Health Evidence Review Commission's Value-based Benefits Subcommittee

May 7, 2015
9:00 AM

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 7, 2015
9:00am - 1:00pm
Clackamas Community College
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 9:00 AM

II. Staff report – Ariel Smits, Cat Livingston, Darren Coffman 9:05 AM

III. Straightforward/consent agenda – Ariel Smits 9:15 AM
A. Straightforward table
B. Revised DMAP List Codes Requiring HERC Action
C. Guideline note errata
D. Gender dysphoria guideline correction
E. Revisions to the prenatal testing guideline
F. Biennial review: open wound of eardrum

IV. New discussion items – Ariel Smits 9:45 AM
A. Yttrium for liver cancer and metastases
B. Left ventricular assist devices as destination therapy
C. Treatment of varicose veins
D. Developmental coordination disorder
E. Unspecified developmental diagnoses

V. Guidelines – Ariel Smits, Cat Livingston 11:15 AM
A. Ventral hernia guideline
B. Penile anomalies

VI. Previous Discussion Items – Ariel Smits 11:45 AM
A. Back line reorganization follow up issues
    A. Renaming the lower surgical line
    B. 62310 placement
    C. Intrathecal/epidural medication pumps
        1. Guideline note 72
    D. Epidural steroid injection guideline wording
    E. Diagnostic guideline D4

VII. Coverage Guidances for review – Cat Livingston 12:15 PM
A. Revascularization for chronic stable angina

VIII.	**Public comment**	**12:55 PM**
IX.	**Adjournment – Kevin Olson**	**1:00 PM**

Value-based Benefits Subcommittee Recommendations Summary
For Presentation to:
Health Evidence Review Commission on March12, 2015

For specific coding recommendations and guideline wording, please see the text of the 3-12-2015 VbBS minutes.

RECOMMENDED CODE MOVEMENT (effective 10/1/15)

- Various straightforward coding changes
- Two dental procedure codes for sealant repair and cleaning of removable appliances were removed from the Prioritized List and placed on the Services Recommended for non-Coverage Table
- The procedure code for IVC filters was added to three lines with lower extremity or lung blood clot diagnostic codes
- Various procedures for treatment of lower urinary tract symptoms resulting from benign prostatic hypertrophy (BPH) were added to the funded BPH line, and several treatments were removed.

RECOMMENDED GUIDELINE CHANGES (effective 10/1/15)

- The cochlear implant guidelines were merged and modified to allow hearing loss of 70dB or greater as the threshold to consider implantation for both children and adults and to change the benefit received from hearing aids from “little or no” to “limited” and define what limited benefit means
- A new guideline was adopted indicating that unilateral hearing loss treatment is only included on funded lines for children through age 20 and outlines what treatments are available for various levels of unilateral hearing loss
- The guideline regarding bone anchored hearing aids (BAHAs) was modified to reflect that BAHAs are only included on funded lines for children up to age 20 with normal hearing in the contralateral ear with or without hearing aids
- A new guideline was adopted allowing up to 8 weeks of proton pump inhibitor (PPI) treatment for gastroesophageal reflux (GERD)
- A new guideline was adopted which specifies that IVC filters are included on covered lines only when a patient has an active peripheral or lung clot and is not a candidate for anti-coagulation medication
- A new ancillary guideline was adopted which specifies that IVC filters are covered for trauma patients requiring prolonged hospitalization when medically appropriate
- A new guideline was adopted regarding coverage of treatments for BPH
- The guideline regarding intraocular steroid injections was modified to include coverage criteria for use in diabetic macular edema

BIENNIAL REVIEW CHANGES (effective 1/1/16)

- The two cochlear implant lines were merged and re-scored, resulting in continued placement in the funded region of the Prioritized List

- A new line for bone and joint conditions at high risk for complications was created along with a guideline specifying when these conditions were eligible for treatment. Scoring of the new line placed it in the funded region, while the existing unfunded benign bone and joint conditions line was rescored to a lower priority position on the List.
- The four current back conditions lines were restructured into four new lines. The new medical treatment line will contain all back pain diagnoses and will include a variety of medical therapies, including lumbar epidural steroid injections. A new guideline was adopted for this medical line. Scoring of the new medical line placed it in the funded region. A new surgical line for urgent surgical conditions was also scored and prioritized in the funded region, with a new guideline. Scoring for a new surgical line for non-urgent surgical conditions placed it in the unfunded region, with the new surgical guideline applying to this line as well. The fourth line is a scoliosis line, whose scoring placed it in the funded region, which has a guideline limiting surgical therapies to children through age 20. A new guideline was adopted which restrict opioid therapy for the treatment of pain associated with back conditions, allowing limited use for 90 days after an acute injury or exacerbation of chronic pain, but not allowing opioid therapy after 90 days. Patients on chronic opioid therapy for back conditions will need to be tapered off. Five current guidelines for back conditions were deleted as they have been incorporated into the new guidelines. The acupuncture guideline was modified to refer to the new back condition medical guideline. The epidural steroid injection guideline was modified to specify what symptoms are required to qualify for the injection and limiting the injections to once, with a second if the first injection provided substantial pain relief for 3 months. The back pain diagnostic guideline was modified to remove the reference to a deleted guideline.

VALUE-BASED BENEFITS SUBCOMMITTEE
Clackamas Community College
Wilsonville Training Center, Rooms 111-112
Wilsonville, Oregon
March 12, 2015
8:30 AM – 1:00 PM

Members Present: Kevin Olson, MD, Chair; David Pollack, MD; Susan Williams, MD; Mark Gibson; Holly Jo Hodges, MD; Laura Ocker, LAc.

Members Absent: James Tyack, DMD; Irene Croswell, RPh.

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

Also Attending: Wally Shaffer, MD and Bruce Austin, DMD, OHA; Valerie King MD, MPH, OHSU Center for Evidence Based Policy; Mary Hlady PT, Oregon PT Association; Nora Stern PT, Providence; Gary Allen, DMD, Advantage Dental; Laura McKeane, AllCare; Frank Warren, MD, The Oregon Clinic; Jane Stephen and Karen Campbell, Allergan; Eric Davis. PK Melethil, and Donald Leary, MS, DC, JD, Health and Wellness; Fiona Clement, USCF; Kevin Wilson, ND.

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

  The meeting was called to order at 8:55 am and roll was called. Minutes from the January, 2015 VbBS meeting were reviewed and approved. Due to the delay in starting the meeting, staff report was not given.

- **Topic: Straightforward/Consent Agenda**

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

  Recommended Actions:
  1) Remove 45378 (Colonoscopy, flexible; diagnostic, including collection of specimen(s) by brushing or washing, when performed) from line 526 FOREIGN BODY IN GASTROINTESTINAL TRACT WITHOUT RISK OF PERFORATION OR OBSTRUCTION
     i. Affirm with MAP that 45378 is on the Diagnostic File
  2) Remove ICD-10 Q77.2 (Cervical rib) from lines 412 SPINAL DEFORMITY, CLINICALLY SIGNIFICANT and 588 SPINAL DEFORMITY, NOT CLINICALLY SIGNIFICANT
     a. Add Q77.2 to line 668 MUSCULOSKELETAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENT

3) Affirm 15777 (Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (ie, breast, trunk)) placement on the Services Recommended for Non-Coverage List.
4) Remove 26045 (Fasciotomy, palmar (eg, Dupuytren's contracture); open, partial) from line 362 DEFORMITY/CLOSED DISLOCATION OF MAJOR JOINT AND RECURRENT JOINT DISLOCATIONS
    a. Add 26045 to line 420 PERIPHERAL NERVE ENTRAPMENT; PALMAR FASCIAL FIBROMATOSIS
5) Add 307.50 (Eating disorder, unspecified) to line 385 BULIMIA NERVOSA and remove from line 153 FEEDING AND EATING DISORDERS OF INFANCY OR CHILDHOOD
6) Change the name of line 385 to BULIMIA NERVOSA AND UNSPECIFIED EATING DISORDERS
7) Revise GUIDELINE NOTE 92, ACUPUNCTURE as shown in Appendix A

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

- **Topic: 2015 CDT code issues**

Discussion: There was no discussion of this topic.

Recommended Actions:
1) Remove D1353 (SEALANT REPAIR-PER TOOTH) from line 57 PREVENTIVE DENTAL SERVICES
2) Advise DMAP to remove D9219 (evaluation for deep sedation or general anesthesia) from the Exempt File
3) Remove D9931 (Cleaning and inspection of a removable appliance) from line 457 DENTAL CONDITIONS (EG. MISSING TEETH, PROSTHESIS FAILURE) and place on the Services Recommended for Non-Coverage Table

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

- **Topic: Cochlear implant guideline/cochlear implant line merge**

Discussion: Smits reviewed the summary document from the meeting packet. Dr. Frank Warren, ENT, from Portland, answered questions from the subcommittee to clarify the summary material. There was no substantial discussion.

Recommended Actions: (Note: the line merge is effective January 1, 2016)

1) Merge lines 283 SENSORINEURAL HEARING LOSS - AGE 5 OR UNDER and 423 SENSORINEURAL HEARING LOSS - OVER AGE OF FIVE into the new line shown below with the line scoring shown below
2) Modify GN31 as shown in Appendix A
3) Delete current GN49

Line:	**XXX**
Condition:	SENSORINEURAL HEARING LOSS (See Guideline Note 31)
Treatment:	COCHLEAR IMPLANT
ICD-9:	389.11-389.12,389.14,389.16,389.18
ICD-10:	H90.3,H90.41-H90.5,Z01.12,Z45.320-Z45.328
CPT:	64505-64530,69930,92562-92565,92571-92577,92590,92591, 92601-92604, 92626-92633,96127-96145,98966-98969,99051,99060,99070,99078,99201-99215, 99281-99285,99341-99355,99358-99378,99381-99404,99408-99412,99429-99449,99487-99498,99605-99607
HCPCS:	G0396,G0397,G0463,G0466,G0467

Scoring—Line XXX
Category: 7
HL: 5 (child weighted)
Suffering: 3 (from 283)
Population effects: 1 (average)
Vulnerable population: 0
Tertiary prevention: 3 (average)
Effectiveness: 4 (evidence/child weighted)
Need for service: 1
Net cost: 2
Score: 960
Approximate line placement: 330

MOTION: To recommend the line merging, line scoring, and guideline note changes as presented. CARRIES 5-0.

- **Topic: Unilateral hearing loss/BAHA guideline clarification**

Discussion: Smits reviewed the summary document from the meeting packet. There was discussion about the benefits of treatment of unilateral hearing loss in adults—whether this was a disability that should be treated. Smits reviewed that the literature does not support that there is sufficient evidence for coverage in adults, unlike children. Pollack asked if there was a subpopulation of adults who would benefit more from coverage; Smits responded that adults with sudden hearing loss may benefit more than adults with gradual hearing loss, but there were issues with defining sudden loss, and the benefits would still focus only on quality of life.

There were specific suggestions made regarding the wording of the proposed new guideline—modifying the reference to the cochlear implant guideline to reflect the deletion of one of the two cochlear implant guidelines approved in the preceding section of the meeting. Suggestions were made regarding the wording of GN103 regarding BAHAs. The reference to "SoftBand BAHA" was changed to a generic reference to headband mounted BAHA devices. The requirement for normal hearing in the contralateral ear was noted to be "with or without a hearing aid."

Recommended Actions:

1) Adopt a new guideline regarding treatment of unilateral hearing loss as shown in Appendix B
2) Modify GN103 for BAHAs as shown in Appendix A

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

- **Topic: Ventral hernia guideline**

Discussion: This topic was tabled until the May, 2015 VBBS meeting.

- **Topic: Prenatal genetic testing guideline**

Discussion: This topic was tabled until the May, 2015 VBBS meeting.

- **Topic: GERD esophagitis/PPI therapy**

Discussion: Livingston reviewed the summary document in the meeting materials. There was minimal discussion.

Recommended Actions:

1) Add a new guideline regarding proton pump inhibitor therapy as shown in Appendix B
2) Modify the treatment description on line 384: "Treatment: Short-term medical therapy, Surgical treatment"

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

- **Topic: Biennial review—benign bone and joint conditions**

Discussion: Smits reviewed the summary document in the meeting materials. Williams supported the changes, noting that many of the conditions on the proposed new, covered line are locally destructive and need treatment.

Recommended Actions: (effective January 1, 2016)

1) Create a new line for benign bone and joint conditions at high risk of complication with the line and scoring as shown below
2) Modify GN137 as shown in Appendix A
    a. Note: "line 533" will need to be changed to new line number
3) Rescore line 533 as shown below
4) Miscellaneous coding changes
    a. Add 214.8 (Lipoma of other specified sites), 228.00 (Hemangioma of unspecified site), 727.02 (Giant cell tumor of tendon sheath), and 727.89 (Other disorders of synovium, tendon, and bursa) to line 533 BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE
    b. Add D17.79 (Benign lipomatous neoplasm of other sites), D18.09 (Hemangioma of other sites), D48.1 (Neoplasm of uncertain behavior of connective and other soft tissue), and M67.8x (Other disorders of synovium, tendon, and bursa), K09.0 (Developmental odontogenic cysts) and K09.1 (Developmental (nonodontogenic) cysts of oral region) to line 533 BENIGN NEOPLASM OF BONE AND ARTICULAR CARTILAGE
        i. Note: K09.0, K09.1 were added to line 533 at HERC as they were not shown in the VBBS summary materials correctly
    c. Remove M67.8x (Other disorders of synovium, tendon, and bursa) from line 51 DEEP ABSCESSES, INCLUDING APPENDICITIS AND PERIORBITAL ABSCESS
    d. Remove D16.00-D16.8 (Benign neoplasms of bone) from line 358 CLOSED FRACTURE OF EXTREMITIES (EXCEPT MINOR TOES)
    e. Remove K09.0 (Developmental odontogenic cysts) and K09.1 (Developmental (nonodontogenic) cysts of oral region) from line 466 BRANCHIAL CLEFT CYST; THYROGLOSSAL DUCT CYST; CYST OF PHARYNX OR NASOPHARYNX and add to line 533

Line:	XXX
Condition:	BENIGN conditions OF BONE AND Joints at high risk for complications (See Guideline Notes 6,7,11,64,65,100,137)
Treatment:	MEDICAL AND SURGICAL TREATMENT, WHICH INCLUDES CHEMOTHERAPY AND RADIATION THERAPY
ICD-9:	213.0-213.9, 214.8, 228.00, 526.0-526.2, 719.2x, 727.02, 727.89, 733.2x

ICD-10: D16.00-16.9, D17.79, D18.09, D48.1, K09.0, K09.1, M12.2xx, M27.1, M27.40, M27.41, M67.8x, M85.40-M85.69

CPT: 11400-11446,12051,12052,13131,17106-17111,20150,20550,20551,20600-20611,20615, 20900,20930-20938,20955-20973,21011-21014,21025-21032,21040,21046-21049,21181, 21552-21556,21600,21930-21936,22532-22819,22851,23071-23076,23101,23140-23156, 23200,24071-24079,24105-24126,24420,24498,25000,25071,25073,25110-25136,25170-25240,25295-25301,25320,25335,25337,25390-25393,25441-25447,25450-25492,25810-25830,26100-26116,26200-26215,26250-26262,26449,27025,27043-27049,27054,27059, 27065-27078,27187,27327,27328,27337,27339,27355-27358,27365,27465-27468,27495, 27630-27638,27645-27647,27656,27745,28039-28045,28100-28108,28122,28124,28171-28175,28820,28825,32553,36680,49411,63081-63103,64774,64792,77014,77261-77295, 77300-77307,77331-77338,77385-77387,77401-77427,77469,77470,79005-79445,96127, 96405,96406,96420-96440,96450,96542-96571,97001-97004,97012,97022,97110-97124, 97140-97530,97535,97542,97760-97762,98966-98969,99051,99060,99070,99078,99184, 99201-99239,99281-99285,99291-99404,99408-99412,99429-99449,99468-99480,99487-99498,99605-99607

HCPCS: G0157-G0161,G0396,G0397,G0406-G0408,G0425-G0427,G0463,G0466,G0467,G6001-G6017

Scoring—Line XXX (comparison scores are from line 533)
Category: 7 (7)
HL: 3 (2)
Suffering: 2 (1)
Population effects: 0 (0)
Vulnerable population: 0 (0)
Tertiary prevention: 1 (0)
Effectiveness: 4 (4)
Need for service: 0.9 (0.5)
Net cost: 3 (3)
Score: 432 (120)
Approximate line placement: 405

Rescoring—Line 533
Category: 7 (7)
HL: 1 (2)
Suffering: 1 (1)
Population effects: 0 (0)
Vulnerable population: 0 (0)
Tertiary prevention: 0 (0)
Effectiveness: 4 (4)
Need for service: 0.2 (0.5)
Net cost: 3 (3)
Score: 32
Approximate line placement: 577

MOTION: To recommend the new line creation, new and existing line scoring, code and guideline note changes as presented for 2016 biennial list. CARRIES 5-0.

- **Topic: Biennial review—Back condition line reorganization**

  Discussion: Smits reviewed the summary document in the meeting materials. Smits and Gingerich presented a PowerPoint outlining the proposed changes, and giving approximate OHP numbers of patients with back diagnoses and approximate costs in 2013 for various treatments for back conditions.

  There was no discussion regarding the proposed new lines or line scoring. The medical guideline (GN XXX) was modified to specify that both prescription and non-prescription medications are available for patients who score as high risk on validated assessment tools. There was no discussion regarding the opioid prescribing guideline. The surgical guideline (GN ZZZ) was modified to specify that it did not apply to the scoliosis line, and to specify that the non-included procedures were not covered for any area of the spine (cervical, thoracic, lumbar, or sacral). The scoliosis guideline (GN AAA) was modified to allow surgery for patients age 20 and younger (instead of 21) to align with other guidelines covering children. The modifications to diagnostic guideline D4 were modified slightly to clarify that the radiculopathic findings need to be objectively demonstrated. One miscellaneous coding recommendation, regarding CPT 63210, was not accepted, and was decided to be a part of the percutaneous intervention discussion.

  The percutaneous interventions for cervical spine pain as well as lumbar epidural steroid injections were discussed in some detail. Due to the weak level of evidence, the subcommittee did not want to add coverage for cervical epidural steroid injections or for cervical radiofrequency neurotomy. These procedures will be added to the Services Recommended for Non-Coverage Table. The subcommittee desired maintaining the current coverage for lumbar epidural steroid injections, placing that procedure on the upper medical back conditions line, with the guideline restricting it to 1 injection with a second injection if the first gave 3 months of sustained pain relief. The definition for radiculopathy in this guideline will be readdressed at the May, 2015 VBBS meeting, as the subcommittee was not completely satisfied with the current wording. Additionally, the subcommittee asked to have further discussion regarding the requirement of PT or other active therapy for patients undergoing lumbar epidural steroid injections.

  Recommended Actions: (effective January 1, 2016)

  1) Adopt the four new back conditions lines and line scoring as shown below
  2) Delete current back condition lines 374, 412, 545, and 588
  3) Adopt the new medical guideline for back conditions, new surgical guideline for back conditions, new guideline for scoliosis, and new guideline for opioid prescribing as shown in Appendix B
  4) Adopt the modified DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN and GUIDELINE NOTE 92, ACUPUNCTURE as shown in Appendix A

5) Delete guideline notes 37, 41, 56, 60, and 94 (see Appendix C)
6) Advise MAP to remove ICD-9 724.3 (Sciatica), ICD-10 M41.40 (Neuromuscular scoliosis, site unspecified), M41.50 (Other secondary scoliosis, site unspecified), M54.3-M54.4 (Sciatica) from the Diagnostic File
7) Advise DMAP to remove 22830 (Exploration of spinal fusion) from the Diagnostic File
8) Remove ICD-9 754.1/ICD-10 Q68.0 (Congenital musculoskeletal deformities of sternocleidomastoid muscle) from line 545 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT and ICD-9 756.3/ICD-10 Q76.6-Q76.9 (Other anomalies of ribs and sternum) and ICD-10 Q68.0 (Congenital musculoskeletal deformities of sternocleidomastoid muscle) from lines 412 SPINAL DEFORMITY, CLINICALLY SIGNIFICANT and 588 SPINAL DEFORMITY, NOT CLINICALLY SIGNIFICANT and place on line 534 DEFORMITIES OF UPPER BODY AND ALL LIMBS
9) Keep 64490-64492 (Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (flouro or CT), cervical) and 64633 and 64634 (Destruction by neurolytic agent, paravertebral facet joint nerve(s), with imaging guidance (fluoroscopy or CT); cervical or thoracic, single or additional facet joints) on the Services Recommended for Non-Coverage Table
10) Place 63210 ((Injection(s), of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, includes contrast for localization when performed, epidural or subarachnoid; cervical or thoracic)) on the Services Recommended for Non-Coverage Table
    a. Advice MAP to remove from the Ancillary File

Line:	MMM
Condition:	CONDITIONS OF THE BACK AND SPINE
Treatment:	RISK ASSESSMENT, PHYSICAL MODALITIES, COGNITIVE BEHAVIORAL THERAPY, MEDICAL THERAPY
ICD-9:	336.0,344.60-344.61,349.2,720.2,720.81,721.0-721.9,722.0-722.9,723.0,723.1, 723.4,723.6-723.9,724.0-724.9,731.0,732.0,737.0-737.2,737.40-737.42,737.8-737.9,738.4-738.5,739.0-739.9,742.59,754.2,756.10-756.19,839.20-839.21,847.0-847.9,V57.1,V57.2x, V57.81-V57.89
ICD-10:	F45.42 (Pain disorder with related psychological factors), G83.4,G95.0,M24.08,M25.78, M40.x,M42.0x,M43.00-M43.28,M43-M43.9,M45.0-M45.8,M46.1,M46.40-M46.49,M46.81-M46.89,M46.91-M46.99,M47.011-M47.16,M47.20-M47.28,M47.811-M47.9,M48.00-M48.27,M48.30-M48.38,M48.9,M49.80-M49.89,M50.00-M50.93,M51.04-M51.9,M53.2x1-M53.2x8, M53.3,M53.80-M53.9,M54.0,M54.11-M54.6,M54.81-M54.9,M62.830,M96.1, M96.2-M96.5,M99.00-M99.09,M99.12-M99.13,M99.20-M99.79,M99.83-M99.84,Q06.0-Q06.3,Q06.8-Q06.9, Q67.5,Q76.0-Q76.4,Z47.82,S13.0xxA-S13.0xxD, S13.4xxA-S13.4xxD,S13.8xxA-S13.8xxD,S13.9xxA-S13.9xxD,S16.1xxA-S16.1xxD,S23.0xxA-S23.0xxD, S23.100A-S23.100D,S23.101A-S23.101D,S23.110A-S23.110D,S23.111A-S23.111D,S23.120A-S23.120D,S23.121A-S23.121D,S23.122A-S23.122D,S23.123A-S23.123D,S23.130A-S23.130D,S23.131A-S23.131D,S23.132A-S23.132D,S23.133A-S23.133D,S23.140A-S23.140D,S23.141A-S23.141D,S23.142A-S23.142D,S23.143A-S23.143D,S23.150A-S23.150D,S23.151A-S23.151D,S23.152A-S23.152D,S23.153A-S23.153D,S23.160A-S23.160D,S23.161A-S23.161D,S23.162A-S23.162D,S23.163A-S23.163D,S23.170A-S23.170D,S23.171A-S23.171D,S23.3xxA-S23.3xxD,S23.8xxA-

