). Table 2 summarizes the range of reported hazard ratios for outcomes incorporating survival in genomically low-risk patients compared to genomically high risk patients. Using the framework proposed by Simon et al. (2009) (excerpted as Figure 1), the authors concluded that Prosigna and EndoPredict have Level B evidence of clinical validity, and Oncotype DX and MammaPrint each have at least one Level A trial.

Table 2. Hazard ratios for outcomes incorporating survival in genomically low-risk patients compared to genomically high-risk patients

Test	Range of reported hazard ratios comparing genomically low-risk to genomically high-risk patients (higher hazard ratios indicate better prognostic performance)
MammaPrint	Distant metastasis-free survival: 2.7 to 5.7 Overall survival: 2.2 to 10.7
Oncotype DX	Distant recurrence-free survival: 2.12 to 6.09
Prosigna	Recurrence-free survival: 1.98
EndoPredict	Local recurrence-free survival: 1.31

Table 1. Elements of tumor marker studies that constitute Levels of Evidence determination*

Category Element	A Prospective	B Prospective using archived samples	C Prospective/ observational	D Retrospective/ observational
Clinical trial	PCT designed to address tumor marker	Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility Accommodation of predictive marker requires PRCT	Prospective observational registry, treatment and follow-up not dictated	No prospective aspect to study
Patients and patient data	Prospectively enrolled, treated, and followed in PCT	Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest	Prospectively enrolled in registry, but treatment and follow-up standard of care	No prospective stipulation of treatment or follow-up; patient data collected by retrospective chart review
Specimen collection, processing, and archival	Specimens collected, processed, and assayed for specific marker in real time	Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion	Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion	Specimens collected, processed and archived with no prospective SOPs
Statistical design and analysis	Study powered to address tumor marker question	Study powered to address therapeutic question and underpowered to address tumor marker question	Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study	Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study
		Focused analysis plan for marker question developed before doing assays	Focused analysis plan for marker question developed before doing assays	No focused analysis plan for marker question developed before doing assays
Validation	Result unlikely to be play of chance	Result more likely to be play of chance that A but less likely than C	Result very likely to be play of chance	Result very likely to be play of chance
	Although preferred, validation not required	Requires one or more validation studies	Requires subsequent validation studies	Requires subsequent validation

* PCT = prospective controlled trial; PRCT = prospective randomized controlled trial; SOPs = standard operating practices.

Figure 1. Excerpted from Simon et al., 2009

The review also summarized studies of clinical utility, including one study each of EndoPredict and Prosigna. The included clinical utility study of EndoPredict (Muller et al., 2013) examined treatment decisions among 167 women with T1-3, N1-3, HER2-negative, HR-positive breast cancer. Before testing, adjuvant chemotherapy was recommended for 63.8% of patients, which decreased to 47.7% after testing. The included clinical utility study of Prosigna (Martin et al., 2015) examined treatment decisions among 200 women with T1-2, N0, HER2-negative, HR-pisitive breast cancer. Before testing, adjuvant chemotherapy was recommended for 30% of patients, which decreased to 28% after testing.

Buus et al., 2016

An additional clinical validity study published after the search dates of the Blok et al. systematic review compared the clinical validity of the EndoPredict EP or EpiClin scores to Oncotype DX RS using the same archived specimens from the ATAC trial (Buus et al., 2016). The ATAC trial was a randomized controlled trial comparing anastrazole, tamoxifen, or a combination of the two medications for adjuvant treatment of postmenopausal women with ER-positive, HER2-negative localized breast cancer. In the trial,

approximately 60% of women were lymph node-negative, 25% had one to three positive lymph nodes, and 10% had more than four positive lymph nodes. The various genomic scores were assessed from 928 specimens from the original trial (680 specimens were from lymph node-negative patients and 248 were from lymph node-positive patients). In the first five years, EP and RS performed similarly in predicting distant recurrence-free survival (LRχ^2 25.7 vs. 26.1, respectively). EPClin (which incorporates clinical features into the algorithm) showed the greatest association with distant recurrence-free survival (LRχ^2 80.0) among tests incorporating genomic information. In years 5 to 10, EPClin had the best correlation with distant recurrence-free survival among the genomic tests (LRχ^2 59.3 vs. 23.6 for EP and 5.6 for RS). However, in both time frames, the clinical treatment score (CTS, a score calculated from information on nodal status, tumor size, tumor grade, and age that was derived from the ATAC dataset) offered the greatest prognostic value (LRχ^2 85.0 in years 0 to 5 and 64.7 in years 5 to 10). An analysis combining the genomic tests with CTS vs. CTS alone showed that each test offered incremental prognostic information over CTS alone, and EPClin + CTS showed the best prognostic performance in years 5 to 10.

Sestak et al., 2017

An additional clinical validity study published after the search dates of the Blok et al. systematic review compared the clinical validity of the EpiClin score, Oncotype DX RS, Prosigna ROR, BCI, CTS, and the four-marker immunohistochemical score (IHC) using the archived specimens from the ATAC trial. The ATAC trial is described above. For this analysis, the various genomic scores were calculated from 774 specimens (591 from patients with lymph node-negative disease and 183 from patients with lymph node-positive disease). In the univariate analysis for predicting distant recurrence at zero to10 years, all the studied indices offered prognostic information but showed greater prognostic discernment in lymph node-negative patients (see Table 3).

Table 3. Hazard ratios for distant recurrence

	HR for distant recurrence (0-10 years) in LN- patients (95% CI)	HR for distant recurrence (0-10 years) in LN+ patients (95% CI)
CTS	1.99 (1.58 to 2.50)	1.63 (1.20 to 2.21)
IHC4	1.95 (1.55 to 2.45)	1.33 (0.99 to 1.78)
RS	1.69 (1.40 to 2.03)	1.39 (1.05 to 1.85)
BCI	2.46 (1.88 to 3.23)	1.67 (1.21 to 2.29)
ROR	2.56 (1.96 to 3.35)	1.58 (1.16 to 2.15)
EPClin	2.14 (1.71 to 2.68)	1.69 (1.29 to 2.22)

Overall, the authors concluded that all of the studied indices offered prognostic information for distant recurrence in postmenopausal women with ER-positive, HER2-negative localized breast cancer, but that the prognostic value is attenuated in LN-positive patients. However, scores that incorporate clinical and genomic variables tended to perform better in LN-positive patients. The study was independently funded, but seven of the authors disclosed various conflicts of interest with the manufacturers of the genomic tests.

Albain et al., 2010

This study was a prospective-retrospective validation of the Oncotype DX RS in patients with node-positive breast cancer. The study used 367 archived specimens from the SWOG 8814 trial, which compared tamoxifen alone to six cycles of adjuvant chemotherapy (cyclophosphamide, doxorubicin, and 5-flouoruracil [CAF]), followed by tamoxifen (CAF-T). Specimens from a third arm of the parent trial, which used concurrent tamoxifen and CAF, were excluded from analysis since this treatment was inferior to CAF-T. Compared to the overall population from the parent trial, patients whose specimens were included in this analysis had slightly fewer positive nodes and smaller tumors.

The authors found that the RS was prognostic for disease-free survival (DFS) among patients in the tamoxifen-only arm of the trial; for low-risk RS, the 10-year DFS was 60% compared to 49% in the intermediate-risk group and 43% in the high-risk group. The rates of 10-year overall survival were 77%, 68%, and 51% in the low-, intermediate-, and high-risk groups respectively. However, the authors observed that the hazard ratios were not constant over time and that for patients who survived beyond five years, the RS was no longer prognostic.