S23.8xxD,S23.9xxA-S23.9xxD,S33.0xxA-S33.0xxD, S33.100A-S33.100D,S33.101A-S33.101D,S33.110A-S33.110D,S33.111A-S33.111D,S33.120A-S33.120D,S33.121A-S33.121D,S33.130A-S33.130D,S33.131A-S33.131D,S33.140A-S33.140D,S33.141A-S33.141D,S33.5xxA-S33.5xxD,S33.9xxA-S33.9xxD,S34.3xxA-S34.3xxD, S39.092A-S39.092D,S39.82xA-S39.82xD,S39.92xA-S39.92xD

CPT: 62311, 64483, 64484, 90785,90832-90838,90853 (mental health visits, counseling), 96150-4 (health and behavior assessment codes), 97001-97004, 97022, 97110-97124, 97140, 97150, 97530, 97535 (PT/OT evaluation and treatment), 97810-97814 (acupuncture), 98925-98929, 98940-98942 (OMT/CMT), 98966-98968, 98969, 99051, 99060, 99070,99078,99201-99215 (outpatient medical visits), 99281-99285 (ER), 99304-99337 (SNF care), 99340-99359, 99366-99404 (risk factor reduction intervention), 99408, 99409, 99411, 99412, 99441-99449, 99487-99490, 99605-99607

HPCPS: G0157-G0160 (PT/OT), G0396-G0397 (SBRT), G0425-G0427 (telehealth), G0463, G0466, G0467, G0469, G0470 (FQHC)

Line: S1

Condition: CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS

Treatment: SURGICAL THERAPY

ICD-9: 344.60-344.61 (cauda equina), 721.1, 721.41-721.42,721.91 (spondylosis with myelopathy); 722.7x (intervertebral disc disorder with myelopathy), 723.0 (spinal stenosis), 724.0x (spinal stenosis), 738.4, 756.11-756.12 (spondylolisthesis), V57.1,V57.2x,V57.81-V57.89

ICD-10: G83.4 (cauda equina), M43.1x (spondylolisthesis), M47.0x, M47.1x (spondylosis with myelopathy), M48.0x (spinal stenosis), M50.0x, M51.0x (intervertebral disc disorder with myelopathy), M53.2x (spinal instabilities), Q76.2 (spondylolisthesis), Z47.82 (aftercare after scoliosis surgery)

CPT: 20660-20665, 20930-20938,21720,21725,22206-22226,22532-22855,29000-29046,29710-29720,62287, 62355-62370, 63001-63091,63170,63180-63200, 63270-63273,63295-63610,63650,63655,63685, 97001-97004, 97022, 97110-97124, 97140, 97150, 97530, 97535 (PT/OT evaluation and treatment), 96150-4 (health and behavior assessment codes), 98966-98968, 98969, 99051, 99060, 99070,99078,99201-99215 (outpatient medical visits), 99217-99239 (hospital), 99281-99285 (ER), 99304-99337 (SNF care), 99401-99404 (risk factor reduction intervention), 99408, 99409, 99411, 99412, 99441-99444, 99446-99449 (critical care), 99605-99607

HPCPS: G0157-G0160 (PT/OT), G0396-G0397 (SBRT), G0406-G0408 (inpatient consultation), G0425-G0427 (telehealth), G0463, G0466, G0467 (FQHC), S2350-S2351 (discectomy with decompression of spinal cord)

Line: S2

Condition: CONDITIONS OF THE BACK AND SPINE

Treatment: SURGICAL THERAPY

ICD-9: 336.0, 349.2,720.81,721.0, 721.2,721.3,721.5-721.8,721.90,722.0,722.10-722.2,722.4-722.6,722.8-722.93, 723.0, 723.1,723.4-723.9, 724.0x,731.0,732.0,737.0-737.2,737.40-737.42,737.8-737.9,738.4-738.5,742.59,754.2,756.10-756.12,839.20-839.21,V57.1,V57.2x, V57.81-V57.89

ICD-10: G95.0, M40.xx,M42.xx,M43.0x, M43.1x, M43.2x, M43.5x, M43.8x, M45.x, M46.0x-M46.9x,M47.2x,M47.8x,M47.9,M48.0x (spinal stenosis), M48.1, M48.3, M48.8, M48.9, M49.8x,M50.1x-M50.9x, M51.1x-M51.9,M53..8x,M53.9,M54.1x,M96.1-M96.5,M99.2x-M99.8x,Q67.5,Q76.0-Q76.3,Q76.4x,S13.0x,S23.0x, S23.1x, S33.0x, S33.1x,S34.3x

CPT: 20660-20665, 20930-20938,21720,21725,22206-22226,22532-22865,27035,29000-29046, 29710-29720,62287,62355-62370,63001-63091,63170,63180-63200, 63270-63273,63295-63610,63650,63655,63685,96150-96154 (health and behavior assessment codes), 97001-97004, 97022, 97110-97124, 97140, 97150, 97530, 97535 (PT/OT evaluation and treatment), 98966-98968, 98969, 99051, 99060, 99070,99078,99201-99215 (outpatient medical visits), 99217-99239 (hospital), 99281-99285 (ER), 99304-99337 (SNF care),

99401-99404 (risk factor reduction intervention), 99408, 99409, 99411, 99412, 99441-99444, 99446-99449 (critical care), 99605-99607
HPCPS: G0157-G0160 (PT/OT), G0396-G0397 (SBRT), G0406-G0408 (inpatient consultation), G0425-G0427 (telehealth), G0463, G0466, G0467 (FQHC), S2350-S2351 (discectomy with decompression of spinal cord)

Line: S3
Condition: SCOLIOSIS
Treatment: MEDICAL AND SURGICAL THERAPY
ICD-9: 737.3x, 737.43, V57.1,V57.2x,V57.81-V57.89
ICD-10: M41.xx
CPT: 20660-20665, 20930-20938,21720,21725,22206-22226,22532-22865,29000-29046,29710-29720,62287,62355-62370,63001-63091,63170,63180-63200,63210,63295-63610,63650, 63655,63685, 96127, 96150-96154 (health and behavior assessment codes), 97001-97004, 97022, 97110-97124, 97140, 97150, 97530, 97535 (PT/OT evaluation and treatment), 97760,97762, 98966-98968, 98969, 99051, 99060, 99070,99078,99201-99215 (outpatient medical visits), 99217-99239 (hospital), 99281-99285 (ER), 99304-99337 (SNF care), 99401-99404 (risk factor reduction intervention), 99408, 99409, 99411, 99412, 99441-99444, 99446-99449 (critical care), 99605-99607
HPCPS: G0157-G0160 (PT/OT), G0396-G0397 (SBRT), G0406-G0408 (inpatient consultation), G0425-G0427 (telehealth), G0463, G0466, G0467 (FQHC)

<u>Scoring—Line MMM medical treatments</u>
Category: 7
HL: 4
Suffering: 3
Population effects: 0
Vulnerable population: 0
Tertiary prevention: 2
Effectiveness: 3
Need for service: 0.8
Net cost: 2
Score: 432
Approximate line placement: 405

<u>Scoring—Line S2 surgical</u>
Category: 7
HL: 4
Suffering: 3
Population effects: 0
Vulnerable population: 0
Tertiary prevention: 0
Effectiveness: 1
Need for service: 0.8
Net cost: 2
Score: 112
Approximate line placement: 535

<u>Scoring—Line S1 urgent surgical</u>
Category: 7
HL: 5
Suffering: 4
Population effects: 0
Vulnerable population: 0
Tertiary prevention: 4
Effectiveness: 3
Need for service: 1
Net cost: 2
Score: 780
Approximate line placement: 350

<u>Scoring—Line S3 scoliosis</u>
Category: 7
HL: 5
Suffering: 3
Population effects: 0
Vulnerable population: 0
Tertiary prevention: 3
Effectiveness: 3
Need for service: 1
Net cost: 2
Score: 660
Approximate line placement: 364

MOTION: To recommend the new back condition lines with line scoring, deletion of current back condition lines, and guideline deletions as

presented for 2016 biennial list. To recommend the new guidelines (medical, surgical, opioid prescribing, and scoliosis), changes to existing guidelines, and miscellaneous code changes as modified for 2016 biennial list. CARRIES 5-0.

- **Topic: Coverage Guidance—IVC filters**

Discussion: Livingston reviewed the evidence and EGBS coverage guidance recommendations regarding IVC filters. Smits reviewed the proposed changes to the Prioritized List based on this draft coverage guidance. There was some discussion about different standards of care for use of IVC filters for use in trauma patients in different health systems in the state; however, it was determined that these filters should be available for use in trauma patients for those systems that chose to use them.

Recommended Actions:

1) Add CPT 37191-37193 to lines 1 PREGNANCY, 217 ACUTE PULMONARY HEART DISEASE AND PULMONARY EMBOLI, 285 BUDD-CHIARI SYNDROME, AND OTHER VENOUS EMBOLISM AND THROMBOSIS
2) Adopt a new guideline for IVC filters for PE/DVT as shown in Appendix B
    a. Note: a minor modification replacing the line numbers with "these lines" in the second paragraph was done by HERC at their March 12, 2015 meeting. The guideline shown is as approved by VbBS.
3) Adopt a new ancillary guideline for IVC filters for trauma/prolonged hospitalization as shown in Appendix B

MOTION: To approve the recommended changes to the Prioritized List based on the draft inferior vena cava filters for pulmonary embolism prevention coverage guidance scheduled for review by HERC at their March 12, 2015 meeting. CARRIES 5-0.

- **Topic: Coverage Guidance—Alternatives to TURP**

Discussion: Shaffer reviewed the evidence and the HTAS coverage guidance for alternatives to TURP. Smits reviewed the proposed changes to the Prioritized List. There was some clarifying discussion.

Recommended Actions:

1) Remove 600.01 (Hypertrophy (benign) of prostate with urinary obstruction and other lower urinary tract symptoms (LUTS)), 600.11 (Nodular prostate with urinary obstruction), 600.21 (Benign localized hyperplasia of prostate with urinary obstruction and other lower urinary tract symptoms (LUTS)), and 600.91 (Hyperplasia of prostate, unspecified, with urinary obstruction and

other lower urinary symptoms (LUTS)) from line 576 UNSPECIFIED URINARY OBSTRUCTION AND BENIGN PROSTATIC HYPERPLASIA WITHOUT OBSTRUCTION

2) Remove 52441 (Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; single implant), 52442 (each additional implant), C9739, and C9740 (Cystourethroscopy, with insertion of transprostatic implant) from line 331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION and add to the Services Recommended for Non-Coverage Table
3) Add 52450 (Transurethral incision of prostate) to lines 218 CANCER OF KIDNEY AND OTHER URINARY ORGANS, 274 CANCER OF BLADDER AND URETER, 331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION, 333 CANCER OF PROSTATE GLAND, 576 UNSPECIFIED URINARY OBSTRUCTION AND BENIGN PROSTATIC HYPERPLASIA WITHOUT OBSTRUCTION
    a. Advise MAP to remove 52450 from the Ancillary File
4) Remove 52647 (Laser coagulation of prostate, including control of postoperative bleeding, complete) from lines 331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION and 333 CANCER OF PROSTATE GLAND and add to the Services Recommended for Non-Coverage Table
5) Remove 52648 (Laser vaporization of prostate, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, internal urethrotomy, and transurethral resection of prostate are included if performed) from line 333 CANCER OF PROSTATE GLAND
6) Add 53850 (Transurethral destruction of prostate tissue; by microwave thermotherapy) and 53852 (Transurethral destruction of prostate tissue; by radiofrequency thermotherapy) to line 331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION
    a. Advise MAP to remove 53830 and 53852 from their Non-Covered File
7) Adopt a new guideline as shown in Appendix B

MOTION: To approve the recommended changes to the Prioritized List based on the draft alternative to TURP coverage guidance scheduled for review by HERC at their March 12, 2015 meeting. CARRIES 5-0.

- **Topic: Intraocular steroids for diabetic macular edema**

Discussion: Smits reviewed the summary document in the meeting materials. Testimony was heard from Allergan, Inc. representatives, who testified in support

of the staff recommendations. The Allergan representative gave information on some comparative pricing for various ocular steroid treatments. Williams raised a concern that patients who fail anti-VEGF might not benefit from intraocular steroids. Smits and the Allergan representative pointed to a study of this population that found benefit. There was some discussion about the concern for the high cataract formation rate, with the additional cost of surgeries for these cataracts. Overall, the subcommittee felt that the evidence supported the use of steroids for diabetic macular edema.

Recommended Actions:

1) Modify GN116 as shown in Appendix A

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

- **Public Comment:**

No additional public comment was received.

- **Issues for next meeting:**
  - Ventral hernia guideline
  - Prenatal genetic testing guideline revisions
  - Lumbar epidural steroid injection guideline revisions
  - Smoking cessation guideline
  - Review of inpatient and outpatient visit codes for “special” lines
  - Yttrium for liver cancer and metastases
  - Penile anomalies guideline
  - Coverage guidance on
    - Planned out-of-hospital birth
  - Developmental coordination disorder and sensory integration disorder

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- **Next meeting:**

May 7, 2015 at Clackamas Community College, Wilsonville Training Center, Wilsonville Oregon, Rooms 111-112.

- **Adjournment:**

The meeting adjourned at 1:00 PM.

Appendix A

Revised Guideline Notes

Effective October 1, 2015

GUIDELINE NOTE 31, COCHLEAR IMPLANTATION~~, AGE 5 AND UNDER~~

Line XXX

~~Children~~ Patients will be considered candidates for cochlear implants if the following criteria are met:

1) Profound sensorineural hearing loss in both ears (defined as 71 ~~91~~dB hearing loss or greater at 500, 1000 and 2000 Hz)
2) Receive ~~little or no~~ limited useful benefit from appropriately fitted hearing aids, defined as a speech discrimination score of <30% on age appropriate testing for children and as scores of 40% or less on sentence recognition test in the best-aided listening condition for adults
3) No medical contraindications
4) High motivation and appropriate expectations (both ~~child~~ patient, and family when appropriate~~, and family~~)

Bilateral cochlear implants are ~~covered~~ included on these lines. Simultaneous implantation appears to be more cost-effective than sequential implantation.

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1,207,374,414,468,545,546

Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:

Line 1 PREGNANCY

Acupuncture pairs on Line 1 for the following conditions and codes.

Hyperemesis gravidarum

ICD-10-CM code: O21.0, O21.1
ICD-9-CM codes: 643.00, 643.03, 643.10, 643.11, 643.13
Acupuncture pairs with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to 2 sessions of acupressure/acupuncture.

Breech presentation

ICD-10-CM code: O32.1xx0, O32.8xx0
ICD-9-CM codes: 652.20, 652.23
Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to 2 visits.

Back and pelvic pain of pregnancy

ICD-10-CM code: O33.0
ICD-9 codes: 648.70, 648.73
Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions.

Appendix A

Line 207 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE

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 15 total sessions, with documentation of meaningful improvement.

Line 374 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Acupuncture is included on Line 374 only for pairing with disorders of the spine with myelopathy and/or radiculopathy represented by the diagnosis codes G83.4, M47.1x, M47.2x, M50.0x, M50.1x, M51.1x, M54.1x/ICD-9-CM ~~344.60, 722.1, 722.2, 722.7 and 724.4~~ 344.6x, 721.1, 721.41, 721.42, 721.91, 722.7x, 723.4, 724.4, with referral, for up to 12 sessions.

Line 414 MIGRAINE HEADACHES

Acupuncture pairs on Line 414 for ICD-10-CM code G43.9/ICD-9-CM 346 Migraine, when referred, for up to 12 sessions.

Line 468 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 468 for osteoarthritis of the knee only, when referred, for up to 12 sessions.

Line 545 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT

Acupuncture pairs on Line 545 with the low back diagnoses (ICD-10-CM codes G83.4, M47.1x, M47.2x, M50.0x, M50.1x, M51.1x, M54.1x/ICD-9-CM ~~344.60, 722.1, 722.2, 722.7 and 724.4~~ 344.6x, 721.1, 721.41, 721.42, 721.91, 722.7x, 723.4, 724.4, when referred, for up to 12 sessions. Acupuncture pairs with chronic (>90 days) neck pain diagnoses (ICD-10-CM M53.82, M54.2, S13.4XXX, S13.8XXX/ICD-9-CM 723.1, 723.8, 723.9, 847.0), when referred, for up to 12 sessions.

Line 546 TENSION HEADACHES

Acupuncture is included on Line 546 for treatment of tension headaches (ICD-10-CM G44.2x/ICD-9-CM 307.81), when referred, for up to 12 sessions.

The development of this guideline note was informed by a HERC evidence-based guideline. See http://www.oregon.gov/oha/herc/Pages/blog-low-back-non-pharmacologic-intervention.aspx

GUIDELINE NOTE 103, BONE ANCHORED HEARING AIDS

Lines 317,450

Bone anchored hearing aids (BAHA, CPT 69714, 69715) are included on these lines when the following criteria are met:

1) The patient is ~~age 5 years or older~~ aged 5-20 years for implanted bone anchored hearing aids; headband mounted BAHA devices may be used for children under age 5
2) Treatment is for unilateral severe to profound hearing loss (defined as 71 dB hearing loss or greater at 500, 1000 and 2000 Hz) when the contralateral ear has normal hearing with or without a hearing aid
3) Traditional air amplification hearing aids and contralateral routing of signal (CROS) hearing aid systems are not indicated or have been tried and are found to be not effective.
4) Implantation is unilateral.

Use of BAHA for treatment of tinnitus is not included on these lines.

Appendix A

GUIDELINE NOTE 116, INTRAOCULAR STEROID TREATMENTS ~~IMPLANTS FOR CHRONIC NON-INFECTIOUS UVEITIS~~

Line 100,363

Intraocular steroid ~~implants~~ treatments (CPT 67027, 67028) are ~~only~~ included on Line 363 for pairing with uveitis (ICD-9-CM codes 360.12, 363.0x, 363.1x, 363.2x, /ICD-10-CM codes H30.0xx, H30.1xx, H30.89x, H30.9xx, H44.11x)~~, and only~~ when the following conditions are met uveitis is chronic, non-infectious, and there has been appropriate trial and failure, or intolerance of therapy, with local and systemic corticosteroids and/or immunosuppressive agents.

Intraocular steroid treatments (CPT 67027, 67028) are included on line 100 for treating chronic diabetic macular edema (ICD-9 362.07/ ICD-10 E11.311) only when there has been insufficient response to anti-VEGF therapies, and only when FDA approved treatments are utilized.

Effective January 1, 2016

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no "red flag" conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table. Electromyelography (CPT 96002-4) is not covered for non-specific low back pain.

Table D4
Low Back Pain - Potentially Serious Conditions ("Red Flags") and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
Cancer	• History of cancer with new onset of LBP	MRI	ESR
	• Unexplained weight loss • Failure to improve after 1 month • Age >50 years • Symptoms such as painless neurologic deficit, night pain or pain increased in supine position	Lumbosacral plain radiography	
	• Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	• Fever • Intravenous drug use • Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	• Urinary retention • Motor deficits at multiple levels • Fecal incontinence • Saddle anesthesia	MRI	None
Vertebral compression fracture	• History of osteoporosis • Use of corticosteroids • Older age	Lumbosacral plain radiography	None
Ankylosing	• Morning stiffness	Anterior-	ESR and/or

Appendix A

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
spondylitis	• Improvement with exercise • Alternating buttock pain • Awakening due to back pain during the second part of the night • Younger age	posterior pelvis plain radiography	CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	• Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month • Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	• Radiculopathic** signs present >1 month • Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI***	Consider EMG/NCV
Spinal stenosis	• Radiating leg pain • Older age • Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None
	• Spinal stenosis symptoms present >1 month	MRI**	Consider EMG/NCV

*** Level of evidence for diagnostic evaluation is variable**

**** Radiculopathic signs are defined for the purposes of this guideline as the objective evidence of ~~as in Guideline Note 37 with~~ any of the following:**

- **A. Markedly abnormal reflexes**
- **B. Segmental muscle weakness**
- **C. Segmental sensory loss**
- **D. EMG or NCV evidence of nerve root impingement**
- **E. Cauda equina syndrome,**
- **F. Neurogenic bowel or bladder**
- **G. Long tract abnormalities**

***** Only if patient is a potential candidate for surgery or epidural steroid injection**

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders. CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-adv-imaging-low-back.aspx

GUIDELINE NOTE 92, ACUPUNCTURE

Lines 1,207,~~374,~~414,468,~~545~~,546,MMM

Inclusion of acupuncture (CPT 97810-97814) on the Prioritized List has the following limitations:

Line 1 PREGNANCY

Acupuncture pairs on Line 1 for the following conditions and codes:

Hyperemesis gravidarum

ICD-10-CM code: O21.0, O21.1

Acupuncture pairs with hyperemesis gravidarum when a diagnosis is made by the maternity care provider and referred for acupuncture treatment for up to 2 sessions of acupressure/acupuncture.

Breech presentation

ICD-10-CM code: O32.1xx0, O32.8xx0

Acupuncture (and moxibustion) is paired with breech presentation when a referral with a diagnosis of breech presentation is made by the maternity care provider, the patient is between 33 and 38 weeks gestation, for up to 2 visits.

Back and pelvic pain of pregnancy

ICD-10-CM code: O33.0

Acupuncture is paired with back and pelvic pain of pregnancy when referred by maternity care provider/primary care provider for up to 12 sessions.

Line 207 DEPRESSION AND OTHER MOOD DISORDERS, MILD OR MODERATE

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 15 total sessions, with documentation of meaningful improvement.

~~Line 374 DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT~~

~~Acupuncture is included on Line 374 YYY only for pairing with disorders of the spine with myelopathy and/or radiculopathy represented by the diagnosis codes G83.4, M47.1x, M47.2x, M50.0x, M50.1x, M51.1x, M54.1x, with referral, for up to 12 sessions.~~

Line MMM CONDITIONS OF THE BACK AND SPINE

Acupuncture is included this line with visit limitations as in Guideline Note XXX.

Line 414 MIGRAINE HEADACHES

Acupuncture pairs on Line 414 for ICD-10-CM code G43.9 Migraine, when referred, for up to 12 sessions.

Line 468 OSTEOARTHRITIS AND ALLIED DISORDERS

Acupuncture pairs on Line 468 for osteoarthritis of the knee only, when referred, for up to 12 sessions.

~~Line 545 ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT~~

~~Acupuncture pairs on Line 545 with the low back diagnoses G83.4, M47.1x, M47.2x, M50.0x, M50.1x, M51.1x, M54.1x, when referred, for up to 12 sessions. Acupuncture pairs with chronic (>90 days) neck pain diagnoses (), when referred, for up to 12 sessions~~.

Line 546 TENSION HEADACHES

Acupuncture is included on Line 546 for treatment of tension headaches G44.2x, when referred, for up to 12 sessions.

GUIDELINE NOTE 105, EPIDURAL STEROID INJECTIONS~~, OTHER PERCUTANEOUS INTERVENTIONS~~ FOR ~~LOW~~ BACK PAIN

Lines ~~75, 159, 297,~~ MMM

Epidural lumbar steroid injections (CPT 62311, 64483, 64484) are included on this line for patients with persistent radiculopathy due to herniated disc, where radiculopathy is ~~as~~ defined ~~in Guideline Note 37~~ as showing objective evidence of one or more of the following:

A) Markedly abnormal reflexes

B) Segmental muscle weakness
C) Segmental sensory loss
D) EMG or NCV evidence of nerve root impingement
~~E) Cauda equina syndrome~~
~~F) Neurogenic bowel or bladder~~
~~G) Long tract abnormalities~~

One epidural steroid injection is included on these lines; a second epidural steroid injection may be provided after 3-6 months only if objective evidence of 3 months of sustained pain relief was provided by the first injection. It is recommended that shared decision-making regarding epidural steroid injection include a specific discussion about inconsistent evidence showing moderate short-term benefits, and lack of long-term benefits. Epidural lumbar steroid injections are not included on these lines for spinal stenosis or for patients with low back pain without radiculopathy.

~~The following interventions are not covered for low back pain, with or without radiculopathy:~~
- ~~facet joint corticosteroid injection~~
- ~~prolotherapy~~
- ~~intradiscal corticosteroid injection~~
- ~~local injections~~
- ~~botulinum toxin injection~~
- ~~intradiscal electrothermal therapy~~
- ~~therapeutic medial branch block~~
- ~~radiofrequency denervation~~
- ~~sacroiliac joint steroid injection~~
- ~~coblation nucleoplasty~~
- ~~percutaneous intradiscal radiofrequency thermocoagulation~~
- ~~radiofrequency denervation~~

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-percutaneous-low-back.aspx

GUIDELINE NOTE 137, BENIGN BONE ~~TUMORS~~ AND JOINT CONDITIONS AT HIGH RISK FOR COMPLICATIONS

Lines XXX, ~~154,358,484,496,~~ 533

Treatment of benign conditions of joints (ICD-9/ICD-10 727.89/M67.8x synovial chondromatosis, ICD-9/ICD-10 228.00/D18.09 synovial hemangioma, ICD-9/ICD-10 214.8/D17.79 lipoma arborescens, ICD-9/ICD-10 727.02/D48.1 tenosynovial giant cell tumor, and ICD-9/ICD-10 719.2x/ M12.2xx villonodular synovitis) are included on Line XXX for those conditions only when there are significant functional problems of the joint due to size, location, or progressiveness of the disease. Treatment of all other benign joint conditions are included on Line 533.

Treatment of benign tumors of bones (ICD-9 213.0-213.9, 526.0-526.2, 733.2x/ICD-10 D16.00-D16.9, K09.0, K09.1, M27.1, M27.40, M27.49, M85.40-M85.69) are included on ~~Lines 154, 358, 484 and 496~~ Line XXX for those neoplasms associated with pathologic fractures, at high risk of fracture, or which cause function problems including impeding joint function due to size, causing nerve compression, have malignant potential or are considered precancerous. Treatment of all other benign bone tumors are included on Line 533.

Appendix B

New Guideline Notes

Effective October 1, 2015

ANCILLARY GUIDELINE A3, IVC FILTERS FOR TRAUMA

It is the intent of the Commission that inferior vena cava (IVC) filter placement (CPT 37191) and subsequent repositioning and removal (CPT 37192, 37193) are covered when medically indicated for hospitalized patients with severe trauma resulting in prolonged hospitalization.

GUIDELINE NOTE XXX, TREATMENT OF UNILATERAL HEARING LOSS

Lines 317, 450

Unilateral hearing loss treatment is Included on these lines only for children aged 20 and younger with the following conditions:

1) For mild to moderate sensorineural unilateral hearing loss (defined as 26-70 dB hearing loss at 500, 1000 and 2000 Hz), first line intervention should be a conventional hearing aid, with second line therapy being contralateral routing of signal (CROS) system
2) For severe to profound unilateral sensorinerual hearing loss (defined as 71 dB hearing loss or greater at 500, 1000 and 2000 Hz), first line therapy should be a contralateral routing of signal (CROS) system with second line therapy being a bone anchored hearing aid (BAHA). BAHA SoftBand therapy may be first line therapy for children under age 5 or patients with severe ear deformities (e.g. microstia, severe canal atresia).

Cochlear implants are not included on these lines for unilateral hearing loss per guideline note 31 COCHLEAR IMPLANTATION.

GUIDELINE NOTE XXX, PROTON PUMP INHIBITOR THERAPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Lines 384, 519

Short term treatment (up to 8 weeks) of GERD with proton pump inhibitor therapy is included on line 384. Long term treatment is included on line 519.

GUIDELINE NOTE XXX, IVC FILTERS FOR ACTIVE PE/DVT

Lines 1, 83, 217, 285, 290

Inferior vena cava (IVC) filter placement (CPT 37191) is included on lines 1, 83, 217, 285, 290 for patients with active deep vein thrombosis/pulmonary embolism (DVT/PE) for which anticoagulation is contraindicated. IVC filter placement is not included on these lines for patients with DVT who are candidates for anticoagulation.

Retrieval of removable IVC filters (CPT 37193) is included on these lines when the benefits of removal outweigh the harms.

Appendix B

GUIDELINE NOTE XXX, TREATMENTS FOR BENIGN PROSTATE ENLARGEMENT WITH LOWER URINARY TRACT SYMPTOMS

Line 331

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 331 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

Effective January 1, 2016

GUIDELINE NOTE XXX, NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE

Line MMM

Patients seeking care for back pain should be assessed for potentially serious conditions ("red flag") symptoms requiring immediate diagnostic testing, as defined in Diagnostic Guideline D4. Patients lacking red flag symptoms should be assessed using a validated assessment tool (e.g. STarT Back Assessment Tool) in order to determine their risk level for poor functional prognosis based on psychosocial indicators.

For patients who are determined to be low risk on the assessment tool, the following services are included on this line:

- Office evaluation and education,
- Up to 4 total visits, consisting of the following treatments: OMT/CMT, acupuncture, and PT/OT. Massage, if available, may be considered.
- First line medications: NSAIDs, acetaminophen, and/or muscle relaxers. Opioids may be considered as a second line treatment, subject to the limitations on coverage of opioids in Guideline Note YYY OPIOID PRESCRIBING FOR CONDITIONS OF THE BACK AND SPINE. See evidence table.

For patients who are determined to be high risk on the validated assessment tool, the following treatments are included on this line:

- Office evaluation, consultation and education
- Cognitive behavioral therapy. The necessity for cognitive behavioral therapy should be re-evaluated every 90 days and coverage will only be continued if there is documented evidence of decreasing depression or anxiety symptomatology, improved ability to work/function, increased self-efficacy, or other clinically significant, objective improvement.

Appendix B

- Prescription and over the counter medications, opioid medications subject to the limitations on coverage of opioids in Guideline Note YYY OPIOID PRESCRIBING FOR CONDITIONS OF THE BACK AND SPINE. See evidence table.
- The following evidence-based therapies, when available, are encouraged: yoga, massage, supervised exercise therapy, intensive interdisciplinary rehabilitation
- A total of 30 visits per year of any combination of the following evidence-based therapies when available and medically appropriate. These therapies are only covered if provided by a provider licensed to provide the therapy and when there is documentation of measurable clinically significant progress toward the therapy plan of care goals and objectives using evidence based objective tools (e.g. Oswestry, Neck Disability Index, SF-MPQ, and MSPQ).
    1) Rehabilitative therapy (physical and/or occupational therapy), if provided according to GUIDELINE NOTE 6, REHABILITATIVE SERVICES. Rehabilitation services provided under this guideline also count towards visit totals in Guideline Note 6
    2) Chiropractic or osteopathic manipulation
    3) Acupuncture

These coverage recommendations are derived from the State of Oregon Evidence-based Guideline on the Evaluation and Management of Low Back Pain available here: http://www.oregon.gov/oha/herc/Pages/blog-low-back-non-pharmacologic-intervention.aspx

Intervention Category*	Intervention	Acute < 4 Weeks	Subacute & Chronic > 4 Weeks
Self-care	Advice to remain active	•	•
	Books, handout	•	•
	Application of superficial heat	•	
Nonpharmacologic therapy	Spinal manipulation	•	•
	Exercise therapy		•
	Massage		•
	Acupuncture		•
	Yoga		•
	Cognitive-behavioral therapy		•
	Progressive relaxation		•
Pharmacologic therapy (Carefully consider risks/harms)	Acetaminophen	•	•
	NSAIDs	•(▲)	•(▲)
	Skeletal muscle relaxants	•	
	Antidepressants (TCA)		•
	*Benzodiazepines***	•(▲)	•(▲)
	*Tramadol, opioids***	•(▲)	•(▲)
Interdisciplinary therapy	Intensive interdisciplinary rehabilitation		•

- Interventions supported by grade B evidence (at least fair-quality evidence of moderate benefit, or small benefit but no significant harms, costs, or burdens). No intervention was supported by grade "A" evidence (good-quality evidence of substantial benefit).

▲ *Carries greater risk of harms than other agents in table.*

NSAIDs = nonsteroidal anti-inflammatory drugs; TCA = tricyclic antidepressants.

*These are general categories only. Individual care plans need to be developed on a case by case basis. For more detailed information please see: http://www.annals.org/content/147/7/478.full.pdf

**Associated with significant risks related to potential for abuse, addiction and tolerance. This evidence evaluates effectiveness of these agents with relatively short term use studies. Chronic use of these agents may result in significant harms.

Appendix B

GUIDELINE NOTE YYY, OPIOID PRESCRIBING FOR CONDITIONS OF THE BACK AND SPINE

Lines MMM, S1, S2, S3

The following restrictions on opioid treatment apply to all diagnoses included on these lines.

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

1) During the first 6 weeks after the acute injury, flare or surgery, 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 lack of current or prior opioid misuse or abuse.
2) Treatment with opioids after 6 weeks, up to 90 days, requires the following
    a. Documented evidence of improvement of function of at least thirty percent as compared to baseline based on a validated tools.
    b. Must be prescribed in conjunction with therapies such as spinal manipulation, physical therapy, yoga, or acupuncture.
    c. 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) Further opioid treatment after 90 days may be considered ONLY when there is a significant change in status, such as a clinically significant verifiable new injury or surgery. In such cases, use of opioids is limited to a maximum of an additional 7 days. In exceptional cases, use up to 28 days may be included on these lines, subject to the criteria in #2 above.

For patients with chronic pain from diagnoses on these lines currently treated with long term opioid therapy, opioids must be tapered off, with a taper of about 10% per week recommended. By the end of 2016, all patients currently treated with long term opioid therapy must be tapered off of long term opioids for diagnoses on these lines. If a patient has developed dependence and/or addiction related to their opioids, treatment is available on line 4 SUBSTANCE USE DISORDER.

Appendix B

GUIDELINE NOTE ZZZ SURGICAL INTERVENTIONS FOR CONDITIONS OF THE BACK AND SPINE OTHER THAN SCOLIOSIS

Lines S1, S2

Surgical consultation/consideration for surgical intervention are included on these lines only for patients with neurological complications, defined as showing objective evidence of one or more of the following:

A) Markedly abnormal reflexes
B) Segmental muscle weakness
C) Segmental sensory loss
D) EMG or NCV evidence of nerve root impingement
E) Cauda equina syndrome
F) Neurogenic bowel or bladder
G) Long tract abnormalities

Spondylolithesis (ICD-9 738.4, 756.11-756.12 / ICD-10 M43.1x, Q76.2) is included on line S1 only when it results in spinal stenosis with signs and symptoms of neurogenic claudication. Otherwise, these diagnoses are included on line S2.

Surgical correction of spinal stenosis (ICD-9 721.1, 723.0, 724.0x / ICD-10 M48.0x) is only included on lines S1 for patients with:

1) MRI evidence of moderate to severe central or foraminal spinal stenosis AND
2) A history of neurogenic claudication, or objective evidence of neurologic impairment consistent with MRI findings.
3)

~~Otherwise, these diagnoses are included on line S2.~~ Only decompression surgery is covered for spinal stenosis; spinal fusion procedures are not covered for this diagnosis. Otherwise, these diagnoses are included on line S2.

For conditions on line S2, surgical interventions may only be considered after the patient has completed at least 6 months of conservative treatment, provided according to Guideline Note XXX NON-INTERVENTIONAL TREATMENTS FOR CONDITIONS OF THE BACK AND SPINE.

The following interventions are not ~~covered~~ included on these lines due to lack of evidence of effectiveness for the treatment of conditions on these lines, including cervical, thoracic, lumbar, and sacral conditions ~~back pain, with or without radiculopathy~~:

- facet joint corticosteroid injection
- prolotherapy
- intradiscal corticosteroid injection
- local injections
- botulinum toxin injection
- intradiscal electrothermal therapy
- therapeutic medial branch block
- radiofrequency denervation
- sacroiliac joint steroid injection
- coblation nucleoplasty
- percutaneous intradiscal radiofrequency thermocoagulation
- radiofrequency denervation

Appendix B

GUIDELINE NOTE AAA, SCOLIOSIS

Line S3

Non-surgical treatments of scoliosis (ICD-9 737.3x,737.43/ICD-10 M41.xx) are included on line CCC when

1) the scoliosis is considered clinically significant, defined as curvature greater than or equal to 25 degrees or
2) there is curvature with a documented rapid progression.

Surgical treatments of scoliosis are included on line ~~CCC~~ S3

1) only for children and adolescents (age ~~21~~ 20 and younger) with
2) a spinal curvature of greater than 45 degrees

Appendix C

Deleted Guidelines

GUIDELINE NOTE 37, DISORDERS OF SPINE WITH NEUROLOGIC IMPAIRMENT

Lines 374,545

Diagnoses are included on Line 374 when objective evidence of neurologic impairment or radiculopathy is present, as defined as:

A) Markedly abnormal reflexes
B) Segmental muscle weakness
C) Segmental sensory loss
D) EMG or NCV evidence of nerve root impingement
E) Cauda equina syndrome,
F) Neurogenic bowel or bladder
G) Long tract abnormalities

Otherwise, disorders of spine not meeting these criteria (e.g. pain alone) fall on Line 545.

GUIDELINE NOTE 41, SPINAL DEFORMITY, CLINICALLY SIGNIFICANT

Line 412

Clinically significant scoliosis is defined as curvature greater than or equal to 25 degrees or curvature with a documented rapid progression. Clinically significant spinal stenosis is defined as having MRI evidence of moderate to severe central or foraminal spinal stenosis in addition to a history of neurogenic claudication, or objective evidence of neurologic impairment consistent with MRI findings (see Guideline Note 37).

GUIDELINE NOTE 56, ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT

Line 545

Disorders of spine without neurologic impairment include any conditions represented on this line for which objective evidence of one or more of the criteria stated in Guideline Note 37 is not available

GUIDELINE NOTE 60, SPINAL DEFORMITY, NOT CLINICALLY SIGNIFICANT

Line 588

Scoliosis not defined as clinically significant included curvature less than 25 degrees that does not have a documented progression of at least 10 degrees

GUIDELINE NOTE 94, EVALUATION AND MANAGEMENT OF LOW BACK PAIN

Lines 374,545

Procedures for the evaluation and management of low back pain are included on these lines when provided subject to the State of Oregon Evidence-based Clinical Guidelines dated 10/2011 located at:
http://www.oregon.gov/oha/OHPR/pages/herc/evidence-based-guidelines.aspx.

Section 2.0

Staff Report

Prioritized List Errata
May, 2015

1) Add the bone transplant CPT code series (CPT 36680,38204-38215,38230-38243) to lines. These were mistakenly left off.
    a. 183 ACUTE LEUKEMIA, MYELODYSPLASTIC SYNDROME Treatment BONE MARROW TRANSPLANT
    b. 335 ACUTE PROMYELOCYTIC LEUKEMIA Treatment BONE MARROW TRANSPLANT
    c. 401 ACUTE MYELOID LEUKEMIA Treatment BONE MARROW TRANSPLANT

Section 3.0

Consent Agenda-

Straightforward Items

Straightforward Issues—May, 2015

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
V10.79	Personal history of other lymphatic and hematopoietic neoplasms	**162** NON-HODGKIN'S LYMPHOMAS **167** NON-HODGKIN'S LYMPHOMAS Treatment: BONE MARROW TRANSPLANT	V10.79 was on 3 lymphoma and leukemia lines from 2013 through 2014, then was moved to the Non-Covered List for the January 1, 2015 List. Similar V codes are on appropriate leukemia or lymphoma lines. All listed subdiagnoses in ICD-9 are lymphoma related.	Add V10.79 to lines 162 and 167. Remove V10.79 from the Services Recommended for Non-Coverage Table
V07.4 Z79.890	Hormone replacement therapy (postmenopausal)	**474** GONADAL DYSFUNCTION, MENOPAUSAL MANAGEMENT	ICD-9 V07.4 and ICD-10 Z79.890 are currently on the Services Recommended for Non-Coverage Table. Both codes can be used for a visit in which a woman is given a prescription for hormone replacement therapy.	Add V07.4 and Z79.890 to line 474 Remove V07.4 and Z79.890 from the Services Recommended for Non-Coverage Table
31561 31588	Laryngoscopy, direct, operative, with arytenoidectomy; with operating microscope or telescope Laryngoplasty, not otherwise specified (eg, for burns, reconstruction after partial laryngectomy)	**70** LARYNGEAL STENOSIS OR PARALYSIS WITH AIRWAY COMPLICATIONS	DMAP requested that 31561 and 31588 be paired with 478.74 (Stenosis of larynx). 478.74 is located on line 71 for surgical treatment and on line 364 DYSTONIA (UNCONTROLLABLE); LARYNGEAL SPASM AND STENOSIS for medical treatments.	Add 31561 and 31588 to line 70

Straightforward Issues—May, 2015

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
27570	Manipulation of knee joint under general anesthesia	**435** INTERNAL DERANGEMENT OF KNEE AND LIGAMENTOUS DISRUPTIONS OF THE KNEE, RESULTING IN SIGNIFICANT INJURY/IMPAIRMENT	DMAP requested that 27570 pair with 718.56 (Ankylosis of joint, lower leg). 718.56 is currently on lines 435 and 616 SPRAINS AND STRAINS OF ADJACENT MUSCLES AND JOINTS, MINOR. 27570 is currently located on lines 362,391,427.	Add 27570 to line 435
743.65	Specified congenital anomalies of lacrimal passages	**398** STRABISMUS WITHOUT AMBLYOPIA AND OTHER DISORDERS OF BINOCULAR EYE MOVEMENTS; CONGENITAL ANOMALIES OF EYE; LACRIMAL DUCT OBSTRUCTION IN CHILDREN **516** DYSFUNCTION OF NASOLACRIMAL SYSTEM IN ADULTS; LACRIMAL SYSTEM LACERATION	DMAP requested that 743.65 be added to line 398. Currently, 743.65 only appears on line 516. Similar codes such as 743.64 (Specified congenital anomalies of lacrimal gland) appear on both lines.	Add 743.65 to line 398
58661	Laparoscopy, surgical; with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)	**291** CANCER OF VAGINA, VULVA, AND OTHER FEMALE GENITAL ORGANS	DMAP requested that 58661 pair with 183.2 (Malignant neoplasm of fallopian tube). 58661 is the laparoscopic alternative to the open removal of adnexal structures (CPT 58943). 58661 is currently on 12 lines.	Add 58661 to line 291

Straightforward Issues—May, 2015

Code	Code Description	Line(s) Involved	Issue	Recommendation(s)
377.00	Papilledema, unspecified	**659** INTRACRANIAL CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY	ICD-9 377.00 is on line 659. This is basically a symptom which needs further evaluation. The ICD-10 equivalent, H47.10, is on the Diagnostic File.	Remove 377.00 from line 659 Advise DMAP to add 377.00 to the Diagnostic Workup file

Revised DMAP List Codes Requiring HERC Action

Question: should certain non-prioritized ICD-10 codes currently on DMAP lists (Diagnostic Workup File, Undefined, Informational, or Services Recommended for Non-coverage) be moved to lines on the Prioritized List?

Question source: HERC staff

Issue: MAP has revised the files that include the diagnosis codes that are not included on the Prioritized List. The current MAP "Exempt" and "Excluded" Lists will no longer exist.

HERC staff have been working with MAP to review and align placement of non-prioritized ICD-10 codes on the MAP lists. As part of this review, several codes have been identified that are better placed on lines of the Prioritized List.