The RS was also predictive of whether patients would benefit from CAF-T. For patients with low-risk RS (< 18), the HR for 10-year DFS with CAF-T compared to tamoxifen alone was 1.02 (95% CI 0.54 to 1.93) and for 10-year overall survival was 1.18 (95% CI 0.55 to 2.54). For patients with intermediate-risk RS (18 to 30), the HR for 10-year DFS with CAF-T compared to tamoxifen alone was 0.72 (95% CI 0.39 to 1.31) and for 10-year overall survival was 0.84 (95% CI 0.40 to 1.78). For patients with high-risk RS (> 31), the HR for 10-year DFS with CAF-T compared to tamoxifen alone was 0.59 (95% CI 0.35 to 1.01) and for 10-year overall survival was 0.56 (95% CI 0.31 to 1.02). The authors observed that the interaction between RS and adjuvant chemotherapy benefit was significant after adjustment for age, race, tumor size, tumor grade, progesterone receptor status, and p53 and HER2 status. However, adjusting for ER level (which contributes to the RS) rendered the interaction non-significant.

Evidence Summary

A growing number of observational clinical utility studies have found that genome expression testing for patients with early-stage breast cancer results in changes to adjuvant treatment recommendations and can help identify low-risk patient groups that are unlikely to benefit from adjuvant chemotherapy. There is no evidence that directly compares different genome expression profiling tests with respect to clinical utility. Although there is a growing body of evidence for the use of these tests in lymph node-positive patients, there is still uncertainty about the effects of these tests on treatment decisions and clinical outcomes in this population, and an evidence-based clinical practice guideline from the American Society of Clinical Oncology in 2016 recommends against their use in lymph node-positive patients.

There are only small, single studies regarding the clinical utility of gene expression profiling for neoadjuvant treatment decisions or for determining the use of radiotherapy after surgery for ductal carcinoma in situ, and these studies have not reported on long-term clinical outcomes.

On the basis of a single RCT, patients (including those with one to three positive nodes, representing about 20% of the overall study population) who were considered high risk by clinical classification but low risk by genomic classification utilizing MammaPrint can forgo adjuvant chemotherapy without a statistically significant reduction in the likelihood of distant metastasis-free survival at five year follow-up. Additional RCTs are underway.

Policy Landscape

Payer Coverage Policies

Medicaid

The Washington Medicaid *Physician-Related Services/Health Care Professional Services Billing Guide (11/12/2017)* specifies coverage for Oncotype DX breast cancer assay and EndoPredict, but does not mention Oncotype DX DCIS, MammaPrint, Prosigna, or BCI. Oncotype DX for breast cancer and EndoPredict are covered when these conditions are met:

- Test is performed within six months of the diagnosis
- Node negative (micrometastases less than 2mm in size are considered node negative)
- Hormone receptor positive
- Tumor size 0.6 to 1.0 cm with moderate/poor differentiation or unfavorable features (i.e., angiolymphatic invasion, high nuclear grade, high histologic grade) OR tumor size >1 cm
- Unilateral disease
- HER2 negative
- Patient will be treated with adjuvant endocrine therapy
- The test result will help the patient make decisions about chemotherapy when chemotherapy is a therapeutic option

Medicare

No National Coverage Determinations were found for the Oncotype DX breast cancer assay, Oncotype DX DCIS, EndoPredict, MammaPrint, Prosigna, or BCI. Local Coverage Determinations (LCDs) were found for Oncotype DX DCIS, EndoPredict, Prosigna, and BCI. No LCDs were found for the Oncotype DX Breast Recurrence Score, or MammaPrint.

Five LCDs were found for Oncotype DX DCIS. The LCDs provide coverage for Oncotype DX DCIS when these conditions are met:

- Pathology (excisional or core biopsy) reveals ductal carcinoma in situ of the breast (no pathological evidence of invasive disease)
- FFPE specimen with at least 0.5 mm of DCIS length
- Patient is a candidate for and is considering breast-conserving surgery alone as well as breast-conserving surgery combined with adjuvant radiation therapy
- Test result will be used to determine treatment choice between surgery alone vs. surgery with radiation therapy
- Patient has not received and is not planning on receiving a mastectomy

One LCD was identified for EndoPredict. This LCD provides coverage for EndoPredict when these conditions are met:

- T1-3, N0-1 breast cancer
- Patient is postmenopausal
- Pathology reveals invasive carcinoma of the breast that is ER positive, HER2 negative
- Patient is either node negative or has one to three positive lymph nodes
- Patient has no evidence of distant metastasis

- Test result will be used to determine treatment choice between endocrine therapy alone vs. endocrine therapy plus chemotherapy

Five LCDs were identified for Prosigna. These LCDs provide coverage for Prosigna for postmenopausal women who have either ER-positive, node-negative, Stage I or Stage II breast cancer, or ER-positive, node-positive (one to three positive nodes), Stage II breast cancer.

Five LCDs were identified for BCI, which provide coverage when these criteria are met:

- Postmenopausal female with non-relapsed, ER-positive breast cancer
- Node negative
- Patient is completing five years of tamoxifen therapy
- Patient is eligible for consideration of extended endocrine therapy based on published clinical trial data or practice guidelines
- Physician or patient is concerned about continuing anti-hormonal therapy because of documented meaningful toxicity or possible significant patient-specific side effects
- The test results will be discussed with the patient, including the limitations of the testing method, the risks and benefits of either continuing or stopping the therapy based on the test, and current cancer management guidelines

Private Payers

The policies for Aetna, Cigna, Moda, and Regence were reviewed for coverage of the Oncotype DX breast cancer assay, Oncotype DX DCIS, EndoPredict, MammaPrint, Prosigna, and BCI.

The Aetna policy (last reviewed 11/7/2017) provides coverage for the Oncotype DX breast cancer assay, EndoPredict, MammaPrint, Prosigna, and BCI under specified criteria. Aetna does not cover Oncotype DX DCIS.

The following are the criteria for Aetna's coverage for each of the tests, the Oncotype DX breast cancer assay, EndoPredict, MammaPrint, Prosigna, and BCI, to assess the necessity of adjuvant chemotherapy in females or males with recently diagnosed breast tumors:

- Adjuvant chemotherapy is not precluded by any other factor (e.g., advanced age or significant comorbidities)
- Prior to testing, the patient and physician have discussed the potential results of the test and agree to use the results to guide therapy (i.e., member will forgo adjuvant chemotherapy if Oncotype DX score is low)

The following are Aetna's additional criteria for the Oncotype DX breast cancer assay:

- Breast cancer is nonmetastatic (node negative) or with one to three involved ipsilateral axillary lymph nodes
- Breast tumor is ER positive
- Breast tumor is HER2 negative or breast tumor is HER2 positive and less than 1 cm in diameter

The following are Aetna's additional criteria for MammaPrint:

- Breast cancer is nonmetastatic (node negative) or with one to three involved ipsilateral axillary lymph nodes
- Breast tumor is ER positive or PR positive
- Breast tumor is HER2 negative

- Member is determined to be at "high clinical risk" of recurrence using Adjuvant! Online (www.adjuvantonline.com)

The following are Aetna's additional criteria for EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, and BCI:

- Breast cancer is nonmetastatic (node negative)
- Breast tumor is ER positive
- Breast tumor is HER2 negative

The Regence policy (last reviewed August 2017) provides coverage for the Oncotype DX breast cancer assay, EndoPredict, and BCI under certain conditions. Regence does not cover Oncotype DX DCIS, MammaPrint or Prosigna.

Regence covers the Oncotype DX breast cancer assay, EndoPredict, and BCI for women with primary breast cancer, Stages I, II, or III, to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy when these criteria are met:

- Individual has had excision of breast mass and full pathologic evaluation of the specimen has been completed (i.e., the test should not be ordered on a preliminary core biopsy)
- Primary tumor size 0.6 cm to 1 cm with moderate/poor differentiation or unfavorable features, OR tumor size of 1 cm or greater
- If there are multiple ipsilateral primary tumors, a specimen from the tumor with the most aggressive histological characteristics should be submitted for testing
- Hormone receptor positive
- HER2 negative
- Negative lymph nodes (nodes with micrometastases of 2 mm or less in size are considered node negative)
- The test result will aid the patient in making a decision regarding chemotherapy when chemotherapy is a therapeutic option

The Cigna policy (effective date 11/15/2017) covers the Oncotype DX breast cancer assay, MammaPrint, and Prosigna under certain conditions, and does not provide coverage for Oncotype DX DCIS, EndoPredict, or BCI.

The following are Cigna's coverage criteria for the Oncotype DX breast cancer assay:

- Recently diagnosed Stage I or Stage II breast cancer
- ER positive
- HER2 negative
- No evidence of distant metastasis
- Either of the following criteria:
  - Axillary-node status is negative (micrometastasis is no greater than 2.0 mm) whether the woman is pre- or postmenopausal
  - Up to three positive axillary nodes in a postmenopausal woman

The following are Cigna's coverage criteria for MammaPrint:

- Stage I or Stage II invasive breast cancer
- High clinical risk of recurrence

- ER positive/progesterone receptor positive
- HER2 negative
- Up to three positive nodes

The following are Cigna's coverage criteria for Prosigna:

- Recently diagnosed Stage I or Stage II breast cancer
- ER positive
- HER2 negative
- Postmenopausal
- No evidence of distant metastasis
- Axillary node status is negative (micrometastasis is no greater than 2.0 mm)

The Moda policy (last reviewed 10/25/2017) provides coverage for the Oncotype DX breast cancer assay with prior authorization. No coverage policy was identified for Oncotype DX DCIS, EndoPredict, MammaPrint, BCI, or Prosigna.

Recommendations from Others

Three guidelines were identified on the use of genome expression profiling for breast cancer:

- *Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women with Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline* (Harris et al., 2016)
- *Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women with Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update* (Krop et al., 2017)
- *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer* (National Comprehensive Cancer Network [NCCN], 2017)
- *Gene Expression Profiling and Expanded Immunohistochemistry Tests for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer Management: MammaPrint, Oncotype DX, IHC4 and Mammostrat* (National Institute for Health Care Excellence [NICE], 2013)

American Society of Clinical Oncology

The 2016 guidelines from the American Society of Clinical Oncology outlined recommendations for each of the genome expression profiling tests for women with early-stage invasive breast cancer and with known ER/PR and HER2 status, as outlined below.

Oncotype DX

- If a patient has ER/PR-positive, HER2-negative (node-negative) breast cancer, the clinician can use Oncotype DX to guide decisions on adjuvant systemic chemotherapy.
- If a patient has ER/PR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use Oncotype DX to guide decisions on adjuvant systemic chemotherapy.
- If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use Oncotype DX to guide decisions on adjuvant systemic therapy.

EndoPredict

- If a patient has ER/PR-positive, HER2-negative (node-negative) breast cancer, the clinician can use EndoPredict to guide decisions on adjuvant systemic chemotherapy.
- If a patient has ER/PR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use EndoPredict to guide decisions on adjuvant systemic chemotherapy.
- If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use EndoPredict to guide decisions on adjuvant systemic therapy.

Prosigna (PAM50 risk of recurrence score)

- If a patient has ER/PR-positive, HER2-negative (node-negative) breast cancer, the clinician can use the Prosigna score, in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy.
- If a patient has ER/PR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use Prosigna to guide decisions on adjuvant systemic therapy.
- If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use Prosigna to guide decisions on adjuvant systemic therapy.

Breast Cancer Index

- If a patient has ER/PR-positive, HER2-negative (node-negative) breast cancer, the clinician can use BCI to guide decisions on adjuvant systemic therapy.
- If a patient has ER/PR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use BCI to guide decisions on adjuvant systemic therapy.
- If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use BCI to guide decisions on adjuvant systemic therapy.

Mammostrat

If a patient has ER/PR-positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use the five-protein assay to guide decisions on adjuvant systemic therapy.

If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use the five-protein assay (Mammostrat) to guide decisions on adjuvant systemic therapy.

MammaPrint

The 2017 guideline update from the American Society of Clinical Oncology focused on modifying the recommendations regarding MammaPrint, based on recently published studies. The new recommendations for MammaPrint are below.

- If a patient has ER/PR-positive, HER2-negative, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy because of its ability to identify a good-prognosis population with potentially limited chemotherapy benefit.
- If a patient has ER/PR-positive, HER2-negative, node-negative breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy, because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer.

- If a patient has ER/PR-positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy because of its ability to identify a good-prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node.
- If a patient has ER/PR-positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population.
- If a patient has HER2-positive breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER2-targeted therapy.
- If a patient has ER/PR-negative and HER2-negative (triple negative) breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic chemotherapy.

National Comprehensive Cancer Network

The NCCN guidelines included discussion of Oncotype DX (21-gene breast cancer assay), MammaPrint (70-gene assay), and Prosigna (50-gene assay). The Oncotype DX assay is to be considered with pT1, pT2, or pT3, and pN0 or pN1mi, and the tumor is greater than 0.5 cm. The guidelines concluded that the Oncotype DX assay was the best validated breast cancer assay.

National Institute for Health Care Excellence

The 2013 NICE guidelines recommended Oncotype DX as an option for guiding adjuvant chemotherapy decisions for people with ER-positive, node-negative, and HER2-negative early breast cancer when the patient is assessed as being at intermediate risk and the Oncotype DX results are likely to help in predicting the course of the disease, and therefore help when making the decision about prescribing chemotherapy. MammaPrint and Mammostrat are only recommended for use in research in patients with ER-positive, node-negative, and HER2-negative early breast cancer. The NICE guidelines did not address Oncotype DX DCIS, EndoPredict, Prosigna, and BCI.

Quality Measures

No quality measures related to genome expression profiling for breast cancer were identified when searching the National Quality Measures Clearinghouse.

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

Suggested citation: Obley, A., Mosbaek, C., King, V., & Shaffer, W. (2017). *Coverage guidance: Genome expression profiling for breast cancer*. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University

Appendix A. GRADE-Informed Framework Element Descriptions

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors., but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical

sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Appendix B. GRADE Evidence Profile

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Breast cancer mortality							
1	RCT	Moderate	N/A	Not serious	Not serious		Moderate ●●●○
Breast cancer morbidity							
1	RCT	Moderate	N/A	Not serious	Not serious		Moderate ●●●○
Quality of Life							
							Insufficient evidence
Harms							
							Insufficient evidence
Change in management							
57	1 RCT, remainder observa-tional studies of various types	Moderate	Not serious	Not serious	Not serious		Moderate ●●●○

Appendix C. Methods

Scope Statement

Populations

Women diagnosed with early-stage breast cancer

Population scoping notes: None

Interventions

Genome expression profiling on cancer tissue

Intervention exclusions: None

Comparators

Usual care, immunohistochemical assays, genome expression profiling tests compared to each other

Outcomes

Critical: Breast cancer morbidity, breast cancer mortality

Important: Quality of life, harms, change in management of breast cancer

Considered but not selected for the GRADE table: Analytic validity, clinical validity

Key Questions

KQ1: What is the comparative effectiveness of genome expression profiling in early-stage breast cancer?

KQ2: How does the comparative effectiveness of genome expression profiling vary by:

a. Age
b. Race or ethnicity
c. Patient and family history
d. Cancer characteristics (e.g., tumor size, tumor grade, type of tumor, nodal status, hormone receptor status, HER2 status, proliferation rate, cancer stage)
e. Menopausal status

KQ3: What are the harms of genome expression profiling for breast cancer?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2012.

The following core sources were searched:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Center for Clinical Effectiveness
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Online Library)
Institute for Clinical and Economic Review (ICER)

Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-Effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms breast cancer and Oncotype (21-gene) or Endopredict (12-gene) or Mammaprint (70-gene) or Mammostrat or Breast Cancer Index (PAM50) or Prosigna. The search was limited to publications in English published since 2012. In addition, a MEDLINE® search was conducted for randomized controlled trials published after the search dates of the most recent systematic review selected for each intervention.

Searches for clinical practice guidelines were limited to those published since 2012. A search for relevant clinical practice guidelines was conducted using MEDLINE® and the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Centers for Disease Control and Prevention (CDC), Community Preventive Services
National Guidelines Clearinghouse
National Institute for Health and Care Excellence (NICE)
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, clinical utility studies, or clinical practice guidelines.