HERC staff recommendation:

1) Make the List changes shown in the table below

ICD-10 Code	Code Description	Current Placement	Recommended Placement	Comments
G89.3	Neoplasm related pain (acute) (chronic)	Exempt	Cancer lines (any line with radiation therapy and/or chemotherapy in the treatment description)	
G89.4	Chronic pain syndrome	Services Recommended for Non Coverage	*For October 1 2015* **612** DISORDERS OF SOFT TISSUE *For January 1, 2016* **533** FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND RELATED DISORDERS	Will match fibromyalgia placement
H32	Chorioretinal disorders in diseases classified elsewhere	Services Recommended for Non Coverage	**363** CHORIORETINAL INFLAMMATION	
Z44.8	Encounter for fitting and adjustment of other external prosthetic devices	Ancillary	**381** DYSFUNCTION RESULTING IN LOSS OF ABILITY TO MAXIMIZE LEVEL OF INDEPENDENCE IN SELF-DIRECTED CARE CAUSED BY CHRONIC CONDITIONS THAT CAUSE NEUROLOGICAL DYSFUNCTION	

Guideline Note Errata

Issues:

1) Changes to Guideline Notes 29 and 51 were made at the January, 2015 VBBS meeting which did not include earlier edits made to these guideline notes. The changes made at the January meeting did not affect the previously changed sections of these guidelines. HERC staff realizes that it was the intent of the Commission to include all the changes adopted at various meetings, but needs to affirm the final approved wording with the Commission. The corrected guideline notes with all intended changes are shown below.
2) Guideline note 25 has errors of omission and typos

HERC staff recommendation:

1) Affirm that the guideline notes shown below are the correct versions to appear in the October 1, 2015 Prioritized List

GUIDELINE NOTE 29, TYMPANOSTOMY TUBES IN ACUTE OTITIS MEDIA

Line 394

Tympanostomy tubes (CPT 69436) are only included on this line as treatment for

1) recurrent acute otitis media (three or more well-documented and separate episodes in six months or four or more well-documented and separate episodes in ~~one year~~ the past 12 months with at least 1 episode in the past 6 months) ~~that fail appropriate medical management~~ in patients who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy, or

~~2) for patients who fail medical treatment secondary to multiple drug allergies or who fail two or more consecutive courses of antibiotics, or~~

3) 2) patients with complicating conditions (immunocompromised host, meningitis by lumbar puncture, acute mastoiditis, sigmoid sinus/jugular vein thrombosis by CT/MRI/MRA, cranial nerve paralysis, sudden onset dizziness/vertigo, need for middle ear culture, labyrinthitis, or brain abscess).

Patients with craniofacial anomalies, Down's syndrome, cleft palate, permanent hearing loss of 25dB or greater independent of otitis media with effusion, and patients with speech and language delay may be considered for tympanostomy if unresponsive to appropriate medical treatment or having recurring infections (without needing to meet the strict "recurrent" definition above).

Removal of retained tympanostomy tubes requiring anesthesia (CPT code 69424) or as an office visit, is included on line 427 as a complication, pairing with 385.83/ H74.8xX

GUIDELINE NOTE 51, CHRONIC OTITIS MEDIA WITH EFFUSION

Line 383, 502

Antibiotic and other medication therapy (including antihistamines, decongestants, and nasal steroids) are not indicated for children with chronic otitis media with effusion (OME) (without another appropriate diagnosis).

Patients with specific higher risk conditions (including craniofacial anomalies, Down's syndrome, and cleft palate, or documented speech and language delay) along with hearing loss and chronic otitis media with effusion are intended to be included on Line 383. Otherwise hearing loss associated with chronic otitis media with effusion (without those specific higher risk conditions) is only included on Line 502.

For coverage to be considered on either Line 383 or 502, there should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if documented hearing loss is greater than or equal to 25dB in the better hearing ear, tympanostomy surgery may be indicated, given short- but not long- term improvement in hearing. Formal audiometry is indicated for children with chronic OME present for 3 months or longer. Children with language delay, learning problems, or significant hearing loss should have hearing testing upon diagnosis. Children with chronic OME who are not at risk for language delay (such as those with hearing loss <25dB in the better hearing ear) or developmental delay (should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected.

Adenoidectomy is not indicated at the time of first pressure equalization tube insertion. It may be indicated in children over 3 years who are having their second set of tubes.

Removal of retained tympanostomy tubes requiring anesthesia (CPT code 69424) or as an office visit, is included on line 427 as a complication, pairing with 385.83/ H74.8xX.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-management-chronic-otitis.aspx

GUIDELINE NOTE 25, MENTAL HEALTH PROBLEMS IN CHILDREN AGE FIVE AND UNDER RELATED TO NEGLECT OR ABUSE

Line 177

ICD-10-CM T76.02xA and T76.02xD (Child neglect or abandonment, suspected), (ICD-10-CM T74.02xA and T74.02xD (Child neglect or abandonment, confirmed), T74.22xA and T74.22xD (Child sexual abuse, confirmed), T76.22xA and T76.22xD (Child sexual abuse, suspected), T76.12xA and T76.12xD (Child physical abuse, suspected, ~~subsequent encounter~~) or T74.12xA and T74.12xD (Child physical abuse, confirmed) and corresponding ICD-9-CM codes 995.52, 995.53, 995,54 and ~~–~~995.59, may be used in any children when there is evidence or suspicion of abuse or neglect. These codes are to be used when the focus of treatment is on the alleged child victim. This can include findings by child welfare of abuse or neglect; or statements of

abuse or neglect by the child, the perpetrator, or a caregiver or collateral report. Although these diagnoses can be used preventively, i.e. for children who are not yet showing symptoms, presence of symptoms should be demonstrated for interventions beyond evaluation or a short-term child or family intervention.

The codes T74.02xA, T74.02xD, T764.02XA, T764.02XD, T74.22xA, T74.22xD, T76.22xA, T76.22xD, T76.12xA, T76.12xD, T74.12xA or T74.12xD and corresponding ICD-9-CM codes 995.52, 995.53, 995,54 and 995.59 may be used in children age five and younger and, in these instances only, is limited to pairings with the following procedure codes:

- Assessment and Screening: 90791, 90792, H0002, H0031, H0032, T1023
- Family interventions and supports: 90832-90838, 90846, 90847, 90849, 90887, H0038, H0045, H2021, H2022, H2027, S5151, S9125, T1005
- Individual counseling and therapy: 90785, 90832-90838, 99201-99215
- Group therapy: 90832-90838, 90853, 90857, H2032
- Case Management: 90882, T1016
- Interpreter Service: T1013
- Medication management is not indicated for these conditions in children age 5 and under.

Gender Dysphoria Guideline Correction

Issue: The current gender dysphoria guideline has a sentence which was from an older version and makes coverage of cross sex hormone therapy unclear. The suggested wording simply clarifies the intent of the Commission.

HERC staff recommendation:

1) Modify GN127 as shown below

GUIDELINE NOTE 127, GENDER DYSPHORIA

Line 413

Hormone treatment ~~is included on this line only for use in delaying the onset of puberty and/or continued pubertal development~~ with GnRH analogues for delaying the onset of puberty and/or continued pubertal development is included on this line for gender questioning children and adolescents. This therapy should be initiated at the first physical changes of puberty, confirmed by pubertal levels of estradiol or testosterone, but no earlier than Tanner stages 2-3. Prior to initiation of puberty suppression therapy, adolescents must fulfill eligibility and readiness criteria and must have a comprehensive mental health evaluation. Ongoing psychological care is strongly encouraged for continued puberty suppression therapy.

Cross-sex hormone therapy is included on this line for treatment of adolescents and adults with gender dysphoria who meet appropriate eligibility and readiness criteria. To qualify for cross-sex hormone therapy, the patient must:

1. have persistent, well-documented gender dysphoria
2. have the capacity to make a fully informed decision and to give consent for treatment
3. have any significant medical or mental health concerns reasonably well controlled
4. have a thorough psychosocial assessment by a qualified mental health professional with experience in working with patients with gender dysphoria

Sex reassignment surgery is included for patients who are sufficiently physically fit and meet eligibility criteria. To qualify for surgery, the patient must:

1. have persistent, well documented gender dysphoria
2. have completed twelve months of continuous hormone therapy as appropriate to the member's gender goals unless hormones are not clinically indicated for the individual
3. have completed twelve months of living in a gender role that is congruent with their gender identity unless a medical and a mental health professional both determine that this requirement is not safe for the patient
4. have the capacity to make a fully informed decision and to give consent for treatment
5. have any significant medical or mental health concerns reasonably well controlled
6. have two referrals from qualified mental health professionals with experience in working with patients with gender dysphoria who have independently assessed the patient. Such an assessment should include the clinical rationale supporting the patient's request for surgery, as well as the rationale for the procedure(s)

Prenatal Genetic Testing Guideline Revisions

Questions:

1) Should Diagnostic Guideline D17, PRENATAL GENETIC TESTING be modified to clarify the CPT codes available for amniocentesis or chorionic villus sampling?
2) Should an additional CPT code be added to D17 for microarray testing?
3) Should various CPT codes used for prenatal testing be moved from the Diagnostic List to Line 1 PREGNANCY?
4) Should Diagnostic Guideline D17, PRENATAL GENETIC TESTING be modified to reflect updated recommendations for chromosomal microarray testing?

Question sources:

1) Holly Jo Hodges, MD, OHP Medical Director
2) Shelly Bosworth, certified genetic counselor from the Center for Genetics and Maternal Fetal Medicine in Eugene

Issues:

Amniocentesis CPT code issue

The CPT codes included in item #8 in the guideline are not an inclusive list of codes used for amniocentesis or chorionic villus sampling (CVS). The current 2 codes only code for the procedure itself, not the subsequent laboratory analysis. These CPT laboratory codes are all either on line 1 or the DMAP Diagnostic List. The medical director request was to clarify which CPT codes should be covered for either amniocentesis or CVS.

From Cori Feist:

- CVS ultrasound and procedure CPT: 59015 (Chorionic villus sampling, any method), 76945 (Ultrasonic guidance for chorionic villus sampling)
- CVS/amniocentesis karyotype CPT: 88235 (Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells), 88267 (Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding), 88280 (Chromosome analysis; additional karyotypes, each study)
- Amniocentesis ultrasound and procedure CPT: 59000 (Amniocentesis; diagnostic), 76946 (Ultrasonic guidance for amniocentesis, imaging supervision and interpretation)
- Interphase FISH for aneuploidy (either CVS or amniocentesis): 88271, 88275
- Chromosomal microarray (either CVS or amniocentesis): 81228 (Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants); some labs use 81229 (Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities) instead

Suggested by other clinicians:

- 88291 Cytogenetics and molecular cytogenetics, interpretation and report

Coding issue

Multiple CPT codes which are only used for amniocentesis or CVS are included in the DMAP Diagnostic List, but they are not visible to providers or medical directors. These codes are more appropriately placed on line 1 PREGNANCY.

CPT codes on Diagnostic List which only apply in pregnancy

76945 Ultrasonic guidance for chorionic villus sampling, imaging supervision and interpretation
76946 Ultrasonic guidance for amniocentesis, imaging supervision and interpretation
88235 Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells
88267 Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
88269 Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding

Microarray testing

Several genetic counselors have noted that the microarray testing section of D17 does not agree with current practice. The question is whether to allow microarray testing before karyotype—this test is faster and provides more information than karyotype. The question is based on the practical question of allowing a faster, more complete test. Shelly Bosworth recommended that item #9 in the guideline be changed to read: "….apparent on imaging, ~~and~~ karyotype is not required ~~normal~~." She felt that this would allow more timely and efficient testing and eliminate what might be an unnecessary test and expense.

In December, 2013, ACOG published an updated committee opinion regarding when fetal chromosomal microarray testing should be performed. This new committee opinion does not agree with the current prenatal genetic testing guideline. The current guideline states that "Array CGH (CPT 81228) when major fetal congenital anomalies apparent on imaging, and karyotype is normal." The ACOG opinion recommends chromosomal microarray analysis 1) in patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis, chromosomal microarray analysis is recommended. This test replaces the need for fetal karyotype; 2) in patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.

The only CPT code for microarray testing in D17 is CPT 81228 (Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)), however, 81229 (Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities) is also commonly used for this procedure.

Prenatal Genetic Testing Guideline Revisions

Expert Input

Cori Feist, certified genetic counselor at OHSU

The current ACOG & SMFM recommendations state array CGH can be used instead of karyotype for anyone having an invasive procedure because of the increased detection of significant abnormalities that would be missed by standard karyotyping. This is especially true when there are fetal structural anomalies.

I agree whole-heartedly with Shelly. But in my opinion, aCGH should be available for anyone who wants it regardless of whether or not there is an anomaly (but ESPECIALLY if there is a birth defect). At OHSU, we offer array to anyone having an invasive procedure and recommend it to anyone with a fetal anomaly. However, karyotype is still useful when Down syndrome/T18/T13 is strongly suspected. It should really be at the discretion of the physician/genetic counselor. I think providers educated about genetics can use their expertise to devise strategies on the most cost-effective, yet appropriate, testing for patients. I fully expect array to replace standard karyotype as a first-tier test. In the future, I expect karyotype to be used only to confirm or further explain array findings.
I expect this to become standard of care within the next 2-3 years. The reason we offer array to anyone is that 1/1,000 live births is affected with a microdeletion or microduplication syndrome that would have been missed by standard karyotype. Most of these syndromes do not have ultrasound findings but have significant morbidity and mortality. These syndromes are only slightly less common than Down syndrome (1/700 live births), which we spend a considerable amount of time and money screening/testing for in pregnancy.

It's also hard to tell a woman having amniocentesis that she can only have karyotype, which will detect about 90-95% of all known chromosome abnormalities, but not an array which will detect >99% of all known chromosome abnormalities. It's like telling her she can only have some of the information about her baby's health, but not all.

Standard karyotype generally costs about $1,000-1,500. The results take about 14 days, so many physicians recommend FISH for rapid results. FISH costs another $1,000-1,500. Prenatal microarray generally costs about $1,500-2,000. Results take 7-10 days because cultured cells are not required.

Prenatal Genetic Testing Guideline Revisions

HERC staff recommendation:

1) Modify Diagnostic Guideline D17 as shown below
    a. CPT code changes
        i. Add CPT 81229 (Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities) to #9, as this CPT code is commonly used for chromosomal array testing.
        ii. Add CPT 76945, 76946, 88235, 88267, 88280, 88291 to #8 to specify the ultrasound and laboratory testing portion of the amniocentesis/CVS
        iii. Alternative: remove all CPT codes from the guideline note. These codes are difficult to ensure complete inclusion.
    b. Simple wording clarification regarding the definition of CVS
    c. Modify the entry for microarray testing
        i. CGH testing provides more information for about the same cost as karyotyping. CGH results are available more quickly and may result in less FISH testing for an overall cost savings. The change also helps to prevent unnecessary duplicative testing
2) Add the following CPT codes to line 1 PREGNANCY and advise DMAP to remove from the Diagnostic List. These codes are only used during pregnancy.
    a. 76945 Ultrasonic guidance for chorionic villus sampling, imaging supervision and interpretation
    b. 76946 Ultrasonic guidance for amniocentesis, imaging supervision and interpretation
    c. 88235 Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells
    d. 88267 Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
    e. 88269 Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding

DIAGNOSTIC GUIDELINE D17, PRENATAL GENETIC TESTING

The following types of prenatal genetic testing and genetic counseling are covered for pregnant women:

1. Genetic counseling (CPT 96040, HPCPS S0265) for high risk women who have family history of inheritable disorder or carrier state, ultrasound abnormality, previous pregnancy with aneuploidy, or elevated risk of neural tube defect.
2. Genetic counseling (CPT 96040, HPCPS S0265) prior to consideration of chorionic villus sampling (CVS), amniocentesis, microarray testing, Fragile X, and spinal muscular atrophy screening
3. Validated questionnaire to assess genetic risk in all pregnant women
4. Screening high risk ethnic groups for hemoglobinopathies (CPT 83020, 83021)
5. Screening for aneuploidy with any of five screening strategies [first trimester (nuchal translucency, beta-HCG and PAPP-A), integrated, serum integrated, stepwise sequential, and contingency] (CPT 76813, 76814, 81508-81511)
6. Cell free fetal DNA testing (CPT 81507) for evaluation of aneuploidy in women who have an elevated risk of a fetus with aneuploidy (maternal age >34, family history or elevated risk based on screening).
7. Ultrasound for structural anomalies between 18 and 20 weeks gestation (CPT 76811, 76812)

8. CVS or amniocentesis (CPT 59000, 59015, 76945, 76946, 88235, 88267, 88280, 88291) for a positive aneuploidy screen, maternal age >34, fetal structural anomalies, family history of inheritable chromosomal disorder or elevated risk of neural tube defect.
9. Array CGH (CPT 81228, 81229) when major fetal congenital anomalies are apparent on imaging, or with normal imaging when array CGH would replace karyotyping ~~and karyotype is normal~~
10. FISH testing (CPT 88271, 88275) only if karyotyping is not possible due a need for rapid turnaround for reasons of reproductive decision-making (i.e. at 22w4d gestation or beyond)
11. Screening for Tay-Sachs carrier status (CPT 81255) in high risk populations. First step is hex A, and then additional DNA analysis in individuals with ambiguous Hex A test results, suspected variant form of TSD or suspected pseudodeficiency of Hex A
12. Screening for cystic fibrosis carrier status once in a lifetime (CPT 81220-81224)
13. Screening for fragile X status (CPT 81243, 81244) in patients with a personal or family history of
    a. fragile X tremor/ataxia syndrome
    b. premature ovarian failure
    c. unexplained early onset intellectual disability
    d. fragile X intellectual disability
    e. unexplained autism through the pregnant woman's maternal line
14. Screening for spinal muscular atrophy (CPT 81401) once in a lifetime
15. Screening those with Ashkenazi Jewish heritage for Canavan disease (CPT 81200), familial dysautonomia (CPT 81260), and Tay-Sachs carrier status (CPT 81255)
16. Expanded carrier screening only for those genetic conditions identified above

The following genetic screening tests are not covered:

1. Serum triple screen
2. Screening for thrombophilia in the general population or for recurrent pregnancy loss
3. Expanded carrier screening which includes results for conditions not explicitly recommended for coverage

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/CoverageGuidances/Prenatal%20Genetic%20Testing.pdf

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine

COMMITTEE OPINION

Number 581 • December 2013

(Replaces No. 446, November 2009)

(See also Practice Bulletin No. 88)

The American College of Obstetricians and Gynecologists Committee on Genetics
Society for Maternal-Fetal Medicine

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

The Use of Chromosomal Microarray Analysis in Prenatal Diagnosis

ABSTRACT: Chromosomal microarray analysis is a technique that identifies chromosomal abnormalities, including submicroscopic abnormalities that are too small to be detected by conventional karyotyping. Like conventional fetal karyotyping, prenatal chromosomal microarray analysis requires direct testing of fetal tissue and thus can be offered only with chorionic villus sampling or amniocentesis. Based on the results of a *Eunice Kennedy Shriver* National Institute of Child Health and Human Development multicenter trial and of prior studies, prenatal chromosomal microarray analysis is most beneficial when ultrasonographic examination identifies fetal structural anomalies. The potential for complex results and detection of clinically uncertain findings identified by prenatal chromosomal microarray testing can result in substantial patient anxiety. This underscores the critical need for comprehensive patient pretest and posttest genetic counseling from qualified personnel about the benefits, limitations, and results of testing so that patients can make informed decisions. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine offer background information as well as recommendations regarding the application of chromosomal microarray technology in the prenatal setting.

Chromosomal microarray analysis is a method of measuring gains and losses of DNA throughout the human genome. It is a high-resolution whole-genome screening that can identify major chromosomal aneuploidy as well as the location and type of specific genetic changes that are too small to be detected by conventional karyotyping. It is considered to be a first-tier test in the genetic evaluation of infants and children with unexplained intellectual disability, congenital anomalies, or autism spectrum disorder. Within this population, chromosomal microarray analysis has been useful in detecting causative genomic imbalances or genetic mutations in as many as 15% of children with a normal conventional karyotype (1, 2).

The utility of microarray in the diagnosis of genetic abnormalities in infants and children stimulated interest in its application in the prenatal setting. Several early descriptive studies demonstrated the potential benefit of chromosomal microarray analysis for fetal abnormalities beyond conventional fetal karyotyping (3–7). Until recently, however, the broad application of this technology was limited by a lack of large population-based studies. In December 2012, researchers published the results of a large cohort study supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) that compared the efficacy of chromosomal microarray analysis with conventional karyotyping in prenatal diagnosis (8). In this joint document, the American College of Obstetricians and Gynecologists (the College) and the Society for Maternal-Fetal Medicine offer recommendations regarding the application of chromosomal microarray technology in the prenatal setting. For recommendations on prenatal testing for aneuploidy, please refer to College Practice Bulletin Number 88, *Invasive Prenatal Testing for Aneuploidy* (9).

Microarray Technology

Chromosomal microarray analysis is a technique that can identify major chromosomal aneuploidy as well as submicroscopic abnormalities that are too small to be detected by conventional karyotyping. In contrast to the

conventional karyotype, which detects primarily genetic abnormalities resulting from large changes in the number or structure of chromosomes, microarray analysis also can provide information at the submicroscopic level throughout the human genome. Duplicated or deleted sections of DNA are known as copy number variants. These submicroscopic rearrangements may account for a sizable portion of the human genetic disease burden, with some estimates as high as 15% (10). The probability of finding significant copy number variants is highly correlated with the presence of structural fetal abnormalities, although significant copy number variants also can be identified in structurally normal fetuses. Another type of DNA alteration is a single-nucleotide polymorphism (SNP). An SNP is a DNA variation in which a single nucleotide in the genome sequence is altered. This can occur between two different individuals or between paired chromosomes of the same individual and may or may not cause disease. In contrast with Down syndrome and other common trisomies, copy number variants or SNPs identified using chromosomal microarray analysis are not associated with increasing maternal age.

There are two types of microarrays used in clinical prenatal testing: comparative genomic hybridization (CGH) and SNP arrays. Although both of these techniques detect copy number variants, they identify different types of genetic variation. With each of these technologies, DNA from a fetal sample is hybridized to a DNA chip or array containing DNA fragments of known identity (known sequences). The fetal DNA to be studied is typically derived from amniocytes or chorionic villi samples. With CGH, the fetal DNA is labeled with one color of fluorescent dye, while the control DNA (of known genetic sequences) is labeled with another color. The relative intensity of the different colors (the relative amount of fetal DNA versus control DNA) is compared. Duplications or deletions are detected as regions with a higher or lower hybridization signal than the control sample. Comparative genomic hybridization detects copy number variation for relatively large deletions or duplications, including whole-chromosome duplications (trisomy), but CGH cannot detect triploidy. With SNP arrays, only fetal DNA is hybridized to the array platform, and the presence or absence of specific known DNA sequence variants is evaluated by signal intensity to provide a genome-wide copy number analysis. Single-nucleotide polymorphism arrays detect homozygosity or heterozygosity (identical or different stretches of DNA) and, therefore, can demonstrate the extent of consanguinity (shown as regions of homozygosity), as well as triploidy and uniparental disomy.