Appendix D. Applicable Codes

CODES	DESCRIPTION	Assay
CPT Codes		
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score	Oncotype DX
81599	Unlisted multianalyte assay with algorithmic analysis	EndoPredict
88381	Microdissection (i.e., sample preparation of microscopically identified target); manual	
81479	Unlisted molecular pathology procedure	MammaPrint, Breast Cancer Index
84999	Unlisted chemistry procedure	MammaPrint
HCPCS codes		
S3854	Gene expression profiling panel for use in the management of breast cancer treatment	EndoPredict, MammaPrint
Multianalyte Assays with Algorithmic Analyses (MAAA) codes		
0008M	Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score	Prosigna

Note: Inclusion on this list does not guarantee coverage.

Breast Cancer Genome Expression Profiling

Question: How should the draft Coverage Guidance **Genome Expression Profiling for Breast Cancer** be applied to the Prioritized List?

Question source: HERC Staff, HTAS

Issue: The HTAS approved the following draft "box language":

The following breast cancer genome profile tests (one test per primary breast cancer) are recommended for coverage in patients with early-stage breast cancer when the patient is willing to use the results of this testing in a shared-decision making process regarding adjuvant chemotherapy, and when the listed criteria are met (lymph nodes with micrometastases less than 2 mm in size are considered node negative):

- Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative *(strong recommendation*).
- Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative, with 1-3 positive nodes *(weak recommendation).*
- EndoPredict (12 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative *(weak recommendation).*
- Prosigna (50 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative *(weak recommendation).*
- MammaPrint (70 gene) 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 *(weak recommendation)*.

EndoPredict, Prosigna, and MammaPrint are not recommended for coverage in early-stage breast cancer with involved axillary lymph nodes *(weak recommendation).*

Oncotype DX Breast DCIS Score is not recommended for coverage *(weak recommendation).*

Breast Cancer Index is not recommended for coverage *(weak recommendation).*

Rationale for Recommendations

Genome expression profiling tests can be used to predict the aggressiveness of breast cancer tumors, and thereby inform decision making on treatments (in particular, those decisions related to the need for adjuvant chemotherapy in early stage disease). The HTAS review focused on the clinical utility of breast cancer gene expression tests, and a brief review of demonstrated clinical validity was added to aid comparison between the various tests.

A growing number of observational clinical utility studies have found that genome expression testing for patients with early-stage breast cancer results in changes to adjuvant treatment recommendations and can help identify low-risk patient groups that are unlikely to benefit from adjuvant chemotherapy. There is no evidence that directly compares different genome expression profiling tests with respect to clinical utility. Retrospective analysis of a prospective randomized adjuvant chemotherapy trial has validated the use of Oncotype DX Breast Recurrence Score in predicting chemotherapy benefit among women with estrogen receptor-positive, HER2 negative breast cancer. One RCT demonstrated no significant difference in five-

year metastasis-free survival and overall survival in the high clinical risk group when MammaPrint genomic classification was used to guide treatment decisions. Values and preferences weigh in favor of this additional testing, which provides reassurance that the risks, side effects, and cost of chemotherapy can be safely avoided.

Although there is preliminary evidence from decision impact studies to support coverage of genome expression profile testing in early-stage breast cancer with positive lymph nodes, there is some uncertainty about the effects of these tests on clinical outcomes in this population, and an evidence-based clinical practice guideline from the American Society of Clinical Oncology in 2016 recommends against their use in lymph node-positive patients. NCCN has noted (in a footnote) that Oncotype DX Breast Recurrence Score can be considered in selected patients with 1-3 involved axillary lymph nodes, to guide the addition of combination chemotherapy to standard hormone therapy. Values and preferences for reliance on such testing will be more variable among patients with lymph node involvement. Despite the weak evidence, we recommend coverage based on the potential benefits of reducing the use of chemotherapy.

Evidence of clinical utility is insufficient at present (small, single studies) to recommend coverage of Oncotype DX Breast DCIS Score to determine the use of radiotherapy following surgery for ductal carcinoma in situ, and insufficient to recommend coverage of Breast Cancer Index to predict the likelihood of benefit from extended (greater than five years) endocrine therapy.

Our recommendation for coverage of Oncotype DX Breast Recurrence Score for patients that are lymph node negative is strong because the ability of that profile test to predict adjuvant chemotherapy benefit has the largest and best-established evidence base. The other coverage recommendations are weak because additional studies may better establish clinical utility and predictive value.

Breast Cancer Genome Expression Profiling

Current Prioritized List Status:

CPT code	Code Description	Current Placement	Test(s) using this code
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score	191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER	Oncotype DX
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score	660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS	Prosigna
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	660	Mammaprint
81479	Unlisted molecular pathology procedure	660	Oncotype DX, Mammostrat, Breast Cancer Index (BCI)
81599	Unlisted multianalyte assay with algorithmic analysis	Suspend for Review	EndoPridict, Mammostrat, BCI
84999	Unlisted chemistry procedure	Diagnostic Procedure File	Mammostrat, BCI
88381	Microdissection (ie, sample preparation of microscopically identified target); manual	Ancillary	
S3854	Gene expression profiling panel for use in the management of breast cancer treatment	Ancillary	MammoPrint, Mammostrat, BCI
0008M	Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin embedded (FFPE) tissue, prognostic algorithm reported as a risk score		Prosigna

Current Prioritized List Guideline

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE
Lines 157,184,191,230,263,271,329

The use of multiple molecular testing to select targeted cancer therapy (CPT 81504) is included on the Services recommended for non-coverage table.

For breast cancer, Oncotype Dx testing (CPT 81519, HCPCS S3854) is included on Line 191 only for early stage breast cancer when used to guide adjuvant chemotherapy treatment decisions for women who are lymph node negative. Oncotype Dx is not included on this line for lymph node-positive breast cancer. Mammaprint, ImmunoHistoChemistry 4 (IHC4), and Mammostrat for breast cancer are included on the Services recommended for noncoverage table.

For melanoma, BRAF gene mutation testing (CPT 81210) is included on Line 230.

For lung cancer, epidermal growth factor receptor (EGFR) gene mutation testing (CPT 81235) is included on Line 263 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 Services recommended for noncoverage table.

For bladder cancer, Urovysion testing is included on Services recommended for noncoverage table.

For prostate cancer, Oncotype DX is not included on Line 329 and Prolaris is included on the Services recommended for noncoverage table.

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

HERC Staff Recommendations:

1) Add the following codes to line 191 CANCER OF BREAST; AT HIGH RISK OF BREAST CANCER and remove from line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS
    a. CPT 81520 (Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score)
    b. 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)
2) Add HCPCS S3854 (Gene expression profiling panel for use in the management of breast cancer treatment) to both lines 191 and 660
    a. Advise HSD to remove from the Ancillary List
3) Revise Guideline Note 148 as shown below (shown including January 2018 revisions)

GUIDELINE NOTE 148, BIOMARKER TESTS OF CANCER TISSUE
Lines 157,184,191,230,263,271,329

The use of multiple molecular testing to select targeted cancer therapy (CPT 81504) is included on line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS ~~the Services recommended for non-coverage table~~.

~~For breast cancer, Oncotype Dx testing (CPT 81519, HCPCS S3854) is included on Line 191 only for early stage breast cancer when used to guide adjuvant chemotherapy treatment decisions for women who are lymph node negative. Oncotype Dx is not included on this line for lymph node-positive breast cancer. Mammaprint, ImmunoHistoChemistry 4 (IHC4), and Mammostrat for breast cancer are included on the Services recommended for noncoverage table.~~

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 (using CPT 81599) 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 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.

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) and Breast Cancer Index (may use CPT 81479, 81599, 84999, S3854) are included on Line 660.

For melanoma, BRAF gene mutation testing (CPT 81210) is included on Line 230 MALIGNANT MELANOMA OF SKIN.