Arrays also can be "targeted" and focus on copy number variants of known pathogenicity instead of testing the entire genome. Targeted arrays are designed to primarily detect copy number variants known to cause clinical findings, while minimizing the detection of variants of uncertain clinical significance. Variants of unknown significance describe identified DNA changes that either have not yet been reliably characterized as benign or pathogenic or that are associated with a variable phenotype (variable penetrance). In contrast, whole-genome arrays are designed to provide greater coverage across the genome and, therefore, optimize detection, but may be more likely to identify differences that have uncertain clinical consequences. Because such a large number of potential findings are possible with any type of microarray technology, databases are used to determine if specific copy number variants have been previously reported and whether they are considered pathogenic, benign, or of unknown significance.

Chromosomal Microarray Versus Karyotype

The primary advantage of chromosomal microarray analysis over the conventional karyotype is the higher resolution, which yields more genetic information. In addition, because DNA usually can be obtained from uncultured specimens, results are usually available more quickly than with karyotyping, which requires cultured cells. Because chromosomal microarray analysis does not require dividing cells, it may be useful in the evaluation of fetal demise or stillbirth, in which the culturing of macerated tissue is frequently unsuccessful (11). In addition, chromosomal microarray analysis is a standardized procedure that involves the use of computerized analysis, whereas karyotyping involves microscopic examination of stained chromosomes and may be more subjective and prone to human error.

In the 2012 NICHD multicenter trial that compared prenatal chromosomal microarray analysis with traditional fetal karyotyping, analysis performed using array CGH identified all clinically significant aneuploidies and unbalanced translocations diagnosed with traditional fetal karyotyping (8). Consistent with previous studies (12), array CGH identified additional clinically significant abnormalities in approximately 6% of fetuses with ultrasonographic abnormalities and a normal conventional karyotype. Further, array CGH detected an abnormality in 1.7% of fetuses with a normal ultrasonographic examination result and a normal karyotype (8). Thus, based on the results of the NICHD multicenter trial and prior studies, prenatal chromosomal microarray analysis is most beneficial when ultrasonographic examination identifies fetal structural anomalies. Unlike conventional karyotyping, chromosomal microarray analysis cannot detect balanced inversions, balanced translocations, or all cases of tissue mosaicism. In addition, not all microarrays can detect triploidy, although most triploid fetuses can be identified by ultrasonography. In the NICHD trial, as anticipated, neither triploidies nor balanced translocations were identified by array CGH, and samples demonstrating chromosomal mosaicism were excluded from the analysis.

A limitation of chromosomal microarray analysis is the potential to identify copy number variants of unknown clinical significance. This occurred in 3.4% of cases in the NICHD trial (8). Such results were classified as "likely benign" in 1.8% of cases and "likely pathogenic" in 1.6%. In some cases, the significance was uncertain because the findings were rare or novel, whereas some results were known to have variable penetrance. That is, such results indicate a susceptibility to a particular outcome, such as autism, but not a certainty that this will occur. In some cases, evaluation of parental samples can help clarify whether or not this is an inherited finding or a new finding in the offspring; however, the clinical outcome may remain unclear. Of note, the interpretation of many such results changed over the course of the study as additional information became available regarding the significance of some copy number variants. Thus, interpretation of results is expected to improve as knowledge of the human genome grows and the use of databases to link clinical findings with copy number variants becomes more robust.

Need for Patient Counseling

In addition to the data regarding genetic testing results, the NICHD study raised several important considerations for the clinical application of chromosomal microarray analysis in the prenatal setting. The potential for detection of clinically uncertain and complicated findings with prenatal chromosomal microarray analysis can result in substantial patient anxiety. This underscores the critical need for comprehensive patient pretest and posttest genetic counseling from qualified personnel such as a geneticist or genetic counselor about the benefits, limitations, and results of testing so that patients can make informed decisions. Information that should be shared with patients who are considering prenatal chromosomal microarray analysis is provided for use before referral for genetic counseling (see Box 1).

In the NICHD study, an independent multidisciplinary advisory group composed of clinical geneticists, cytogeneticists, and a genetic counselor was convened to evaluate all copy number variants not known to be benign to determine how patients with these findings should be counseled. Following the NICHD trial, a subset of women in the study who received abnormal results was interviewed regarding their experience (13). In general, the women reported a need for extensive support and counseling regarding the analysis. Although the NICHD trial included an informed consent process, many of these women reported a lack of good understanding of the potential for uncertain results and noted feeling great distress on receiving such information and then needing to decide how to proceed with the pregnancy (13).

In addition to copy number variants of uncertain clinical significance, chromosomal microarray analysis can detect genetic abnormalities associated with adult-onset disorders (eg, *BRCA* mutations or Charcot-Marie-Tooth disease), which may be inherited from an asymptomatic parent. In addition, some types of arrays can identify evidence of consanguinity and nonpaternity. The type and amount of information reported varies depending on the type of array used as well as the policy of the laboratory that performs the analysis (14). Therefore, genetic counseling and informed consent is essential before patients undergo testing with this technology.

Box 1. Information to Share With Patients Before Prenatal Chromosomal Microarray Analysis

- Chromosomal microarray analysis will identify almost all of the abnormalities that are identified by fetal karyotyping and may identify additional specific genetic diseases. It will not identify all genetic disorders.
- Diseases may be identified for which the clinical presentation may vary greatly and range from mild to severe. It may not be possible to predict what the outcome will be in a given patient.
- The test may identify consanguinity (a close blood relationship or incest) or nonpaternity.
- Genetic changes may be identified that may or may not cause disease. Samples from both parents may be required to help understand the significance of these results.
- Test results may identify adult-onset diseases that will not affect health during the newborn period or childhood but may have unknown severity later in life. Identification of such findings may also indicate that one of the parents has the same adult-onset disease but has not yet developed symptoms.

Recommendations

The College and the Society for Maternal-Fetal Medicine offer the following recommendations for the use of chromosomal microarray analysis in prenatal diagnosis:

- In patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis, chromosomal microarray analysis is recommended. This test replaces the need for fetal karyotype.
- In patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.
- Most genetic mutations identified by chromosomal microarray analysis are not associated with increasing maternal age; therefore, the use of this test for prenatal diagnosis should not be restricted to women aged 35 years and older.

- In cases of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired, chromosomal microarray analysis on fetal tissue (ie, amniotic fluid, placenta, or products of conception) is recommended because of its increased likelihood of obtaining results and improved detection of causative abnormalities.
- Limited data are available on the clinical utility of chromosomal microarray analysis to evaluate first-trimester and second-trimester pregnancy losses; therefore, this is not recommended at this time.
- Comprehensive patient pretest and posttest genetic counseling from qualified personnel such as a genetic counselor or geneticist regarding the benefits, limitations, and results of chromosomal microarray analysis is essential. Chromosomal microarray analysis should not be ordered without informed consent, which should be documented in the medical record and include discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease.

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The use of chromosomal microarray analysis in prenatal diagnosis. Committee Opinion No. 581. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;122:1374–7.

Open Wound of Ear Drum

Question: Should we merge lines containing open wound of ear drum diagnoses?

Question source: HERC staff

Issue: Up to and including the present Prioritized list, there have been two lines for open wound of ear drum, a surgical line (currently line 436) which contains only two diagnosis codes (ICD-9 872.61, 872.71 open wound of ear drum complicated and uncomplicated) and a medical line (currently line 563) which contained a range of diagnosis codes, including open wound of ear drum and perforation of ear drum. The chronic otitis media line (currently line 481) contains a range of diagnosis codes for perforations of the ear drum as well as the surgical treatment codes.

In October, 2013, the surgical line for open wound of ear drum was merged with the chronic otitis media line. The surgical open wound of the ear drum was a covered line at the time, and merged into the chronic otitis media line, which was uncovered. This merge was done because there was only one diagnosis code on the open wound of the ear drum line that was not duplicated on the chronic otitis media line and all the appropriate treatment CPT codes were on the chronic otitis media line. There was concern that the covered wound line would start to be used for treatment of what were actually perforations and belonged on the chronic otitis media line. There was also a thought that open wounds of the ear drum due to trauma/injury are not treated significantly differently in practice from spontaneous ruptures of the ear drum and therefore should not be on different priority lines.

During the 2013 line merge discussion, it was not recognized or discussed that there was also a medical line for open wound of the ear drum. This line has a lower priority that the chronic otitis media line. This medical line contains only one ICD-9 diagnosis (872.71 Open wound of ear drum, complicated) which is not also found on the chronic otitis media line.

During the ICD-10 ENT review, the ENT experts advised moving all the ear drum perforation codes (H72.xx) off of the chronic otitis media line and onto the two open wound of ear drum lines. However, the equivalent ICD-9 codes were not moved from the chronic otitis media line during the conversion back to the “bilingual list.”

The usual treatment for a perforation or wound of the ear drum is observation. Most heal on their own, or require antibiotic ear drops. Those openings that do not spontaneously close and that cause hearing loss are normally closed with a surgical tympanoplasty.

HERC staff summary

1) The ICD-10 reviewers and VBBS/HERC have previously indicated that wounds of the eardrum should be prioritized similarly to spontaneous perforations of the ear drum.
2) Currently, perforations of the ear drum are prioritized with chronic otitis media.

Open Wound of Ear Drum

January 1, 2015 Prioritized List

Line: 436
Condition: OPEN WOUND OF EAR DRUM
Treatment: TYMPANOPLASTY
ICD-9: 872.61,872.71
ICD-10: H72.00-H72.13,H72.2x1-H72.93,S09.20xA-S09.20xD,S09.21xA-S09.21xD, S09.22xA-S09.22xD
CPT: 64505-64530,69450,69610-69643,96127,98966-98969,99051,99060,99070,99078, 99184,99201-99239,99281-99285,99291-99404,99408-99412,99429-99449, 99468-99480,99487-99498,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463,G0466,G0467

Line: 481
Condition: CHRONIC OTITIS MEDIA (See Guideline Notes 51,64,65,76)
Treatment: PE TUBES/ADENOIDECTOMY/TYMPANOPLASTY, MEDICAL THERAPY
ICD-9: 380.50-380.53,381.10-381.89,382.1-382.3,382.9,383.1,383.20-383.31,383.9, 384.20-384.9
ICD-10: H65.20-H65.33,H65.411-H65.93,H66.10-H66.23,H66.3x1-H66.3x9,H68.001-H68.009,H68.021-H68.139,H69.00-H69.03,H70.10-H70.13,H70.90-H70.93,H73.10-H73.13,H73.811-H73.93,H74.01-H74.09,H74.40-H74.43,H74.8x1-H74.93,H95.111-H95.119,H95.131-H95.199
CPT: 42830-42836,64505-64530,69210-69222,69310,69420-69511,69601-69650,69700, 69801,69905,69910,69979,92562-92565,92571-92577,92590,92591,96127,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404, 99408-99412,99429-99449,99468-99480,99487-99498,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463,G0466,G0467

Line: 563
Condition: OPEN WOUND OF EAR DRUM (See Guideline Notes 64,65)
Treatment: MEDICAL THERAPY
ICD-9: 384.20,384.21,384.22,384.23,384.24,384.25,872.61,872.71
ICD-10: H72.00-H72.13,H72.2x1-H72.93,S09.20xA-S09.20xD,S09.21xA-S09.21xD, S09.22xA-S09.22xD
CPT: 96127,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285, 99291-99404,99408-99412,99429-99449,99468-99480,99487-99498,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463,G0466,G0467

January 1, 2016 Prioritized List

479 CHRONIC OTITIS MEDIA; OPEN WOUND OF EAR DRUM

561 OPEN WOUND OF EAR DRUM Treatment: MEDICAL THERAPY

Open Wound of Ear Drum

HERC staff recommendation:

1) Merge line 561 OPEN WOUND OF EAR DRUM Treatment: MEDICAL THERAPY with line 479 CHRONIC OTITIS MEDIA, OPEN WOUND OF EAR DRUM Treatment: PE TUBES/ ADENOIDECTOMY/ TYMPANOPLASTY, MEDICAL THERAPY and keep at line 479 for the January 1, 2016 Biennial Review Prioritized List
    a. ICD-9 (872.71 Open wound of ear drum, complicated) would be added to line 479
    b. All ICD-10 codes for perforation of ear drum (H72.xx and S02.2xx) would be added to line 479
    c. Follows previous VBBS/HERC intent to merge the open wound of ear drum line with the chronic otitis media line
2) **Other options (not preferred)**:
    a. Keep line 561 as a medical treatment only line. This is highly problematic as line 479 already contains medical therapy procedure codes.
    b. Put all wound/perforation diagnosis codes on line 561, remove from line 479. Add all tympanoplasty CPT codes to line 561. Rename line 561 OPEN WOUND AND PERFORATIONS OF EAR DRUM, Treatment MEDICAL AND SURGICAL TREATMENT. This is problematic as it prioritizes repair of ear drum perforations/wounds lower than treatment of chronic otitis media, which is not the previous prioritization intent
    c. Return to the previous line structure, with two separate lines for surgical and medical treatment of open wounds of the eardrum. These lines would contain both open wound and perforation diagnoses per the ICD-10 reviewers. This is problematic as it allows treatment for ear drum perforations/wounds which is not available currently.

Section 4.0

New Discussion Items

Yttrium Internal Radiation Therapy for Liver Cancer

Question: should yttrium internal radiation therapy (CPT 79445) be covered for liver cancers or isolated colon cancer metastases to the liver?

Question source: Alison Little, MD, MPH, OHP medical director

Issue: Yttrium-90 is a radioactive element that can be injected into the arterial system of the liver to treat non-surgically resectable liver cancer or liver metastases from colon cancer. This treatment was removed from the Prioritized List in 2006. Dr. Little requested a re-review of this topic, as she found a Hayes report giving limited support to this therapy.

From Dr. Little:

> from Hayes (TACE is the arterial embolization, TARE is the yttrium):
> Per Hayes, TACE is accepted treatment (Grade B), and one RCT found prolonged survival. For TARE for treatment of primary liver cancer, they give it a C rating, and state the following: "Transarterial radioembolization (TARE) with yttrium-90 (90Y) appears to have comparable clinical outcomes to other intra-arterial therapies (IATs), specifically transarterial chemoembolization (TACE), as well as sorafenib." The majority of the studies for TARE versus TACE report comparable results for survival and tumor response, with limited inconsistent evidence suggesting that TARE may result in better survival. Limited inconsistent evidence suggests that TARE may have more favorable time to progression compared with TACE. TARE with 90Y has consistently fewer overall hospitalization days versus TACE, but inconsistent results for rehospitalization. The evidence for TARE with 90Y suggests comparable safety, with more hepatic dysfunction, postembolization syndrome, and lymphopenia, but less hematologic complications, abdominal pain, and fever than TACE."

From the April, 2006 HOSC minutes (line 489 was liver cancer):

> Treatment of Liver Cancer: Little explained that the Commission previously considered embolization for tumor destruction using yttrium and elected not to place it on the list; however, the code for embolization remains. A case at OMAP resulted in her questioning whether appropriate treatments were listed on this line. Olson explained the different treatments, as follows: Radiofrequency ablation is insertion of a an ultrasound catheter with use of heat to kill tissue, cryotherapy is the same thing except using a liquid nitrogen probe, chemoembolization is when a catheter is inserted into an artery that feeds the tumor, chemotherapy is infused then the artery is embolized with gel foam. The yttrium procedure does not involve embolization. All of these are used to treat both primary liver cancer and metastatic colon cancer. Saha asked if any of these treatments were controversial except the yttrium. Olson stated that for colon cancer metastatic only to the liver, resection can result in 25% long-term survival. Hepatic artery infusion with 5-FU improved outcomes as well. The data on RFA and cryotherapy is weaker. Chemoembolization results in shrinkage of tumor, but causes severe side-effects. RFA and yttrium have fewer side effects. Hepatic artery infusion is also effective, but systemic chemotherapy has improved to the point that it is rarely done anymore. Saha clarified that the task today is to determine if any of these treatments should be removed from the List. Olson stated that there are some cases where an isolated metastasis is too close to the bile duct to operate, and in those cases it makes sense to use RFA or cryo. He also said that yttrium treatment costs approximately $70,000.
> Decision: Line 489: Delete 79445 – Radiopharmaceutical therapy, by intra-arterial particulate

Yttrium Internal Radiation Therapy for Liver Cancer

Current Prioritized List status:
79445 (Radiopharmaceutical therapy, by intra-arterial particulate administration) is on 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

Line 320 CANCER OF LIVER

Evidence

1) **NICE 2013,** guidance for use of yttrium 90 SIRT for primary hepatocellular carcinoma
    a. Current evidence on the efficacy and safety of selective internal radiation therapy (SIRT) for primary hepatocellular carcinoma is adequate for use with normal arrangements for clinical governance, consent and audit. Uncertainties remain about its comparative effectiveness, and clinicians are encouraged to enter eligible patients into trials comparing the procedure against other forms of treatment.
        i. 2 non-randomized comparative studies (n=331 patients)
            1. SIRT vs transarterial chemoembolization (TACE)
            2. Both found improved response rates for SIRT
            3. One study found improved survival for SIRT (42 months vs 19 months)
            4. One study found increased length of time to progression for SIRT
        ii. 1 non-randomized comparative study (N=26 patients)
            1. SIRT vs cisplatin
            2. Found no significant differences in quality of life or functional assessment between treatment groups
        iii. 2 case series (N=326 patients), SIRT treatment
        iv. Death, radiation pneumonitis, post-embolization syndrome (fatigue, flu-like symptoms) and local ulceration were listed as complications
            1. Death and post-embolization syndrome rates no different from TACE
        v. Other comments: The Committee noted wide variation in the published evidence about prior and adjunctive treatments that patients received. This made interpretation of the effect of SIRT difficult.
2) **NICE 2013**, guidance on SIRT for primary intrahepatic cholangiocarcinoma
    a. Current evidence on the safety and efficacy of selective internal radiation therapy (SIRT) for primary intrahepatic cholangiocarcinoma is limited in both quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.
3) **CTAF 2010**, SIRT for inoperable colorectal metastases to the liver

a. Twenty-two case series with data on patients with metastatic colorectal cancer have demonstrated that it is feasible to deliver radiation therapy to liver tumors and achieve at least partial remission in a substantial proportion of patients with relatively few serious adverse events. Procedure specific adverse events such as radiation pneumonitis, GI ulceration and radiation induced liver disease have been characterized and pretreatment planning strategies have been developed to limit their frequency and severity. The results of the two randomized trials described above are encouraging, but not definitive. Both demonstrated improvements in disease-free survival and a trend towards longer overall survival. However, the trials were very small (less than 100 patients in total) and the response rates in the control groups were lower than expected. Furthermore, the control groups did not use the standard first-line therapy for colorectal cancer metastatic only to the liver. Ongoing clinical trials that are randomizing over 800 newly diagnosed patients to first line chemotherapy with or without RE should define the efficacy of combined therapy and the associated additional toxicity. Similarly, the data on the utility of RE as salvage therapy for patients who have failed multiple rounds of chemotherapy is limited and immature.

b. It is recommended that radioembolization for the treatment of inoperable liver metastases from colorectal cancer does not meet CTAF TA Criterion 2 through 5 for improvement in health outcomes.

4) **Townsend 2009**, Cochrane review of yttrium selective internal radiation therapy (SIRT) for liver metastases
   a. N=1 study (21 patients) comparing SIRT + systemic chemotherapy with systemic chemotherapy alone
      i. There was a significant improvement in progression free survival and median survival associated with SIRT, both for the total studied population and for those disease limited to the liver. There was an increase in toxicity with the use of SIRT.
   b. N=1 study (63 patients) comparing SIRT and regional chemotherapy with regional chemotherapy alone.
      i. There was no significant difference in progression free survival and median survival seen with SIRT, in either the total patient group or in the 22 patients with disease limited to the liver. There was no significant increase in toxicity with the addition of SIRT to regional chemotherapy.
   c. There were no randomised studies comparing SIRT with best supportive care in patients with refractory disease, and no randomised studies assessing the effect of SIRT in patients with resectable liver metastases.
   d. **Authors' conclusions** There is a need for well designed, adequately powered phase III trials assessing the effect of SIRT when used with modern combination chemotherapy regimens. Further studies are also needed for patients with refractory disease with a particular focus on the impact on quality of life.
5) **Vente 2009,** meta-analysis of yttrium-90 radioembolization for liver malignancies
   e. For colorectal liver metastases (mCRC), in a salvage setting, response was 79% for 90Y-RE combined with 5-fluorouracil/ leucovorin (5-FU/LV), and 79% when combined with 5-FU/LV/oxaliplatin or 5-FU/LV/irinotecan, and in a first-line setting 91% and 91%, respectively.
   f. For hepatocellular carcinoma (HCC), response was 89% for resin microspheres and 78% for glass microspheres.
   g. No statistical method is available to assess median survival based on data presented in the literature.

h. Conclusion: In mCRC, 90Y-RE delivers high response rates, especially if used neoadjuvant to chemotherapy. In HCC, 90Y-RE with resin microspheres is significantly more effective than 90Y-RE with glass microspheres. The impact on survival will become known only when the results of phase III studies are published.

Other guidelines

1) **NCCN 2015**, hepatocellular carcinoma
    a. Locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as part of a strategy to bridge patients to other curative therapies.
    b. Radioembolization (RE) with yttrium-90 is listed as a locoregional therapy
    c. Listed as category 2B
    d. Sorefenib is recommended as first line, with locoregional therapy second line in the majority of these cases
    e. Evidence reviewed that yttrium-90 RE has been found to be safe and effective in the treatment of non-resectable cholangiocarcinoma
    f. For HCC, ablation therapy should be first line, and locoregional therapy, including yttrium RE should only be considered when ablation is not feasible

Other policies

1) Aetna 2014
    a. Covers yttrium SIRT for non-resectable primary HCC and for select, rare metastatic liver disease. Does not cover for most metastases to the liver, including colorectal carcinoma.

2) Cigna 2006
    a. Covers yttrium SIRT for non-resectable primary HCC and for colorectal cancer metastatic to the liver

Summary: Based on limited data, yttrium-90 appears to have comparable impact on liver cancer and liver metastases as transarterial embolization. Trusted sources recommend utilization, in limited circumstances.

Utilization:
FFS reports 2 requests in the past year. Most CCOs report 0-1 request for yttrium-90 therapy in the past year.