For lung cancer, epidermal growth factor receptor (EGFR) gene mutation testing (CPT 81235) is included on Line 263 CANCER OF LUNG, BRONCHUS, PLEURA, TRACHEA, MEDIASTINUM AND OTHER RESPIRATORY ORGANS only for non-small cell lung cancer. KRAS gene mutation testing (CPT 81275) is not included on Line 263.

For colorectal cancer, KRAS gene mutation testing (CPT 81275) is included on Line 157. BRAF (CPT 81210) and Oncotype DX (81525) are not included on Line 157. Microsatellite instability (MSI) is included on ~~the Services recommended for noncoverage table~~ line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For bladder cancer, Urovysion (88120, 88121) testing is included on ~~Services recommended for noncoverage table~~ line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS.

For prostate cancer, Oncotype DX Genomic Prostate Score (81479), Prolaris Score Assay (81541), and Decipher RP (81479) are included on Line 660.

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

2) Modify GN173 as shown below
    a) Remove entries for CPT 81520 (Prosigna) and CPT 81521 (MammaPrint)
    b) Add CPT 81479 (Unlisted molecular pathology procedure) to GN173 for Oncotype DX Breast DCIS Score and Breast Cancer Index
        i. Note: already on line 660 but not in GN173 table
    c) Add CPT 81525 (Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score) to line 660/GN173
        i. Note: currently listed on Services Recommended for Non-Coverage
    d) Add 88120, 88121 (Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis) to line 660/GN173 for Urovysion
        i. Keep on line 271 CANCER OF BLADDER AND URETER for other testing

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

Line 660

The following Interventions are prioritized on Line 660 CONDITIONS FOR WHICH CERTAIN INTERVENTIONS ARE UNPROVEN, HAVE NO CLINICALLY IMPORTANT BENEFIT OR HAVE HARMS THAT OUTWEIGH BENEFITS:

Breast Cancer Genome Expression Profiling

Procedure Code	Intervention Description	Rationale	Last Review
81479	• Oncotype DX Breast DCIS Score • Breast Cancer Index • Oncotype DX Genomic Prostate Score • Decipher RP for prostate cancer	Unproven Intervention	May, 2018 (breast) Coverage Guidance Blog (Breast) January, 2018 (prostate)
~~81521~~	~~Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes~~	~~Unproven intervention~~	~~August, 2015~~
81504	Biomarker tests for tumor tissue: • Mammostrat and ImmunoHistoCHemistry 4 (IHC4) for breast cancer • Microsatellite instability (MSI) for colorectal cancer • Urovysion for bladder cancer (88120, 88121) • Multiple molecular testing to select targeted cancer therapy	Insufficient evidence of effectiveness. More costly than equally effective therapies for this condition	August, 2015 Coverage Guidance Blog May, 2018 Coverage Guidance Blog (Breast)
81525	Oncotype DX for colon cancer	Insufficient evidence of effectiveness	November, 2015
88120, 88121	Urovysion for bladder cancer	Insufficient evidence of effectiveness	
HEALTH TECHNOLOGIES CURRENTLY UNDER REVIEW			
~~81520~~	~~Gene expression profiling algorithm for breast cancer mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping),~~	~~Under review by HTAS~~	~~N/A~~

HERC Coverage Guidance: Genome Expression Profiling for Breast Cancer
Disposition of Public Comments

Table of Contents

Commenters

Identification	Stakeholder
A	Jay Andersen, MD *[Submitted March 23, 2018]*
B	Karen Heller, MS, CGC, Medical Policy Manager, Myriad Genetics, Inc. *[Submitted March 29, 2018]*
C	Calvin Chao, MD, Vice President of Global Medical Affairs, Genomic Health *[Submitted March 30, 2018]*
D	David B. Page, MD *[Submitted April 2, 2018]*

Public Comments

ID/#	Comment	Disposition
A1	I have concerns regarding the potential exclusion of Oncotype DX testing for lymph node positive patients with Medicaid insurance. It is my understanding that the data reviewed to date was not all-inclusive, and did not include the Clalit (Israel's) Health Services data or the prospective West German Study Group, PlanB study published in the JCO, nor is there acknowledgment of the NCCN guidelines which recommend consideration of Oncotype DX testing for patients with 1-3 positive nodes. In order to appreciate the merits and clinical utility of Oncotype DX testing in this subset of patients, I recommend a comprehensive review, including the following references and data points. Clearly, incorporation of Oncotype DX data permits the	*Thank you for your comments.* *Some of the studies cited here were included in the evidence review, but others were published after the search dates. Specific responses are detailed below under each study.* *The NCCN guidelines were included in the coverage guidance. The specific portion about LN-positive patients stated: "The NCCN Panel has noted in a footnote that the 21-gene RT-PCR assay recurrence score can be*

ID/#	Comment	Disposition
	physician to adequately characterize risk and tailor therapy accordingly. As result, we actually administer less chemotherapy which spares patients unnecessary toxicities with limited benefits. However, historically, lymph node positive patients typically receive chemotherapy. Thus, we rely upon accurate, predictive and prognostic models validated in clinical trials to guide us in circumstances where chemotherapy may be safely omitted. After review of these data, I am trust that you will appreciate the merits of Oncotype DX testing in appropriate lymph node positive patients and will permit testing in the Medicaid population. -Clinical validation of the Oncotype DX Breast Recurrence Score assay was shown in multiple large studies involving N+ patients: Southwest Oncology Group (SWOG) 8814; and Arimidex, Tamoxifen Alone or in Combination (ATAC). Additional supportive evidence comes from the Eastern Cooperative Oncology Group (ECOG) 2197, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28, and Programme Action Concertée Sein (PACS) 01 studies. - Results from multiple prospective studies of the Oncotype DX Breast Recurrence Score assay confirm the findings made in the initial clinical validation studies: 5-year outcomes in the phase III randomized West German Study Group (WSG) PlanB study, and 5-year outcomes in the Surveillance, Epidemiology, and End Results (SEER) and Clalit Health Services registries. -Multiple clinical utility studies worldwide demonstrate that the Recurrence Score® result changes adjuvant treatment recommendations, yielding an overall reduction in chemotherapy recommendations, and health economic studies show the assay to be cost-effective and/or cost-saving. The Oncotype DX Breast Recurrence Score assay	*considered in selected patients with 1-3 involved ipsilateral ALNs to guide the addition of combination chemotherapy to standard hormone therapy based on the retrospective study by Albain et al."* *The Albain study was separately discussed in the coverage guidance at the direction of the subcommittee.* *In general, clinical validity studies were beyond the scope of this coverage guidance, but their results* are *noted.*

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	provides useful information to newly diagnosed, ER+, N+ patients based on individual tumor biology. The assay estimates each patient's risk of distant recurrence and anticipated benefit of chemotherapy, which helps guide adjuvant treatment decision-making.	
A2	**West German Study Group PlanB Trial** The WSG PlanB trial is a multicenter, prospective, randomized, phase 3 study that used the Oncotype DX® assay as a treatment decision tool for patients with N+ early stage breast cancer. Eligible patients had HER2-negative, N+ disease (pN1-3), or high-risk node-negative disease (defined as T3 or T4; grade 2 or 3, elevated uPA/PAI-1 levels, or age ≤35 years).[9,10] Hormone receptor (HR)-negative patients and HR+ patients with Recurrence Score (RS) results >11 were randomized to one of two adjuvant taxane-based chemotherapy regimens. HR+ patients with RS 0-11 were assigned to receive endocrine therapy alone (n=348). The primary endpoint of the study was disease-free survival (DFS); secondary endpoints included overall survival (OS) and toxicity. The 3-year and 5-year DFS results for patients with pN0-pN1 breast cancer,[9,10] who received endocrine therapy alone with RS 0-11 or adjuvant chemotherapy with RS >11, show the similarity of both 3-year and 5-year DFS among patients with RS 0-11 and 12-25 . These results are consistent with those of TAILORx in node-negative patients with RS 0-10, for whom the 5-year DFS was 93.8% (95% confidence interval [CI] 92.4%, 94.9%).[11] A subsequent analysis showed that distant disease-free survival (DDFS) at 5 years was 97.9% for patients with RS 0-11 and pN1 breast cancer treated with endocrine therapy alone (note: the corresponding 5-year DDFS for patients with pN0 breast cancer was 97.7%).[12]	*The original WSG PlanB trial was a randomized study comparing two chemotherapy regimens. A protocol amendment in 2009 allowed for patients with low risk scores (RS < 11) to omit adjuvant chemotherapy in favor of endocrine therapy alone, but the outcomes for those patients are better described as the findings of a prospective cohort. In addition, after the protocol amendment, only patients with pN0-N1 disease were included, and the small number of patients with pN2-N3 disease were excluded from analysis.* *The initial three-year results of the WSG PlanB Study for patients with pN0-N1 disease (Gluz et al., 2016) were summarized in the coverage guidance. The five-year outcomes cited here were published after the search dates (October 2017), and extend and corroborate the three-year outcomes included in the coverage guidance, as the commenter noted.* *Citation 12, which reports results of the study by nodal status, is a meeting abstract and therefore out of scope.*
A3	**SEER Registry** Findings of two outcomes-based studies, one using the SEER registry and another using the Clalit Health Services registry, corroborate those of the PlanB trial. The SEER registry is an authoritative source of cancer incidence and survival statistics that	*Citations 13 and 14 present descriptive information based on the SEER registry data for patients who had received RS testing. They do not provide direct comparative data on the use of adjuvant chemotherapy,*

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	collects population-based data for about 30% of the US. In an initial analysis of over 44,000 patients with ER+ early stage breast cancer with a Recurrence Score result that included 4,691 patients with N+ disease (defined as micrometastases and 1-3 positive nodes), the 5-year estimates of breast cancer-specific mortality (BCSM) were significantly different for Recurrence Score groups (p<0.001): 1.0% (95% CI 0.5%, 2.0%) for patients with RS <18; 2.3% (95% CI 1.3%, 4.1%) for patients with RS 18-30, and 14.3% (95% CI 8.4%, 23.8%) for patients with RS ≥31.[13] Adjuvant chemotherapy was reportedly used by 23%, 47%, and 75% of patients with RS <18, RS 18-30, and RS ≥31, respectively. Moreover, like the findings in node-negative patients, age, tumor grade, tumor size, race, or socioeconomic status, were not informative in N+ patients with RS <18 who had very low rates of BCSM at five years. A subsequent SEER analysis that included 6,768 patients with micrometastases (n=2,820), 1-3 positive nodes (n=3,663), or ≥4 positive nodes (n=285) confirmed initial findings in the N+ SEER patient population.[14] In particular, 5-year breast cancer-specific survival (BCSS) was highly favorable for patients with RS <18 and micrometastases up to two positive nodes.	*and therefore do not contribute to estimates of clinical utility for these tests.* *Additionally, the information included here only describes the rates of adjuvant chemotherapy by recurrence score for patients with one positive node. The rates of adjuvant chemotherapy, even at low recurrence scores (RS < 18), were greater in women with 2 to >4 positive nodes (31% to 59%).* *The authors further cautioned that chemotherapy use is underreported in the SEER database and that further analyses that account for treatment are needed, "…in particular, a comparison of survival among those who did and did not receive chemotherapy is of interest."*
A4	**Clalit Health Services Registry** Findings from a registry of the Clalit Health Services (CHS), the largest health maintenance organization in Israel. A CHS registry study examined the relationship between Recurrence Score results, adjuvant treatment, and outcomes among 709 patients with N+ disease (micrometastases and 1-3N+). Among the subset with RS <18 who received no adjuvant chemotherapy (n=342), 5-year distant recurrence was 2.7% and 5-year BCSM was 0.6% (Figure 1). Among all patients with RS <18 (n=379), of whom 7% had adjuvant chemotherapy, 5-year distant recurrence was 1.2% for those with micrometastases, 4.4% with 1N+, and 5.4% with 2-3N+ (Figure 2). In a multivariable analysis that included tumor size, nodal status, and Recurrence Score group, only tumor size (p=0.04) and Recurrence Score group (p=0.001) were significantly associated with distant recurrence risk.[15]	*This study, which was published after the search dates for the coverage guidance review, reported registry data for 709 patients with N1mi (42%) or 1 to 3 positive nodes (58%) who had RS testing between 2006 and 2012 with a median follow-up period of 5.9 years. Adjuvant chemotherapy was used in 7.1% of the RS < 18 patients, 39.5% of the RS 18 to 30 patients, and 86.1% of the RS > 31 patients. In addition to the results provided by the commenter, an analysis of recurrence risk by chemotherapy treatment found recurrence rates of 7.7% for chemotherapy-treated patients vs. 2.9% in untreated patients with RS < 18, and 1.0% in chemotherapy-treated*

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		patients vs. 9.7% in untreated patients with RS 18 to 30. The authors noted that because adjuvant treatment decisions in CHS rely heavily on the RS results, the analysis of outcomes by chemotherapy use must be interpreted cautiously.
A5	**Clinical Validation Studies** The Oncotype DX Breast Recurrence Score assay has been validated in in two trials (SWOG 8814 and TransATAC), with additional supportive clinical evidence from three trials (ECOG 2197, NSABP B-28, and PACS-01). **SWOG 8814** An evaluation of postmenopausal, N+, ER+, early stage breast cancer patients from the SWOG-8814 trial showed the Recurrence Score result to be prognostic for DFS and OS in N+ patients treated with tamoxifen alone. Patients with low Recurrence Score results had a better prognosis than patients with high Recurrence Score results.[16,17] The Recurrence Score result was also shown to be predictive of cyclophosphamide/doxorubicin/fluorouracil (CAF) therapy benefit. Patients with lower Recurrence Score results had little, if any, benefit in terms of DFS from sequential CAFàtamoxifen (CAF-T) therapy vs. tamoxifen alone (HR=1.02; stratified log rank p=0.97). In contrast, patients with higher Recurrence Score results had a statistically significant benefit with sequential CAF-T therapy vs. tamoxifen alone (HR=0.59; stratified log rank p=0.033). **TransATAC** A validation study was conducted in HR+, postmenopausal patients enrolled in the ATAC trial.[4] In this study, 1,231 tumor samples from the two monotherapy arms were used to determine whether the Recurrence Score result was predictive of the risk of distant recurrence (prognosis). Of these, 306 samples were from patients with N+	*Clinical validity studies were beyond the scope of this coverage guidance. Nevertheless, the results from the studies listed here were included in the systematic review by Blok et al. (2018), and the findings of the SWOG 8814 trial were separately summarized at the direction of the subcommittee. Citations 19 and 20 are meeting abstracts.*

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	disease. The Recurrence Score result was shown to predict distant recurrence in N+ patients treated with either tamoxifen or anastrozole. N+ patients with low, intermediate, and high Recurrence Score values had an average 9-year risk of distant recurrence of 17%, 28%, and 49%, respectively (Figure 4). Risk of distant recurrence was shown to increase with the number of positive nodes: patients with 1-3 positive nodes experienced a lower risk of distant recurrence compared with patients with ≥4 positive nodes.[4] **Studies Supportive of the Clinical Validation Studies** **ECOG 2197 Trial** An early study of the Oncotype DX assay in an N+ setting involved a cohort of patients whose tumor blocks were collected in the ECOG 2197 trial. An analysis was performed on samples of 465 patients with HR+ disease, including both pre- and postmenopausal patients and both node-negative and N+ (1-3 positive nodes) disease, all treated with anthracycline-based chemotherapy (doxorubicin/cyclophosphamide [AC] or doxorubicin/docetaxel [AT]).[18] Patients with low Recurrence Score results had lower 5-year recurrence rates than patients with high scores (node-negative 4% vs. 13%; N+ 5% vs. 25%). At 10-year follow up, the Recurrence Score value continued to be a highly significant predictor of distant recurrence ($p<0.0001$). The authors concluded that the Recurrence Score result may potentially be used to distinguish patients who do well with standard chemotherapy regimens from those who may be suitable candidates for clinical trials evaluating alternative chemotherapy regimens or other strategies. **NSAPB B-28 Trial** A study was conducted in a cohort of patients who participated in the NSABP B-28 trial, which compared four cycles of AC vs. AC followed by paclitaxel in 3,060 N+	