HERC staff recommendation:

1) Add yttrium-90 radioembolization (CPT 79445) as a treatment to Line 320 CANCER OF LIVER

NICE National Institute for Health and Care Excellence

Selective internal radiation therapy for primary hepatocellular carcinoma

Issued: July 2013

NICE interventional procedure guidance 460

guidance.nice.org.uk/ipg460

Healthcare Improvement Scotland

NICE has accredited the process used by the NICE Interventional Procedures Programme to produce interventional procedures guidance. Accreditation is valid for 5 years from January 2010 and applies to guidance produced since January 2009 using the processes described in the 'Interventional Procedures Programme: Process guide, January 2009' and the 'Interventional Procedures Programme: Methods guide, June 2007'. More information on accreditation can be viewed at www.nice.org.uk/accreditation

NICE accredited
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1 Guidance

1.1 Current evidence on the efficacy and safety of selective internal radiation therapy (SIRT) for primary hepatocellular carcinoma is adequate for use with normal arrangements for clinical governance, consent and audit. Uncertainties remain about its comparative effectiveness, and clinicians are encouraged to enter eligible patients into trials comparing the procedure against other forms of treatment.

1.2 Patients with primary hepatocellular carcinoma should be selected for treatment by SIRT or for entry into trials by a multidisciplinary hepatobiliary cancer team.

1.3 SIRT should only be carried out by clinicians with specific training in its use and in techniques to minimise the risk of side effects from the procedure.

1.4 Clinicians should enter details about all patients undergoing SIRT for primary hepatocellular carcinoma onto the UK SIRT register. They should audit and review clinical outcomes locally and should document them and consider their relationship to patient characteristics.

2 The procedure

2.1 Indications and current treatments

2.1.1 Hepatocellular carcinoma is the most common type of primary liver cancer.

2.1.2 The choice of treatment for primary hepatocellular carcinoma depends on a number of factors, including the exact location and stage of the cancer, and the patient's liver function. The aim of treatment is normally to slow progression with a view to improving quality of life and prolonging survival. In some patients surgical removal with curative intent may be possible: this may sometimes be achieved by downstaging the tumour using other treatment modalities first. Treatment options include chemotherapy (intravenous or by hepatic artery infusion), surgical excision, transarterial chemo-embolisation (TACE) and radiofrequency ablation.

2.2 Outline of the procedure

2.2.1 Selective internal radiation therapy (SIRT) for primary hepatocellular carcinoma involves infusion of microspheres loaded with yttrium-90, which aims to deliver radiation directly into the tumour, minimising the risk of radiation damage to healthy surrounding tissues.

2.2.2 Before undertaking the treatment, a nuclear medicine liver-to-lung shunt study is carried out to assess the risk of radioactive microspheres causing lung damage. Radiographic imaging and selective coil embolisation of arteries to the stomach and duodenum are also commonly carried out.

2.2.3 Using local anaesthesia, radioactive microspheres that are designed to lodge in the small arteries are injected into branches of the hepatic artery, usually by a percutaneous femoral approach.

2.2.4 The procedure may be repeated depending on the response.

> Sections 2.3 and 2.4 describe efficacy and safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the overview.

2.3 Efficacy

2.3.1 A non-randomised comparative study of 86 patients, with 43 treated by SIRT and 43 treated by TACE, reported overall median survival of 42 months in the SIRT group compared with 19 months in the TACE group (p=0.008). A case series of 325 patients reported overall median survival was 12.8 months; this varied significantly by disease stage (Barcelona Clinic Liver Cancer [BCLC] stage A: 24.4 months; BCLC stage B: 16.9 months; BCLC stage C: 10 months).

2.3.2 The non-randomised comparative study of 86 patients reported a partial response (assessed using World Health Organization [WHO] criteria) in 61% (26/43) of patients treated by SIRT (median follow-up 34 months) and 37%

(13/35) of patients treated by TACE (median follow-up 52 months). This difference was not significant (p=0.07).

2.3.3 A non-randomised comparative study of 245 patients, with 123 treated by SIRT and 122 treated by TACE, reported an overall response rate (assessed using WHO criteria) in 49% (60/123) of patients treated by SIRT (median follow-up 23 months) and 36% (44/122) of patients treated by TACE (median follow-up 33 months) (p=0.05).

2.3.4 The non-randomised comparative study of 86 patients reported downstaging from stage T3 to stage T2 in 58% (25/43) of patients in the SIRT group and 31% (11/35) of patients in the TACE group at a 'median time to downstaging was within 6 months' (p=0.02).

2.3.5 A case series of 291 patients treated by SIRT reported that 12% (34/291) of patients underwent treatment with curative intent: 32 went on to have liver transplants and 2 had resection of their tumours (median follow-up 31 months).

2.3.6 A case series of 35 patients treated by SIRT reported that 8 patients were downstaged and underwent liver transplantation (timing ranged from 12 days to 210 months after treatment).

2.3.7 The non-randomised comparative study of 245 patients reported a significantly longer median time to progression of 13.3 months in patients treated by SIRT compared against 8.4 months in patients treated by TACE (p=0.05).

2.3.8 A non-randomised comparative study of 28 patients, with 14 treated by SIRT and 14 treated by cisplatin, reported health-related quality of life measured on the Functional Assessment of Cancer Therapy – Hepatobiliary (FACT-Hep) questionnaire (scored on a scale of 0–4; higher score indicating better quality of life or fewer symptoms). The overall health-related quality of life score was 47 for the SIRT group (n=9) and 52 for the cisplatin group (n=5) at 6-month follow-up. This difference was reported as not significant (p value not reported).

2.3.9 The Specialist Advisers listed efficacy outcomes as tumour response, overall survival, quality of life, increased time to progression, downsizing or

downstaging to potentially curative treatments, and bridging to liver transplantation.

2.4 Safety

2.4.1 Death within 30 days was reported in 7% (2/27) of patients treated by SIRT and in 9% (4/44) of patients treated by chemo-embolisation in a non-randomised comparative study of 71 patients.

2.4.2 Radiation pneumonitis was reported in 4 patients between 1 and 6 months after treatment by SIRT (a scan to determine lung shunting had been performed before SIRT) in a case series of 80 patients. All patients were treated by steroids. Three patients died of progressive respiratory failure and 1 from progressive cancer.

2.4.3 Ulceration caused by radiation was reported in 11% (3/27) of patients who were treated by SIRT (after prophylactic coil embolisation of the gastroduodenal arteries) and gastritis and/or temporary ulceration was reported in 20% (9/44) of patients treated by chemo-embolisation in the non-randomised comparative study of 71 patients. Two patients in the SIRT group were treated by subtotal gastrectomy; there were no further details on the other patient (median follow-up 6 months).

2.4.4 Cholecystitis reported as 'possibly related to treatment' occurred in 2 patients in the case series of 80 patients treated by SIRT (both treated by emergency cholecystectomy 21 and 243 days after treatment).

2.4.5 Radiation-induced biliary stricture was described in a case report. The patient became progressively jaundiced and fatigued, with mild or moderate bilirubin toxicity (timing not reported).

2.4.6 Bone marrow suppression resulting in transient thrombocytopenia was reported 1 month after SIRT in a case report.

2.4.7 Post-embolisation syndrome was reported in 60% of patients in both the SIRT and TACE groups (absolute numbers not reported) in the non-randomised

comparative study of 86 patients. The symptoms (fatigue and transient non-specific flu-like symptoms) lasted 7 to 10 days in the SIRT group (no further details).

2.4.8 The Specialist Advisers listed additional anecdotal adverse events as fibrosis and skin ulceration; and additional theoretical adverse events as liver failure, portal hypertension, and radiation-induced liver disease.

2.5 Other comments

2.5.1 The Committee noted wide variation in the published evidence about prior and adjunctive treatments that patients received. This made interpretation of the effect of SIRT difficult.

2.5.2 The Committee noted that safety outcomes from older published studies may not reflect current practice in which prophylactic coil embolisation is used.

3 Further information

3.1 For related NICE guidance see the NICE website.

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.

About this guidance

NICE interventional procedure guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS. It is for healthcare professionals and people using the NHS in England, Wales, Scotland and Northern Ireland, and is endorsed by Healthcare Improvement Scotland for implementation by NHSScotland.

This guidance was developed using the NICE interventional procedures guidance process.

We have produced a summary of this guidance for patients and carers.

Changes after publication

September 2013: minor maintenance.

Your responsibility

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

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to 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.

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NICE National Institute for Health and Care Excellence

Selective internal radiation therapy for primary intrahepatic cholangiocarcinoma

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NICE interventional procedure guidance 459

guidance.nice.org.uk/ipg459

Healthcare Improvement Scotland

NICE has accredited the process used by the NICE Interventional Procedures Programme to produce interventional procedures guidance. Accreditation is valid for 5 years from January 2010 and applies to guidance produced since January 2009 using the processes described in the 'Interventional Procedures Programme: Process guide, January 2009' and the 'Interventional Procedures Programme: Methods guide, June 2007'. More information on accreditation can be viewed at www.nice.org.uk/accreditation

NICE accredited
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1 Guidance

1.1 Current evidence on the safety and efficacy of selective internal radiation therapy (SIRT) for primary intrahepatic cholangiocarcinoma is limited in both quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

1.2 Clinicians wishing to undertake SIRT for primary intrahepatic cholangiocarcinoma should take the following actions.

- 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, the use of NICE's information for the public is recommended.

1.3 Patients with primary intrahepatic cholangiocarcinoma should be selected for treatment by SIRT or for entry into trials by a multidisciplinary hepatobiliary cancer team.

1.4 SIRT should only be carried out by clinicians with specific training in its use and in techniques to minimise the risk of side effects from the procedure.

1.5 Clinicians should enter details about all patients undergoing SIRT for primary intrahepatic cholangiocarcinoma onto the UK SIRT register. They should audit and review clinical outcomes locally and should document them and consider their relationship to patient characteristics.

1.6 NICE encourages research to guide future use of SIRT for primary intrahepatic cholangiocarcinoma. This should document patient characteristics, tumour response, survival and quality of life measures, and details of other treatments used adjunctively or sequentially. NICE may review the procedure on publication of further evidence.

2 The procedure

2.1 Indications and current treatments

2.1.1 Intrahepatic cholangiocarcinoma is a rare type of primary liver cancer originating in the bile ducts.

2.1.2 The choice of treatment depends on a number of factors, including the exact location and stage of the cancer, and the patient's liver function. Cholangiocarcinoma is not usually diagnosed before the symptoms of biliary obstruction occur, by which time the cancer may be too advanced for curative surgical resection. Occasionally, surgical removal with curative intent may be possible: this may sometimes be achieved by downstaging the tumour using other treatment modalities first. The standard options for palliative treatment include chemotherapy, surgical bypass of the bile duct or the insertion of a stent using surgical, endoscopic or percutaneous techniques.

2.2 Outline of the procedure

2.2.1 Selective internal radiation therapy (SIRT) for primary intrahepatic cholangiocarcinoma involves infusion of microspheres loaded with yttrium-90, which aims to deliver radiation directly into the tumour, minimising the risk of radiation damage to healthy surrounding tissues.

2.2.2 Before undertaking the treatment, a nuclear medicine liver-to-lung shunt study is carried out to assess the risk of radioactive microspheres causing lung damage. Radiographic imaging and selective coil embolisation of arteries to the stomach and duodenum are also commonly carried out.

2.2.3 Using local anaesthesia, radioactive microspheres that are designed to lodge in the small arteries are injected into branches of the hepatic artery, usually by a percutaneous femoral approach.

2.2.4 The procedure may be repeated depending on the response.

Sections 2.3 and 2.4 describe efficacy and safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the overview.

2.3 Efficacy

2.3.1 A case series of 24 patients reported a median survival of 4 months in patients with previous exposure to systemic chemotherapy (n=7), and a median survival of 32 months in patients who were chemotherapy-naive (n=17) (p=0.03). A case series of 19 patients reported a median survival of 12 months from first treatment.

2.3.2 The case series of 24 patients reported stable disease (using World Health Organization [WHO] criteria) in 68% (15/22) of patients, partial response in 27% (6/22) of patients, and disease progression in 5% (1/22) of patients at a median follow-up of 18 months.

2.3.3 Downstaging to resection was reported in 1 patient in the case series of 24 patients (timing of resection unclear; median follow-up of study was 18 months). Downstaging to resection was reported in 1 patient who had a partial response to treatment in a case series of 25 patients (timing of resection unclear; median follow-up of study was 8 months).

2.3.4 Bridging to liver transplantation was reported in 1 patient in the case series of 24 patients at a median follow-up of 18 months.

2.3.5 The Specialist Advisers listed efficacy outcomes as overall survival, tumour response, quality of life, increase in time to progression, downsizing or downstaging to potentially curative treatments, and bridging to liver transplantation.

2.4 Safety

2.4.1 Death within 30 days was reported in 2 patients (1 patient had pulmonary embolus and the other patient had a tumour burden greater than 50%; no further details available) in the case series of 24 patients.

2.4.2 Gastroduodenal ulcer was reported after SIRT in 1 patient in the case series of 24 patients. No details were given about when the ulcer occurred; it was treated by gastrojejunostomy.

2.4.3 Fatigue (64%), nausea (16%) and vomiting (8%) (numbers of patients not reported) were reported in the case series of 25 patients at a median follow-up of 8 months.

2.4.4 Severe thrombocytopenia (within 30 days of first treatment) was reported in 1 patient in the case series of 19 patients.

2.4.5 Pleural effusion (no further details given) was reported in 9% (2/22) of patients in the case series of 24 patients at a median follow-up of 18 months.

2.4.6 The Specialist Advisers listed additional anecdotal adverse events as fibrosis and skin ulceration; and additional theoretical adverse events as liver failure, portal hypertension, and radiation-induced liver disease.

2.5 Other comments

2.5.1 The Committee noted that primary intrahepatic cholangiocarcinoma is a rare condition with a variable natural history, so that the accumulation of useful evidence is difficult. This underpinned the recommendation to encourage research.

3 Further information

3.1 For related NICE guidance see the NICE website.

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September 2013: minor maintenance.

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CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

TITLE: **SELECTIVE INTERNAL RADIATION THERAPY OR RADIOEMBOLIZATION FOR INOPERABLE LIVER METASTASES FROM COLORECTAL CANCER**

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CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

SELECTIVE INTERNAL RADIATION THERAPY OR RADIOEMBOLIZATION FOR INOPERABLE LIVER METASTASES FROM COLORECTAL CANCER

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for the use of radioembolization for the treatment of metastases to the liver from colorectal cancer. Surgery is the primary treatment of liver metastases, but when surgery is not an option radioembolization may be an attractive alternative.

BACKGROUND

In 2009, the American Cancer Society estimates that there will be 146,970 new cases of colon cancer and 49,920 deaths from colon cancer.[1] Among cancers in the United States, only lung cancer causes more deaths. The liver is the most common site for metastatic colon cancer. Many therapies have been developed to treat liver metastases including surgery, cryoablation, radiofrequency ablation, hepatic arterial chemotherapy (HAC) infusion, trans-arterial chemoembolization (TACE), radioembolization (RE), and external-beam radiation therapy. The only approach shown to cure patients is surgical resection of the metastases, usually in conjunction with neoadjuvant or adjuvant chemotherapy. However, it is not always possible to remove all of the tumors while preserving hepatic function. In some cases, patients initially deemed inoperable are treated with combination chemotherapy and re-evaluated for surgery after chemotherapy.

The primary goal for the treatment of inoperable metastatic colorectal cancer is palliative, not curative. Advances in chemotherapy, including oxaliplatin, irinotecan, and targeted antibodies, have doubled median survival for this population from less than one year to more than two years.[2-5] Systemic chemotherapy is the recommended initial treatment for inoperable metastatic disease and survival benefit has been demonstrated for both second-line and third-line chemotherapy.[6] Overall survival has been the primary outcome used to assess the value of new chemotherapeutic regimens, though progression free survival usually has correlated with overall survival and quality of life in these studies.[3, 7]

The National Comprehensive Cancer Network (NCCN) recommends against debulking surgery or ablation of metastatic tumors unless done for cure.[6] However, less than 15% of patients with liver metastases have

operable disease on presentation.[8] In their first update of the 2010 colon cancer practice guideline, there was no consensus on the appropriate use of other liver directed therapies such as ablation or embolization.[6]

Selective internal radiation therapy (SIRT), aka radioembolization

Liver cells are very sensitive to radiation and this has limited the use of external beam therapy to the liver even with intensity modulated radiation therapy. RE takes advantage of the fact that the blood flow that supports tumors in the liver is primarily from the hepatic artery while blood flow supporting normal liver tissue is primarily from the portal vein.[9] The most common delivery systems use either glass or resin microspheres impregnated with Yttrium-90, although other radioisotopes have been used. The microspheres are released in the hepatic artery and lodge in the distal arterioles, primarily within tumors. One of the potential benefits is that delivery is not dependant on the number or location of the tumors, because blood will flow from the hepatic artery to tumors even if they were not identified on pre-procedure imaging. Yttrium-90 emits only beta-radiation, which penetrates between three and twelve millimeters into tissue. Thus minimal normal liver tissue surrounding the tumor is affected by the radiation.

RE is normally performed as an outpatient procedure, but requires multidisciplinary treatment planning involving medical oncology, radiation oncology, hepatobiliary surgery and interventional radiology. Prior to the procedure patients usually are required to have a transfemoral hepatic angiogram to assess the arterial supply of the liver with embolization of branches bypassing the liver. This is followed by injection of technetium-labeled macroagglutinated albumin into the hepatic artery with SPECT scanning to evaluate the percentage of injected material shunted to the lungs or gastrointestinal (GI) tract rather than the liver. If the albumin scan indicates that there may be more than 30 Grey of radiation exposure to the lungs or significant flow to the GI tract, then the procedure should not be performed because of the risk of significant radiation pneumonitis and of gastric and duodenal ulceration.[10] It may not be safe to perform the procedure in patients with limited flow through the portal vein, prior radiation therapy to the liver, or limited hepatic reserve.[10]

The most common side effects are flu-like symptoms, fatigue, fever, abdominal pressure and nausea. Patients are generally premedicated with corticosteroids and anti-emetic medications to minimize these side effects. More serious adverse events include radiation induced liver disease, radiation pneumonitis from microspheres shunting around the liver and into the lungs, and GI tract ulcerations. Meticulous planning with

pre-procedure angiography, shunt studies, and careful dosimetry has decreased the occurrence of these toxicities.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

SIR-Spheres® (Sirtex Medical Inc., Lake Forest, IL) received FDA Premarket Approval (PMA) clearance on March 5, 2002. SIR –Spheres are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

TheraSphere® (MDS Nordion, Inc., Ottowa) received FDA Humanitarian Device Exemption (HDE) on August 11, 1998. TheraSphere is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters.

.**TA Criterion 1 is met.**

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “radioembolization,” “SIRT,” “Therasphere,” “SIR-spheres” and “selective internal radiation therapy.” These were cross-referenced with the keywords “liver” and “colorectal”. The search was performed for the period from 1966 through January 2010. The bibliographies of systematic reviews and key articles were manually searched for additional references. References were also solicited from the manufacturers and local experts. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. This review focuses on the essential patient oriented outcomes: overall survival, quality of life, and treatment-related toxicities. Progression-free survival and response rates are secondary outcomes of interest.

The search identified 932 potentially relevant trials. After elimination of duplicate and non-relevant references, 86 articles were reviewed in full. A large number of case series were excluded because they were duplicate reports, not report any of the essential clinical outcomes or because they were mixed series of tumors without separate reporting of outcomes for liver metastases from colorectal cancer.[11-39] The remaining twenty-five references describe two randomized trials[40, 41], one small retrospective study comparing RE to chemoembolization (n=36) [42], and twenty-two case-series.[43-64] The two randomized trials used control groups treated with therapies that are no longer standard today and they were too small (total randomized n = 95) to provide conclusive answers concerning net health outcomes. The search also identified many reviews[65-71] assessing the role of RE including one recent Cochrane review.[66]

Level of Evidence: 2, 3, and 5.

TA Criterion 2 is not met.

- **In the absence of Level 1 studies, technologies may meet this criterion if, overall, Level 2-4 studies indicate that:**

  a. The technology provides substantial benefits to important health outcomes and

  b. The new technology has been shown to be safer or more beneficial than existing technologies or alternative treatments in comparative studies.

TA Criterion 3: The technology must improve net health outcomes.

Case Series

Table 1 summarizes the outcomes from the published case series of RE for the treatment of colorectal cancer metastases to the liver. Patients in these series were an average age of 60 to 65 years old and about one third were women. All had inoperable liver metastases from colorectal cancer. They represented a wide range of patients from those receiving their initial treatment for metastatic colorectal cancer to those who had already failed two or more different chemotherapeutic regimens. The wide variation in outcomes reflects this clinical heterogeneity. The reported response rates varied from 0% to 90% and the median overall survival from the time of RE varied from 4.5 months to 14.5 months. Given that the median overall survival for patients with metastatic colon cancer is now greater than 29 months[5], these outcomes are not impressive. However, as noted above, all of these patients have inoperable metastases and many have

exhausted first and second line therapies. Thus, their prognosis is worse than the average patient. In order to elucidate the potential value of RE, comparative trials need to be done with clear definition of the patient population and either carefully matched or preferably randomized controls.

Non-randomized, controlled studies

The comparative studies are summarized in Table 2. Hong et al. described a retrospective comparison of RE to TACE as salvage therapy for patients with liver dominant colorectal cancer.[42] Patients were excluded if they had advanced liver disease (severe ascites, encephalopathy, elevated bilirubin) or had poor functional status (Eastern Cooperative Oncology Group performance status greater than 2). The investigators compared 15 patients treated with RE (age 64 years, 27% female) to 21 patients treated with chemoembolization (age 67 years, 48% female). Approximately 20% of patients in each group had been treated with external beam radiation and radiofrequency ablation. Similarly, about 20% of patients in each group had liver resections prior to the transarterial therapy. All had been treated with modern systemic chemotherapy. The time from diagnosis of liver metastases to the study intervention was 23 months in the RE group and 18 months in the chemoembolization group and extrahepatic metastases were more common in the RE group (43% versus 33%). The chemoembolization drugs included cisplatin, doxorubicin, and mitomycin C. Multiple treatments were performed for 19% of the RE group and 43% of the chemoembolization group. Median overall survival was similar in the two groups: 6.9 months for the RE group and 7.7 months for the chemoembolization group ($p = 0.27$). Overall survival at one, two, and five years was 34%, 18%, and 0% for the RE group and 43%, 10% and 0% for the chemoembolization group. All patients in both groups experienced some minor complications including abdominal pain, nausea, fever, leucocytosis, and fatigue. One patient in the chemoembolization group suffered a pulmonary embolus, but recovered fully. There were no major complications in the RE group.