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	patients.[19] An analysis of a subset of 1,065 ER+ patients who were tested using the Oncotype DX assay showed that the Recurrence Score result was a significant predictor of outcome (p<0.001 for DFS, OS, distant recurrence-free interval [DRFI], and BCSS). The analysis showed that for patients with low, intermediate, and high Recurrence Score results, 80.9%, 64.9%, and 55.8% of patients, respectively, were free of distant recurrence at 10 years. A multivariable model showed that the Recurrence Score result was prognostic for DFS, DRFI, and OS, independently of other indicators including number of nodes, tumor size, tumor grade, treatment, and type of surgery. This large study demonstrated that the Recurrence Score result is strongly predictive of the 10-year risk of distant recurrence, OS, and BCSS in women with N+ breast cancer treated with chemotherapy. **PACS-01 Trial** A second study (PACS-01) conducted by Penault-Llorca et al. was similar to the B-28 study in design and evaluated the association between the Oncotype DX Recurrence Score result and the risk of distant recurrence in HR+, N+ breast cancer patients treated with endocrine therapy plus adjuvant fluorouracil, epirubicin, and cyclophosphamide with or without docetaxel (FEC vs. FEC-D).[20] A cohort of 530 patients were included in the primary analysis and showed that the Recurrence Score result was a significant predictor of DRFI (HR=4.1 for a 50-point difference, p<0.001), DFS (HR=3.3, p<0.001) and OS (HR=5.0, p<0.001). In multivariate analyses, the Recurrence Score result provided independent prognostic information beyond clinicopathologic factors including treatment, age, tumor size and grade, number of positive nodes, surgery type, and Ki-67 status (p<0.001). These data further confirm the prognostic significance of the Recurrence Score results previously reported from multiple studies in HR+, N+ breast cancer patients treated with adjuvant endocrine and chemotherapy.	

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A6	**Summary** There is a continuum of biology that extends beyond nodal status in breast cancer and studies have consistently validated and reinforced the value of the Oncotype DX Breast Recurrence Score assay in ER+ patients along this node-negative-to-N+ continuum. Like the experience in node-negative disease, the assay has been shown to be both prognostic and predictive of chemotherapy benefit in patients with N+ disease. Use of the Oncotype DX assay for patients with 1-3 positive nodes may identify patients with lower risk of distant recurrence who are unlikely to benefit significantly from chemotherapy. Conversely, the assay identifies those at high risk of recurrence who are likely to derive significant benefit from the addition of adjuvant chemotherapy to hormonal therapy. Decision impact studies show that the Oncotype DX assay changes treatment decisions, and economic studies report the assay to be cost-effective/cost-saving. The Oncotype DX Breast Recurrence Score assay is a quantitative RT-PCR assay that measures the expression of 21 genes (16 cancer-related, 5 reference genes) in triplicate from fixed paraffin-embedded breast cancer tissue. The assay has been validated to predict the risk of distant tumor recurrence and the likelihood of chemotherapy benefit in patients with ER+ early stage breast cancer. The Oncotype DX Breast Recurrence Score assay provides valuable information beyond traditional clinical and pathologic measures.	*Thank you for your comments. Irrespective of the clinical validity data, the subcommittee found that there was considerably less clinical utility evidence for the use of genome expression profiling in LN-positive patients compared to LN-negative patients. As a weak recommendation, additional clinical utility evidence in this population could change the recommendation.*
B1	We respectfully submit the following suggested changes to the coverage guidance on Genome Expression Profiling for Breast Cancer*:* The following breast cancer genome profile tests (one test per primary breast cancer) are recommended for coverage in patients with early-stage breast cancer when the patient is willing to use the results of this testing in a shared-decision making process regarding adjuvant chemotherapy, and when the listed criteria are met. Lymph nodes with micrometastases less than 2 mm in size are considered node negative.	*Thank you for your comments. Your suggestions for revisions to the box language will be reviewed by the subcommittee. Substantive issues are addressed separately below.*

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	• Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative *(strong recommendation).* ~~Lymph nodes with micrometastases less than 2 mm in size are considered node negative.~~ • EndoPredict (12 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative or lymph node positive (up to 3 nodes) *(weak recommendation).* • Prosigna (50 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative *(weak recommendation).* • MammaPrint (70 gene) 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 *(weak recommendation).* Oncotype DX Breast Recurrence Score, ~~EndoPredict,~~ Prosigna, and MammaPrint are not recommended for coverage in early-stage breast cancer with involved axillary lymph nodes *(weak recommendation).* Oncotype DX Breast DCIS Score is not recommended for coverage *(weak recommendation).* Breast Cancer Index is not recommended for coverage *(weak recommendation).*	
B2	1) The statement about lymph nodes with micrometastases being considered node negative should apply to all tests, and therefore we suggest moving it to the top for clarity.	*Thanks you for your comment. The statement in the coverage guidance that lymph nodes with micrometastases are considered node negative does apply to all of the tests.*
B3	2) In addition to coverage for lymph node negative breast cancer, we request that EndoPredict be covered for breast cancers that include up to 3 positive axillary lymph nodes:	*In general, clinical validity was out of scope for this coverage guidance. However, at the request of the subcommittee, clinical validity data was summarized, including the study cited here (Sestak et al., 2018).*

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	a) Clinical validation data support EndoPredict's prognostic ability for node positive patients: In a clinical validation study using the TransATAC cohort, 248 out of 928 patients were node positive. For the node positive group, EndoPredict's (EPclin's) hazard ratio (measuring the ability to separate low and high risk groups) was 9.49 (p=0.0001). Nineteen percent of patients were classified as low risk and they experienced a 5% rate of distant recurrence at 10 years.[1] This suggests that EndoPredict can identify a significant number of node positive patients with such a low risk of distant recurrence that they can safely forgo chemotherapy. A subset analysis of the data from the ABCSG6 and ABCSG8 cohorts confirmed similar findings. In that study, 537 out of 1702 patients were node positive. For the node positive group, the EndoPredict (EPclin) hazard ratio was 4.70 (p<0.001). Thirty percent of patients were classified as low risk and they had a 5.1% rate of distant recurrence at 10 years.[2] The Noridian LCD includes a table that summarizes the data points from these 2 studies.[3] Sestak calculated the C-index to be 0.671 for EndoPredict for a subset of 227 node positive patients from the TransATAC cohort, suggesting a good fit between the EndoPredict prognostic prediction and actual outcomes.[4] b) Data demonstrate that medical management decisions are made for node positive patients based on the results of EndoPredict: Muller demonstrated a change in therapy for 38% of patients when EndoPredict is used. Within this cohort, 37% of patients were node positive.[5] A large, population based study of 10,434 node positive patients who received a different breast cancer assay demonstrated that use of the assay was associated with a 79% reduction in chemotherapy recommendations compared to 21,991 patients who did not receive the assay.[6] c) Guidelines and other coverage decisions would support coverage for node positive breast cancer. Medicare coverage includes node positive disease;[3] a similar policy for	*The Muller data pertaining to clinical utility were summarized in the coverage guidance. It should be noted that although 38% of patients in the study were LN-positive, the data regarding changes to treatment decisions were reported in aggregate and not by lymph node status.* *The report by Jasem et al. (2017) was included in the coverage guidance.* *Medicare coverage policy and criteria were reviewed in the coverage guidance. The Washington Medicaid draft decision is noted. The specific NCCN recommendations for LN-positive patients are detailed above in comment A1. However, the statement here that "other prognostic multigene assays may be considered" (NCCN footnote hh on page BINV-6) does not apply to LN-positive patients.*