This was a small, unmatched, retrospective comparison that found no significant differences between two salvage procedures for patients with metastatic colorectal cancer. Because of the small size, the study had limited power to detect any differences between the two procedures. Furthermore, the unmatched, observational study design means that the study is likely subject to selection bias. For instance there were large differences in the proportion of women in the two groups, the presence of extrahepatic metastases, and the proportion of patients with multilobar metastases. It is difficult to draw any meaningful conclusions about health outcomes from this study.

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Table 1: Case series describing the outcomes following radioembolization of liver metastases from colorectal cancer

Study Key authors Location	Sphere type	N	Intervention	Response rate, %	Time to progression, months	Median survival, months
Ariel 1982	Yttrium microspheres	40	RE + HAC:	40	NR	29 month average
Anderson 1992	TheraSpheres	7	RE	0	NR	11
Andrews 1994	TheraSpheres	17	RE	29	NR	13.8
Gray 1992	SIR-Spheres	29	RE	45	NR	NR
Stubbs 1999	SIR-Spheres	30	RE	70	NR	6.7
Gray 2000	SIR-Spheres	71	RE	75	NR	9.9
Stubbs 2001	SIR-Spheres	30	RE	73	NR	9.8
Wong 2002	TheraSpheres	8	RE	24	NR	NR
Lewandowski 2005	TheraSpheres	27	RE	35	NR	9.3
Lim 2005	SIR-Spheres	32	RE	31	5.3	NR
Murthy 2005	SIR-Spheres	12	RE + Chemo	0	NR	4.5
Kennedy 2006	SIR-Spheres	208	RE	35	NR	4.5 non-responders 10.5 responders
Mancini 2006	SIR-Spheres	35	RE	12	NR	NR
Stubbs 2006	SIR-Spheres	100	RE + HAC	74	NR	11
Rowe 2007	SIR-Spheres		RE			9.0
Sharma 2007	SIR-Spheres	20	RE+ Chemo	90	9.3	NR
Jakobs 2008	SIR-Spheres	41	RE	17		10.5
Sato 2008	TheraSpheres	51	RE	NR	NR	15 2 year: 27%
Stuart 2008	SIR-Spheres	13	RE		3.7	12
Cianni 2009	SIR-Spheres	41	RE	46	9.2	12
Mulcahy 2009	TheraSpheres	72	RE	40	NR	14.5
Van Hazel 2009	SIR-Spheres	25	RE + Chemo	48%	6.0	12.2

Table 2: Comparative studies of radioembolization of liver metastases from colorectal cancer

Study Key authors Location	Sphere type	N	Study arm: n	Age, yrs Sex, %F	Prior treatment	Response rate	Time to progression, months	Median survival, months	RECIST Grade 3 or 4 Toxicity, n	Quality of life
Randomized trials										
Gray 2001 Australia	SIR-Spheres	70	HAC + RE: 36 HAC: 34	60 23%	14% with prior chemotherapy	44 18 p=0.01	16 10 p=0.001	17 16, p=0.18 2 year: 39% vs. 29%	23 23	Improved in both arms over 18 months. No differences between groups.
Van Hazel 2004 Australia	SIR-Spheres	21	Chemo + RE: 11 Chemo: 10	65 14%	None	78 0	18.6 3.6 p=0.0005	29.4 11.8, p=0.025 2 year: 64% vs. 20%	13 5	No difference at three months, p=0.96.
Comparative study Retrospective										
Hong 2009 Baltimore, MD	TheraSpheres	36	RE: 15 TACE: 21	66 39%	100% prior chemotherapy.	NR	NR	6.9 7.7, p=0.27 2 year: 18% vs. 10%	NR	NR

Randomized trials

The first randomized trial of RE was published by Gray et al in 2001.[41] They randomized 74 patients with bilobar, non-resectable liver metastases to monthly HAC with floxuridine or the same therapy plus a single infusion of yttrium-90 microspheres. Recruitment was stopped early (original goal was 95 patients) when the United States Food and Drug Administration indicated that time to disease progression would be an acceptable endpoint for approval of the microspheres. All patients had completed resection of the primary colorectal cancer and had non-resectable metastases limited to the liver or the lymph nodes draining the liver. During the laparotomy for placement of a permanent hepatic artery catheter, extrahepatic metastases were found in four patients. These four patients were ineligible for the trial and were excluded from the published analyses. Of the remaining 70 patients, 36 received RE plus HAC and 34 received HAC alone. The two groups had similar demographics and tumor characteristics including lymph node involvement, tumor differentiation, prior chemotherapy, percentage of liver involvement by the tumor, and time from bowel resection to randomization. The response rate, as measured by tumor area, was greater in patients who received RE (44% versus 18%, $p = 0.01$). The median time to tumor progression using the same standard was also longer in the RE group (15.9 versus 9.7 months, $p = 0.001$). However, overall survival did not differ between the two groups (median 17 months versus 16 months, $p = 0.18$). A post hoc analysis suggested that there may be a survival benefit after 15 months of follow-up. Quality of life generally improved in both groups over the first 18 months of the study and there were no significant differences between the two groups, although none of the data were presented. There were more grade 1 and 2 toxicities in the RE group, primarily due to elevation in liver tests, nausea, and diarrhea. However, the number of grade 3 and 4 toxicities was the same in each group (23 events in each).

The second randomized trial was a phase 2 study published in 2004 by the same research group in Australia.[40] This trial included patients with bilobar liver metastases from colorectal cancer that could not be treated with surgical resection or any local ablation therapy. In addition, the patients could not have received prior chemotherapy or radiation therapy for the liver metastases. The investigators randomized 21 patients to either systemic chemotherapy with fluorouracil and leucovorin ($n = 10$) or the same chemotherapy plus one treatment with RE on the third or fourth day of the second cycle of chemotherapy ($n = 11$). The two groups had similar demographics and tumor characteristics including extrahepatic metastases, tumor differentiation, and the percentage of liver involvement by the tumor. Prior to treatment, two of the patients in the chemotherapy only group died (20%); all patients in the RE group received treatment as randomized. All 21 patients were included in the intention-to-treat analysis. Eight patients in the RE group had a confirmed partial response; none of the chemotherapy only group had a partial response ($p < 0.001$). The time to disease progression was significantly longer in the RE group (18.6 versus 3.6 months, $p < 0.0005$).

Similarly, median overall survival was significantly longer in the RE group (29.4 versus 12.8 months, $p < 0.025$). Improvements in quality of life were similar in both groups ($p = 0.96$). Grade 3 and 4 toxicities were more common in the combined therapy group (13 versus 5, p not reported). Toxicities in the RE group included one patient who developed a liver abscess, a second patient who developed radiation-induced cirrhosis, and a third patient who developed recurrent neutropenia and died from sepsis.

Harms

There are a large number of publications in the literature describing the side effects and more significant adverse events associated with RE.[12-14, 17, 67, 72-81] Patients commonly experience post-embolization symptoms including fever, nausea, vomiting, fatigue, anorexia and some abdominal pain. In the trials and case series reviewed for this assessment, between 20% and 55% of patients reported some of these symptoms. Pre-medication with corticosteroids followed by a steroid taper helps limit the inflammation thought to be partially responsible for these symptoms. Anti-emetics are routinely given with the procedure and on an as needed basis during one to two weeks following the procedure.

More serious radiation induced liver disease can lead to veno-occlusive disease, cirrhosis, and liver failure. One large case series, which included both primary and secondary liver tumors treated with RE, reported radiation induced liver disease in 4.1% of treated patients (28/680).[75] Older patients, smaller patients, those with pre-existing liver disease, and those requiring embolization of the entire liver are at highest risk of serious liver injury. Thoughtful patient selection and careful dosimetry limit the risk of this potentially life-threatening complication.

Radiation pneumonitis is a known complication of RE. Careful measurement of the lung shunt fraction and reducing the amount of microspheres injected if the shunt fraction is high can largely prevent this complication. Recent series suggest that the incidence of radiation pneumonitis should be less than 1%.[12]

Gastric and duodenal ulcerations are also potential complications related to shunting of blood carrying microspheres from the hepatic artery into the splanchnic circulation, usually through anatomic variants in the vasculature.[72-74, 76, 79] Pretreatment angiography is essential both to identify arteries to avoid when planning the microsphere infusion and to embolize those arteries leading to the GI tract that cannot be avoided. GI tract ulcers may occur in as many as 5% of patients.[74, 78, 82]

Finally, as with any transarterial catheter based therapy, there is always some risk of vascular injury, plaque emboli, and infection. Other reported complications include liver abscesses, lymphopenia, and biliary tree injury.[67, 75, 78]

Summary

The three comparative studies all used different control interventions. The non-randomized study did not demonstrate any convincing improvements over chemoembolization. However, in both randomized trials, RE clearly had an impact on response rates and time to progression. In addition, compared with 5-fluoruracil and leucovorin, it appeared to improve overall mortality. However, there are several important concerns. First, the chemotherapy used as the control would not be considered the standard first line treatment and the response rates in the control arms (0% and 18%) were much lower than usually observed with chemotherapy. Recent clinical trials of first line systemic chemotherapy for inoperable liver metastases report 50% or higher response rates.[83] Furthermore, the trials were small and chance events may influence the findings. For instance, it is notable that 20% of patients in the control arm of the trial by Van Hazel et al died before receiving chemotherapy. The common toxicities were generally mild and the more serious grade 3 and 4 toxicities were relatively uncommon. Overall, the results suggest that there may be a role for RE, but the lack of a mortality benefit in the larger trial and the extremely small numbers in the second trial preclude definite conclusions.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

It is not straightforward to identify the appropriate alternative therapy with which to compare RE. In patients who have not received systemic chemotherapy to treat inoperable metastases to the liver, multi-agent chemotherapy based on oxaliplatin or irinotecan would be the appropriate comparator. In patients with tumors amenable to radiofrequency ablation, that may be an appropriate comparator. Finally, the appropriate treatment option for patients who have failed multiple rounds of systemic therapy. HAC and TACE are often tried, but as noted above, the most recent expert panel convened by the NCCN could not come to a consensus on the appropriate use of these therapies.[6]

There are currently at least two large trials (SIRFLOX and FOXFIRE) randomizing over 800 patients to first line chemotherapy with or without Yttrium microsphere radioembolization. Another trial is randomizing 250

patients to radiofrequency ablation, chemoembolization, or RE. There are also at least a dozen smaller trials evaluating RE with second or third line chemotherapy or in the setting of salvage therapy. The appropriate clinical trial data to guide patients and clinicians in deciding when to use RE in the treatment of inoperable liver metastases should be available in the next few years. Until the availability of additional data, TA criterion 4 is not met.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

To date, clear improvements compared with standard surgery have not been demonstrated outside of the investigational setting. While RE has been performed in many centers for several years, TA criterion 4 must be met for TA criterion 5 to be considered met.

TA Criterion 5 is not met.

CONCLUSION

Colorectal cancer commonly metastasizes to the liver. Surgical resection of the liver tumors can be curative, but it is not always possible to perform the surgery and preserve a viable liver. The current standard of care is to use multi-agent systemic chemotherapy to treat inoperable liver metastases. External beam radiation therapy is rarely used because normal liver tissue is very sensitive to radiation. RE capitalizes on the differing blood supplies of normal liver tissue and liver tumors to deliver high dose radiation directly to the tumor while sparing most of the normal liver.

Twenty-two case series with data on patients with metastatic colorectal cancer have demonstrated that it is feasible to deliver radiation therapy to liver tumors and achieve at least partial remission in a substantial proportion of patients with relatively few serious adverse events. Procedure specific adverse events such as radiation pneumonitis, GI ulceration and radiation induced liver disease have been characterized and pretreatment planning strategies have been developed to limit their frequency and severity.

The results of the two randomized trials described above are encouraging, but not definitive. Both demonstrated improvements in disease-free survival and a trend towards longer overall survival. However, the trials were very small (less than 100 patients in total) and the response rates in the control groups were lower than expected. Furthermore, the control groups did not use the standard first-line therapy for colorectal cancer metastatic only to the liver. Ongoing clinical trials that are randomizing over 800 newly diagnosed patients to first line chemotherapy with or without RE should define the efficacy of combined therapy and the associated additional toxicity. Similarly, the data on the utility of RE as salvage therapy for patients who have failed multiple rounds of chemotherapy is limited and immature.

RECOMMENDATION

It is recommended that radioembolization for the treatment of inoperable liver metastases from colorectal cancer does not meet CTAF TA Criterion 2 through 5 for improvement in health outcomes.

February 17, 2010

This is the first review of this technology by the California Technology Assessment Forum

The California Technology Assessment Forum voted to accept the recommendation as written.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center (TEC) has not conducted an assessment of this technology..

Centers for Medicare and Medicaid Services (CMS)

CMS does not have a National Coverage Determination for this technology.

California Radiological Society (CRS)

A CRS representative will be in attendance at the meeting.

American Society of Therapeutic and Radiation Oncology (ASTRO)

An ASTRO representative provided testimony at the meeting on behalf of ASTRO, ACRO and the CRS.

Society for Interventional Radiology (SIR)

A SIR representative provided testimony at the meeting.

American College of Radiation Oncology (ACRO)

An ACRO representative will be in attendance at the meeting.

American Gastroenterological Association (AGA)

An AGA representative provided testimony at the meeting.

Association of Northern California Oncologists (ANCO)

ANCO was invited to provide an opinion regarding this technology and representation at the meeting.

Medical Oncology Association of Southern California (MOASC)

MOASC was invited to provide an opinion regarding this technology and representation at the meeting.

American Cancer Society (ACS)

The ACS does not have a specific recommendation or guidelines related to this cancer related topic. The absence of ACS comments reflects neither favorably or unfavorably on this procedure. A representative will not be attending the meeting.

ABBREVIATIONS

CTAF	California Technology Assessment Forum
HAC	Hepatic artery chemotherapy
TACE	Transarterial chemoembolization
RE	Radioembolization
NCCN	National Comprehensive Cancer Network
SIRT	Selective internal radiation therapy
GI	Gastrointestinal
FDA	Food and Drug Administration
PMA	Premarket Approval
IHAC	Intra-hepatic artery chemotherapy
HDE	Humanitarian Device Exemption
HCC	Hepatocellular carcinoma
DARE	Database of Abstracts of Reviews of Effects
NR	Not reported
RECIST	Response Evaluation Criteria on Solid Tumors

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Selective internal radiation therapy for liver metastases from colorectal cancer (Review)

Townsend A, Price T, Karapetis C

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[Intervention Review]

Selective internal radiation therapy for liver metastases from colorectal cancer

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ABSTRACT

Background

Liver metastases are often the dominant site of metastatic disease in colorectal cancer. Selective internal radiation therapy (SIRT) involves embolising radiolabeled spheres (SIR-Spheres) into the arterial supply of the liver with the aim of improving the control of liver metastases.

Objectives

To assess the effectiveness and toxicity of SIRT in the treatment of metastatic colorectal cancer liver metastasis when given alone or with systemic or regional hepatic artery chemotherapy.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane library 2008 issue 2, MEDLINE (1966 to October 2008), EMBASE (1980 to October 2008), and Pubmed (October 2008). The proceedings of ASCO (1985 to 2008) and ASCO GI (2004 to 2008) were also searched. The manufacturers of SIR-Spheres were contacted and asked whether they were aware of any other unpublished studies.

Selection criteria

Randomised controlled trials comparing SIRT and chemotherapy (systemic and/or regional) with chemotherapy alone, or comparing SIRT alone with best supportive care in patients with metastatic colorectal cancer.

Data collection and analysis

Two authors (AT/TP) extracted data and assessed the trial quality. The study authors were contacted and individual patient data was obtained. Results were analysed separately for patients with and without extra-hepatic disease.

Main results

A single study of 21 patients compared SIRT and systemic chemotherapy (fluorouracil and leucovorin) with chemotherapy alone. There was a significant improvement in progression free survival and median survival associated with SIRT, both for the total studied population and for those disease limited to the liver. There was an increase in toxicity with the use of SIRT. A second study of 63

eligible patients compared SIRT and regional chemotherapy (floxuridine) with regional chemotherapy alone. There was no significant difference in progression free survival and median survival seen with SIRT, in either the total patient group or in the 22 patients with disease limited to the liver. There was no significant increase in toxicity with the addition of SIRT to regional chemotherapy. There were no randomised studies comparing SIRT with best supportive care in patients with refractory disease, and no randomised studies assessing the effect of SIRT in patients with resectable liver metastases.

Authors' conclusions

There is a need for well designed, adequately powered phase III trials assessing the effect of SIRT when used with modern combination chemotherapy regimens. Further studies are also needed for patients with refractory disease with a particular focus on the impact on quality of life.

PLAIN LANGUAGE SUMMARY

Radioactive beads given in addition to chemotherapy does not improve control of cancer nor survival in patients with colorectal cancer and metastasis in the liver.

Bowel cancer commonly spreads to the liver. In most patients this cannot be removed by an operation and cure is not possible. Chemotherapy treatment can help control the growth of the cancer and improve survival. Radioactive beads can be injected into the blood vessels of the liver to try and control the cancer in the liver. In one study that had 21 participants, radioactive beads (injected into the blood vessels of the liver) given with chemotherapy (into the veins of the arm) was more effective at controlling the cancer and improving how long people lived than chemotherapy given on it's own. However, in this study more people who received the radioactive beads suffered from side effects and this study used an older type of chemotherapy that is less effective than the newer treatments that are now available. In a second study with 63 participants, radioactive beads were given with chemotherapy that was injected directly into the blood vessels of the liver. In this study there was no extra benefit in the control of cancer growth or survival for those participants who received radioactive beads in addition to the chemotherapy. More studies are needed with a particular focus on whether radioactive beads provides extra benefit when given with newer chemotherapy treatments, and if radioactive beads provide benefit when given on their own.

BACKGROUND

Colorectal Cancer

Colorectal cancer is the third leading cause of cancer death in the United States and Europe (Grothey 2004; Jemal 2002). The liver is often the dominant site of metastatic disease and is a significant clinical problem. While resection of liver metastases results in five year survival rates of 30-40% (Adam 2004) and offers the potential for cure, fewer than 15% of patients with metastatic disease are suitable for resection at diagnosis (Delaunoit 2005). Most patients have extra-hepatic disease, or are unresectable due to tumour size and number, location, or inadequate residual liver.

For patients with unresectable disease, treatment with best supportive care alone is associated with a median survival of <10 months (Delaunoit 2005; Scheithauer 1993). The use of combination chemotherapy regimens utilising fluorouracil and oxaliplatin or irinotecan have improved median survival times to between15 to 21.5 months (Grothey 2004; Tournigand 2004). Chemotherapy can also result in significant tumour down-staging allowing for subsequent resection of liver metastases. For these patients five year survival of 33% can be achieved. However, only a small proportion of patients with initially unresectable liver disease (3.3-12.5%) become suitable for resection following systemic chemotherapy (Adam 2004; Delaunoit 2005).

Selective Internal Radiation Therapy

In an attempt to improve upon the long term outcome for those patients who do not have resectable disease and to achieve better control of liver metastases, multiple loco-regional strategies have been trialled, including radio-frequency ablation, intra-arterial chemotherapy and selective internal radiation therapy (SIRT).

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ONCOLOGY

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Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis

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Abstract Radioembolization with yttrium-90 microspheres (^{90}Y-RE), either glass- or resin-based, is increasingly applied in patients with unresectable liver malignancies. Clinical results are promising but overall response and survival are not yet known. Therefore a meta-analysis on tumor response and survival in patients who underwent ^{90}Y-RE was conducted. Based on an extensive literature search, six groups were formed. Determinants were cancer type, microsphere type, chemotherapy protocol used, and stage (deployment in first-line or as salvage therapy). For colorectal liver metastases (mCRC), in a salvage setting, response was 79% for ^{90}Y-RE combined with 5-fluorouracil/leucovorin (5-FU/LV), and 79% when combined with 5-FU/LV/oxaliplatin or 5-FU/LV/irinotecan, and in a first-line setting 91% and 91%, respectively. For hepatocellular carcinoma (HCC), response was 89% for resin microspheres and 78% for glass microspheres. No statistical method is available to assess median survival based on data presented in the literature. In mCRC, ^{90}Y-RE delivers high response rates, especially if used neoadjuvant to chemotherapy. In HCC, ^{90}Y-RE with resin microspheres is significantly more effective than ^{90}Y-RE with glass microspheres. The impact on survival will become known only when the results of phase III studies are published.

Keywords Yttrium-90 · Radioembolization · Colorectal · HCC · Meta-analysis

Introduction

Internal radiation therapy through transarterial delivery of beta-emitting yttrium-90 (^{90}Y)-loaded microspheres, often referred to as ^{90}Y radioembolization (^{90}Y-RE), is an emerging technique for the treatment of patients with unresectable primary or metastatic liver tumors [1, 2]. The efficacy of this radioembolization technique is based on the fact that intrahepatic malignancies derive their blood supply almost entirely from the hepatic artery, as opposed to the normal liver, which mainly depends on the portal vein for its blood supply [3]. The microspheres are injected selectively into the proper hepatic artery and subsequently become lodged in the microvasculature surrounding the tumor. Very high irradiation doses are delivered to the tumors, whereas the surrounding liver parenchyma is largely spared [4].

Two FDA-approved ^{90}Y microsphere products are in clinical use at present: TheraSphere® (MDS Nordion Inc., Kanata, Ontario, Canada), which are glass microspheres, and the resin-based SIR-Spheres® (SIRTeX Medical Ltd., Sydney, New South Wales, Australia) (Table 1). The glass microspheres are approved for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with hepatocellular carcinoma (HCC). The resin microspheres have FDA premarket approval for the treatment of hepatic metastatic colorectal cancer (mCRC), with adjuvant hepatic arterial infusion of floxuridine. However,

Table 1 Yttrium-90 microsphere products characteristics

Microsphere product	Yttrium-90 characteristics				Matrix material	Density (g/ml)	Diameter (μm)	Administered amount of particles (mg)	Administered number of particles	Standard dose (MBq)	Activity per microsphere (Bq)
	$T_{1/2}$ (h)	Cross section[a] (barn)	β^- energy (keV)	Mean tissue range (mm)							
TheraSphere® (MDS Nordion Inc.)	64.0	1.3	2,280 (99.9%)	3.9	Glass	3.3	25±10	110[b]	4,000,000	5,000	1,250[b]–2,500
SIR-Spheres® (SIRTeX Ltd.)					Resin	1.6	32±10	1,370[b]	50,000,000	3,000	50[b]

[a]Thermal neutron cross section of yttrium-89
[b]Calculated values

patients suffering from other liver dominant cancers have also undergone therapy with these ^{90}Y microspheres. These include, among others, liver metastases of breast cancer, pancreatic cancer, and neuroendocrine tumors [5, 6]. Since in most studies that have been published the majority of patients underwent ^{90}Y-RE in a salvage setting, and most of the literature comprised phase I and II studies with small patient numbers, the overall response and real impact on survival are not known. In order to assess the effect of ^{90}Y-RE for primary and secondary liver malignancies, a systematic meta-analysis has been performed of the available literature.