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	Medicaid recipients would enable similar access and consistency of care. After completing a comparable evidence review, Washington Medicaid has published a draft coverage decision that includes node negative and node positive breast cancer (up to 3 positive nodes).[7] The NCCN breast cancer treatment guidelines state that Oncotype DX (or other prognostic multigene assays) may be considered in select node positive patients to help assess risk of recurrence and to guide the addition of adjuvant chemotherapy.[8]	
C1	On behalf of Genomic Health, I am submitting these comments regarding the Oregon Health Authority Health Evidence Review Commission's (HERC) draft coverage guidance "Genome Expression Profiling for Breast Cancer," which was posted for public comment on March 2, 2018. Genomic Health, Inc. is the world's leading provider of genomic-based diagnostic tests that optimize cancer care, including addressing the overtreatment of the disease, one of the greatest issues in healthcare today. With its Oncotype IQ® Genomic Intelligence Platform, the company is applying its world-class scientific and commercial expertise and infrastructure to lead the translation of clinical and genomic big data into actionable results for treatment planning throughout the cancer patient journey, from diagnosis to treatment selection and monitoring. Genomic Health is the sole source laboratory for the Oncotype DX Breast Recurrence Score for early-stage breast cancer. We commend the HERC's recommendation for coverage of the Oncotype DX Breast Recurrence Score given the preponderance of clinical evidence supporting the test. We respectfully disagree with the HERC's position that the Oncotype DX Breast Recurrence Score not be recommended for coverage in early-stage breast cancer patients with involved axillary lymph nodes. The coverage guidance states "there is insufficient evidence to support coverage of genome expression profile testing in early-stage breast cancer with positive lymph nodes." However, in reviewing the draft coverage guidance, we noted that several key studies regarding the Recurrence	*Thank you for your comments.*

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	Score in node positive patients were not included in the HERC's review indicating that conclusions about the evidence of the Recurrence Score in this patient population are not based on the full set of clinical evidence. We are submitting these comments to highlight these studies and to request the HERC incorporate them into review prior to finalizing this coverage guidance. A citations list of studies that we are requesting be included in the HERC's review is provided with this comment letter.	
C2	Approximately 32% of newly diagnosed breast cancer patients will have regional lymph node involvement without distant metastasis.[1] Guidelines recommend the addition of adjuvant chemotherapy to hormonal therapy in those with endocrine receptor positive, node-positive disease. However, not all patients benefit equally from chemotherapy.[2] As a result, validated prognostic and predictive clinical tools, like the Oncotype DX Breast Recurrence Score, are needed to better inform treatment decisions within the node-positive patient population. The following are key points from several published studies that were not included in the HERC's review: • Clinical validation of the Oncotype DX Breast Cancer Assay was previously established in two large prospective/retrospective studies involving node positive (N+) patients. Results from the Southwest Oncology Group (SWOG) 8814 and the Arimidex, Tamoxifen Alone or in Combination (ATAC) trials) constitute Level 1B evidence for clinical validation in this node positive population. The HERC review seems only to have included the SWOG 8814 study. We request inclusion of the ATAC trial (Dowsett et al. 2010) in HERC's review. • Given the consistency of the results for both node-negative and node-positive patients with respect to Oncotype DX Breast Recurrence Score's ability to predict chemotherapy benefit, the NCCN guidelines incorporated	*Clinical validity studies were beyond the scope of this coverage guidance. Nevertheless, the results from the studies listed here were included in the systematic review by Blok et al. (2018), and the findings of the SWOG 8814 trial were separately summarized at the direction of the subcommittee.* *The NCCN guideline on the use of 21-gene RS in LN-positive patients is noted above in response to comment A1.* *Citations 3 to 5 are discussed above in response to comments A2 to A4.* *Citation 6 (Torres et al., 2018) is a new clinical utility study that was published after the search dates of the coverage guidance. In this study, 67 patients with ER-positive, HER2-negative, and 1 to 3 positive axillary nodes who were eligible for adjuvant chemotherapy had pre-RS treatment recommendations recorded, and these recommendations were compared to actual treatments received after the RS was assessed. For the 38 patients with a low RS (< 18), 29 had initially received a recommendation for adjuvant chemotherapy; 11 patients*

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	the Recurrence Score as clinically appropriate for patients with 1-3 positive lymph nodes beginning in 2015. • Recent results from multiple prospective studies of the Oncotype DX Breast Recurrence Score confirm the findings of the initial clinical validation studies thus confirming the safety and effectiveness of the Recurrence Score for patients with 1-3 positive nodes.[3-5] • In the Clalit Health System Registry, women with node-positive disease and a Recurrence Score <18, who were treated with endocrine therapy alone, had only a 2.7% risk of distant recurrence at five years, which demonstrates the safety and effectiveness of withholding chemotherapy in this group of patients.[3] • The WSG PlanB, multicenter, prospective, randomized, phase 3 study used the Recurrence Score to guide treatment decisions for patients with early-stage, node-positive disease. Patients with Recurrence Score less than 11 receiving endocrine therapy alone had a 5-year disease free survival rate of 94%, consistent with node-negative patients in other studies.[4] • Breast cancer specific mortality outcomes from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) Program corroborate those of the WSB PlanB trial and the Clalit Health System Registry. In the SEER registry, 5 year breast cancer specific mortality was 0.9% in patients with micrometastases or 1 positive node(representing 81% of the total study population) who had a Recurrence Score less than 18.[5] • Most recently, a prospective decision impact study demonstrated a 36% change in treatment decisions for early breast cancer patients receiving the Recurrence Score. In the patient group with a Recurrence Score less than 18, 47% of treatment decisions were changed from chemotherapy with endocrine therapy to endocrine therapy alone.[6] These results are similar to previously published decision impact studies.[7-10]	*ultimately received adjuvant chemotherapy. For the 23 patients with an intermediate RS of 18 to 30, 20 had initially received a recommendation for adjuvant chemotherapy; 18 patients ultimately received adjuvant chemotherapy. For the six patients with a high RS (> 31), four had initially received a recommendation for adjuvant chemotherapy; six patients ultimately received adjuvant chemotherapy. The authors noted that this is the first decision-impact study examining an exclusively LN-positive population. This observation underscores the paucity of clinical utility data that is specific to LN-positive patients.*

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	These prospective outcome studies show remarkably consistent outcomes at five years in node positive women with a low Recurrence Score who do not receive chemotherapy and the data support what was found in the original prospective–retrospective validation studies in node- positive patients. The preponderance of evidence on long-term clinical outcomes plus published clinical utility data clearly supports use of the Recurrence Score in guiding treatment decisions in node-positive women. Based on these data, we request HERC reconsider its assessment of the Oncotype DX Breast Recurrence Score and issue a recommendation of coverage for the test in node-positive women with early-stage breast cancer.	
D1	I am emailing to express my serious concerns about retraction of insurance coverage for Oncotype testing and other genomic profiling for node-positive early stage breast cancer patients in the adjuvant setting. As you are well aware, many clinicians use these tests to justify omission of chemotherapy in lower-risk node-positive disease. We have prospective data (MINDact) for MammaPrint, and we have bountiful retrospective data for Oncotype, with promise of prospective validation via the RxSPONDER trial (pending results). Please reconsider. I wish the best for my future patients, and strive to use chemotherapy only when it is likely to benefit the patient.	*Thank you for your comments. The subcommittee appreciates the perspectives of clinicians who use these tests in practice.*

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Section 9.0

New Discussion Items

Non-Axial Manipulation

Question: Where should the procedure code for non-axial chiropractic/osteopathic manipulation be placed?

Question source: CCO medical directors

Issue: CPT 98943 (Chiropractic manipulative treatment (CMT); extraspinal, 1 or more regions) was on the "Excluded" file for many years. During a clean-up of that file, the code was moved to the Ancillary List. This procedure code is used by chiropractors and osteopaths for treatment of conditions such as ankle or wrist sprains. The CCO medical directors are concerned that this code is being used for treatment of conditions such as constipation in children.

HERC staff recommendation:

1) Add CPT 98943 (Chiropractic manipulative treatment (CMT); extraspinal, 1 or more regions) to line 605 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR
    a. Advise HSD to remove CPT 98943 from the Ancillary list