Methods

Identification of studies

A comprehensive search was carried out using several databases in order to identify relevant studies from 1986 onwards. The following search strategy was used to search the MEDLINE database with PubMed: ("yttrium" [MeSH Terms] OR yttrium [Text Word]) AND ("liver" [MeSH Terms] OR liver [Text Word]). The limit "humans" was used. The EMBASE database was searched with the limit human using: ("yttrium"/exp OR "yttrium") AND ("liver"/exp OR "liver"). The Cochrane library database was searched with the keywords "yttrium" and "liver". The search was completed by searching the reference lists and related articles of all relevant articles found. In addition, the reference lists of two presentations given at a workshop held in Chicago 4–5 May 2007 [7] and the list of publications in the clinicians' section of the webpage of SIRTeX Medical Ltd. [8] and the Resource Library on the webpage of MDS Nordion Inc. [9] were screened.

Inclusion and exclusion criteria

All abstracts of relevant studies were reviewed with a set of predefined inclusion and exclusion criteria. All articles from 1986 onwards which presented data concerning tumor response or survival of patients with primary or secondary liver malignancies after treatment with ^{90}Y glass or ^{90}Y resin microspheres were included for further data extraction. This resulted in 44 articles (Fig. 1). Articles written in a language other than English or German were excluded; articles that presented data that were thought to have been presented previously were used once. Consequently, one article was excluded because it was written in Chinese, and another was excluded, since it was thought to present data that were also presented in another larger trial. This resulted in 42 articles from which data were extracted.

Data extraction

After the initial assessment for inclusion the following data were extracted from the 42 articles selected: study design, number, and demographic data of patients; minor extrahepatic disease included/excluded, previous therapies targeted on the liver tumor, administered dosage, site of microsphere delivery, use of angiotensin II, number of microsphere treatments, (neo)adjuvant therapies, tumor response measured by CT, MRI, and/or ^{18}F-FDG-PET, serum markers measurements (CEA, AFP), time to progression, and survival.

After initial data extraction, the exclusion criteria were reassessed. It became clear that most studies presented adequate data on patients with HCC or with mCRC, and that response was usually measured by CT. The meta-analysis was therefore limited to these two tumor types. In order to perform a meta-analysis, additional exclusion criteria were incorporated. Articles that did not present data about HCC and/or mCRC and articles only presenting data on groups with mixed primary disease were excluded from the meta-analysis. Articles that did not present tumor response measured by CT scans or that did not present data on median survival times were also excluded. Following the additional exclusion criteria, an additional 12 articles were excluded from the meta-analysis.

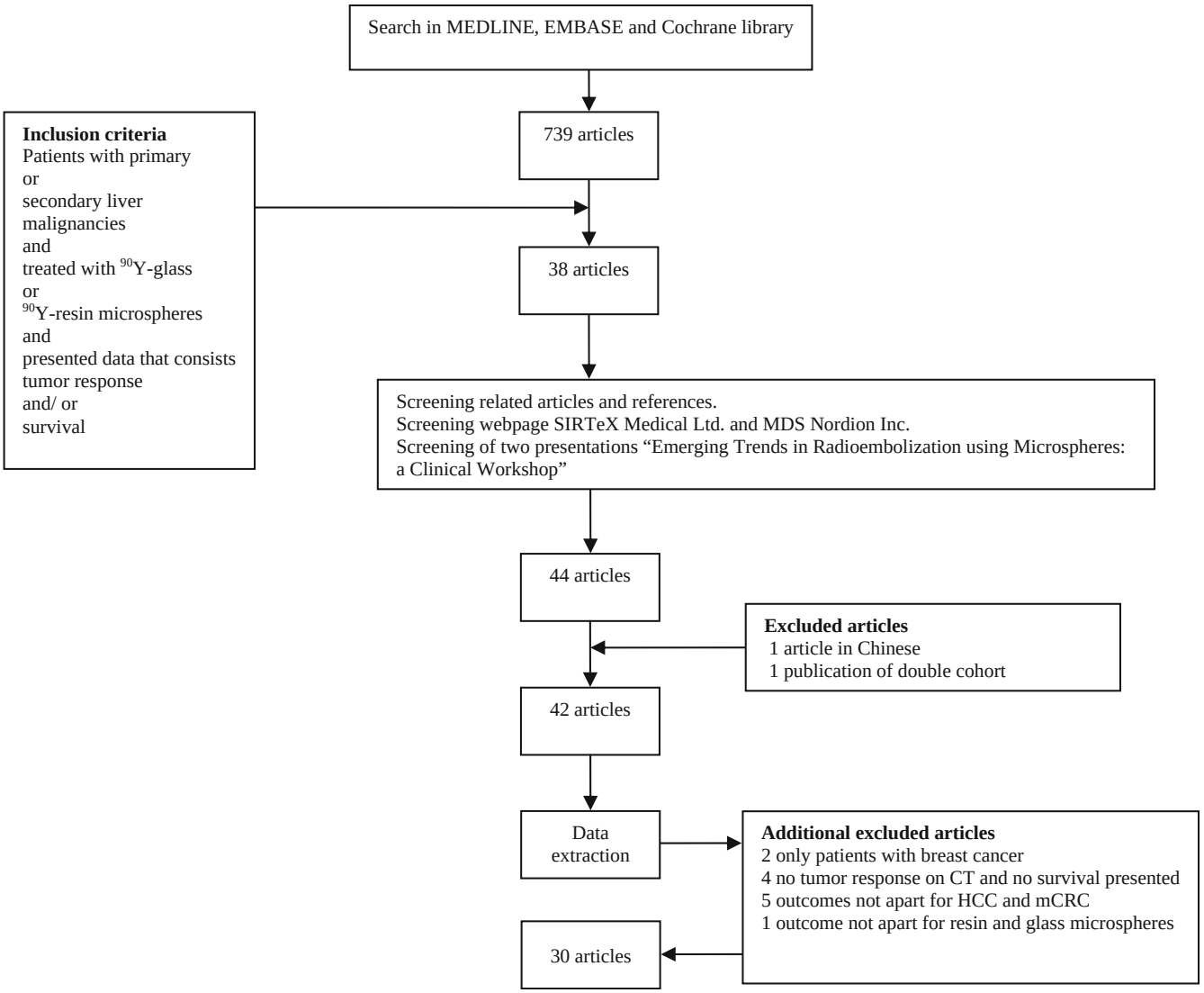

Fig. 1 Flowchart summarizing the selection of relevant articles

Data structuring

The 30 remaining articles were divided into two groups, according to tumor type, i.e., mCRC or HCC. The pathology of these two types of liver tumors is very different. Colorectal carcinoma initially metastasizes to one or a few focal parts of the liver, whereas HCC usually spreads diffusely throughout the liver. Response to chemotherapy is also very different in these tumor types. This resulted in the formation of two groups (mCRC and HCC), for which the studies were compared on design and patient population, in order to assess the comparability of the results.

In the group of patients with mCRC, after data extraction the use of different (generations of) chemotherapy regimens was identified as a major source of heterogeneity. Two covariates were therefore included in the meta-regression model: (1) whether the older generation of cytostatic agents (5-FU/LV or floxuridine) or the newer generation (5-FU/LV + oxaliplatin (FOLFOX) or 5-FU/LV + irinotecan (FOLFIRI)) was used, and (2) whether ^{90}Y-RE was given as a salvage therapy or as a first-line treatment with adjuvant chemotherapy. No separation was made between the microsphere product that was used (glass or resin), because of the small number of patients with mCRC treated with the glass microspheres (ca. 8%).

In view of the chemoresistant nature of HCC [10], previously given therapy was not observed as a source of heterogeneity. Therefore, the main source of heterogeneity observed in this group was the microsphere product used, either glass or resin. This resulted in the formation of two subgroups.

To allow comparability of results with regard to tumor response, the category of 'any response' (AR) was

introduced. The AR category comprises all patients originally from the categories complete response, partial response, and stable disease.

Meta-analysis

The study of Andrews et al. [11] included just one HCC patient. This patient was therefore not included in the analysis. The proportions of patients with AR were modeled by a meta-regression analysis according to Hamza et al. [12]. This method uses the exact binomial likelihood approach instead of an approximate method based on the normal distribution of within-study variability. A random effects model was applied since considerable heterogeneity was observed between the studies. The meta-regression analysis was performed using PROC NLMIXED in SAS version 9.1 as described by Hamza et al.

Results

Thirty articles were included in the meta-analysis. In 999 out of 1,217 patients, tumor response was assessed by CT. The proportion of AR for HCC and mCRC combined varied between 0.29 and 1.00 with a median value of 0.82. Treatment with glass microspheres showed a lower response (AR=0.77) than treatment with resin microspheres (AR=0.85) (p=0.07), with an estimated odds ratio of 0.56 (95% CI 0.29–1.06).

Colorectal liver metastases

In a total of 19 eligible studies 792 patients with mCRC had undergone ^{90}Y-RE [6, 11, 13–29]. In 18 studies tumor response was assessed in a total of 681 patients. Of these patients 486/681 had received ^{90}Y-RE in a salvage setting, of which 124/486 had been previously treated and/or co-treated with 5-FU/LV or floxuridine, and 362/486 had been given the newer-generation cytostatic agents. One hundred and ninety-five patients had received ^{90}Y-RE as a first-line treatment, of which 175/195 were treated with adjuvant 5-FU/LV or floxuridine and 20/195 with FOLFOX.

The specific cytostatic agent(s) ("old" versus "new") that were used did not affect response (p=0.96). Whether ^{90}Y-RE was offered in a salvage setting or as a first-line therapy affected tumor response significantly (p=0.07). The estimated proportions of AR, based on the regression model, were 0.79 and 0.79 in salvage setting and 0.91 and 0.91 in the first-line, for the older and newer chemotherapy, respectively.

Median survival after ^{90}Y-RE, irrespective of differences in determinants (microspheres type, chemotherapy protocol, and stage: salvage or first-line), varied from 6.7 to 17.0 months. The reported median survival from diagnosis of mCRC ranged from 10.8 to 29.4 months (Table 2).

Two randomized controlled trials were performed in patients with unresectable mCRC. In 2001, Gray et al. presented the results for 76 patients who had been randomized to either ^{90}Y-RE (resin) as neoadjuvant to hepatic arterial infusion (HAI) of floxuridine or to HAI alone [14]. Patients in the combination arm showed a significantly greater response when measured by tumor volume, and a significantly increased time to progression. AR was 78% and 59% (p=0.03) for the combination arm and the HAI-alone arm, respectively, and time to progression, based on tumor area measurements, was 15.9 months vs. 9.7 months (p=0.001), respectively. In 2004, Van Hazel et al. reported on the outcome in 21 previously untreated patients with mCRC [15] in a similar study, in which it was demonstrated that the addition of a single administration of resin microspheres prior to 5-FU/LV significantly increased response, time to progression, and survival. In this phase II trial AR was 100% in the combination arm vs. 60% in the chemotherapy-alone arm (p<0.001), time to progression 18.6 and 3.6 months (p<0.0005), respectively, and survival 29.4 and 12.8 months (p=0.02). Thirty-six months postrandomization 36% of patients in the combination arm were still alive, whereas no patients from the 5-FU/LV-alone arm were alive at that time.

Hepatocellular carcinoma

In 14 articles clinical data were presented on tumor response and survival for 425 patients with HCC who had received ^{90}Y-RE [11, 18, 24, 30–40]. Twelve studies presented data of tumor response for a total of 318 patients. Treatment with resin microspheres was associated with a significantly higher proportion of AR than glass microsphere treatment (0.89 vs. 0.78 (p=0.02)).

Median survival was reported in seven studies in which survival time was defined as survival from treatment or from diagnosis or recurrence. Median survival from microsphere treatment varied between 7.1 and 21.0 months, and median survival from diagnosis or recurrence was 9.4–24.0 months (Table 3).

Discussion

This meta-analysis showed that in patients with mCRC the tumor response of ^{90}Y-RE is high, with AR rates of approximately 80% in a salvage setting, and over 90% when used as first-line treatment, as neoadjuvant to chemotherapy. The response rates reported for studies in which 5FU/LV was combined with irinotecan or oxaliplatin were similar to those of studies in which only 5FU/LV was used. This can probably be explained by differences in the criteria for tumor response that were used (WHO versus RECIST criteria [41]).

Regarding the question as to which microsphere is most effective in the treatment of mCRC—glass or resin—no

Table 2 Tumor responses and median survivals after ^{90}Y-RE in mCRC

Study	Number (n)	Results									
		Tumor response on CT								Median survival (months)	
		CT performed in	Response measured at (months post ^{90}Y-RE)	RECIST[a]	CR (%)	PR (%)	SD (%)	AR (%)	PD (%)	From diagnosis	From ^{90}Y-RE
Resin microspheres											
Gray et al. (1992) [13]	29	22	3	–	0	45	37	82	18	NR	NR
Stubbs et al. (1999) [29]	30	27	3	–	0	70	19	89	11	10.8 (range 1.9–41.0)	6.7 (range 1.0–15.8)
Gray et al. (2000) [28]	71	51	3	–	0	75	12	86	14	17.3	9.9
Gray et al. (2001)[b] [14]	36	36[c]	3	–	6	44	28	78	14	NR	17.0
Stubbs et al. (2001) [16]	50	44	3	–	0	73	18	91	9	14.5 (range 1.9–91.4)	9.8 (range 1.0–30.3)
Van Hazel et al. (2004)[b] [15]	11	11	3	Yes	0	91	9	100	0	29.4	NR
Lim et al. (2005) [18]	30	30	2	Yes	0	33	27	60	40	NR	NR
Lim et al. (2005) [19]	32	32	2	Yes	0	31	28	59	41	NR	NR
Murthy et al. (2005) [17]	12	9	NR	Yes	0	0	56	56	44	24.6	4.5
Mancini et al. (2006) [20]	35	35	1.5	Yes	0	12	76	88	13	NR	NR
Kennedy et al. (2006) [21]	208	208	3	–	0	36	55	91	10	NR	Responders 10.5 Non-responders 4.5
Stubbs et al. (2006) [22]	100	80	3	–	1	73	20	94	6	16.2 (range 1.1–101.6)	11 (range 0.1–76.6)
Jakobs et al. (2007) [24]	18	18	2–3	–	0	NS	NS	76	24	NR	NR
Sharma et al. (2007) [23]	20	20	3	Yes	0	90	10	100	0	NR	NR
Glass microspheres											
Anderson et al. (1992) [25]	7	7	2	–	0	0	86	86	14	NR	11 (range 5–25+)
Andrews et al. (1994) [11]	17	17	2	–	0	29	29	59	41	NR	13.8
Wong et al. (2002) [26]	8	8	3	–	12	12	38	63	38	NR	NR
Lewandowski et al. (2005) [27]	27	26	3	–	0	35	52	87	13	NR	9.3 (95% CI 7.2–13.3)
Sato et al. (2008) [6]	51	51	5.3	–	NR	NR	NR	NR	NR	NR	15.2

CR complete response, *PR* partial response, *SD* stable disease, *AR* any response (= CR + PR + SD), *PD* progressive disease, *NR* not reported, *NS* not specified

[a]Response measured and presented according to RECIST criteria [41]

[b]Response and survival for ^{90}Y-RE arm alone

[c]CT of 3 out of 36 patients not assessable

conclusions can be reached since only 8% of the patients with mCRC were treated with the glass microspheres. Furthermore, the meta-analysis showed that resin microspheres were significantly more effective in treating HCC than glass microspheres (AR 89% vs. 78% (p=0.02)). This is a rather unexpected finding, because only the glass microspheres are FDA-approved for treating HCC, whereas the resin microspheres are approved for mCRC, not HCC. It may be postulated that this outcome is the consequence of the substantial difference in numbers of microspheres that are infused: a dose of glass microspheres consists of 4 million microspheres, whereas a dose of resin microspheres usually contains 50 million microspheres [42]. It has been reported in the literature that administration of resin microspheres had to be prematurely halted, before the predetermined amount of radioactivity was instilled, due to macroscopic embolization [43]. In contrast, the relatively very low number of glass microspheres per dose is associated with microscopic embolization [39]. However, the low number of particles infused in the case of the glass microspheres may be a disadvantage when targeting a tumor type that is often diffusely spread throughout the liver at the time of diagnosis [44]; the radiation dose would be distributed in and around the tumors too heterogeneously to be able to deliver a tumoricidal dose to the entire lesion even if the total

Table 3 Tumor responses and median survivals after ^{90}Y-RE in HCC

Study	Number (n)	Results									
		Tumor response on CT								Median survival (months)	
		CT performed in	Response measured at (months post ^{90}Y-RE)	RECIST[a]	CR (%)	PR (%)	SD (%)	AR (%)	PD (%)	From diagnosis (or reoccurrence)	From ^{90}Y-RE
Resin microspheres											
Lau et al. (1994) [31]	18	18	2	–	0	44	44	89	11	NR	7.1
Lau et al. (1998) [32]	71	71	2	–	0	27	65	92	8	9.4 (range 1.8–46.4)	NR
Lim et al. (2005) [19]	5	4	2	Yes	0	25	50	75	25	NR	NR
Sangro et al. (2006) [33]	24	21	2	–	NS	NS	NS	88	12	NR	7.1 (95% CI 2.1–12)
Jakobs et al. (2007) [24]	5	5	2–3	Yes	0	NS	NS	100	0	NR	NR
Glass microspheres											
Houle et al. (1989) [34]	7	7	NR	–	0	0	29	29	71	NR	NR
Andrews et al. (1994) [11]	1	1	2	–	0	0	0	0	100	NR	NR
Dancey et al. (2000) [35]	22	19	2–3	–	5	16	58	79	21	NR	12 (range 2–42)
Carr et al. (2004) [36]	65	65	3	–	3	28	40	71	29	Okuda I 12 (95% CI 2–42) Okuda II 10 (95% CI 6–20)	NR
Geschwind et al. (2004) [30]	100	NR	NR	NR	NR	NR	NR	NR	NR	NR	Okuda I 21.0 Okuda II 1.0
Liu et al. (2004) [37]	11	11	1–1.5	–	9	72	0	82	18	NR	NR
Salem et al. (2005) [38]	43	43	Varying	–	NS	NS	NS	79	21	Okuda I 24 (95% CI 18–28) Okuda II 12 (95% CI 9–17)	NR
Kulik et al. (2006) [40]	35	34	6 (0.8–16)	–	NS	NS	NS	88	12	NR	NR
Sato et al. (2006) [39]	19	19	5 (1.5–14)	–	NS	NS	NS	79	21	NR	NR

CR complete response, *PR* partial response, *SD* stable disease, *AR* any response (= CR + PR + SD), *PD* progressive disease, *NR* not reported, *NS* not specified

[a]Response measured and presented according to RECIST criteria [41]

amount of radioactivity of a dose of glass microspheres is at least 50% higher than is the case in the resin microspheres (Table 1). Another (theoretical) consideration is that the macroembolic effect of the resin microspheres is accompanied by a greater lack of oxygen resulting in ischemia and therefore enhanced efficacy. On the other hand, shortage of oxygen might also diminish the tumoricidal effect of ionizing radiation due to a lack of oxygen radicals that is produced in this environment.

However, this macroembolic effect can be associated with clinical signs, the so-called postembolization syndrome (PES), which is reported to frequently occur following resin microspheres infusion, but not often subsequent to administration of the minimally embolic glass microspheres. PES is characterized by fatigue, nausea, fever, right upper quadrant pain, and/or vomitus, all of which are transitory and can be effectively controlled by outpatient medication [21, 39, 45–47].

Serious complications have been reported when microspheres were inadvertently deposited in excessive amounts in organs other than the liver. Conditions that have been reported include gastrointestinal ulceration/bleeding, gastritis/duodenitis, cholecystitis, pancreatitis, and radiation pneumonitis [42, 45, 48–52]. Training, careful patient selection, meticulous pretreatment assessment, and coiling of relevant vasculature reduce complication rates massively [53]. Radiation-induced liver disease following ^{90}Y-RE has been reported sporadically [15, 54]. Careful patient selection and individualized dose calculation minimize the risk of this complication. Profound and persistent lympho-

penia, with rapid onset and in some cases lasting over 12 months, though without clinical consequences, has been reported in patients with HCC following ^{90}Y-RE with glass microspheres [36, 38]. This complication has not been observed subsequent to ^{90}Y-RE with resin microspheres (as monotherapy). The underlying mechanism is not clear but myelosuppression is not probable since leaching of radioactivity from the glass microspheres does not take place [55]. However, following ^{90}Y-RE, in addition to the liver tumors and to some extent the liver parenchyma, a radiation dose is delivered to the blood each time it passes the liver, which might explain this adverse laboratory event.

Unfortunately, in this meta-analysis overall tumor response could only be assessed as 'any response', which is caused by the reality that response categories were not uniformly defined in the analyzed studies. It is expected that this problem of being able to compare tumor response will disappear in the near future, since the RECIST criteria, published in 2001 [41], are evermore applied. In accordance with the RECIST criteria, tumor response in malignant liver disease is assessed using cross-sectional anatomic imaging (CT, MRI), by measuring tumor size. However, lesion size reduction does not always occur even if treatment is effective. This is associated with different peri- and endotumoral processes that can occur post ^{90}Y-RE, e.g., peritumoral edema and hemorrhage, and ring enhancement [56]. Therefore, actual tumor response may often be better than is reported, based on CT measurements alone. In a significant number of cases 'stable disease' could actually be minor, partial, or even complete response. In order to improve sensitivity in assessing tumor response, it is therefore strongly recommended that ^{18}F-FDG-PET or functional MRI (diffusion-weighted MRI) is added to post-treatment response assessment protocols [56–59].

Only two randomized controlled trials were found in the literature, both on resin microspheres and mCRC. The results were encouraging, showing a major survival benefit for the ^{90}Y-RE + chemo arm. However, since then larger controlled trials have commenced, in which more effective chemotherapeutics were used [60].

In this paper the emphasis was placed on ^{90}Y-RE in patients with unresectable HCC and mCRC. Nonetheless, patients with liver metastases from primaries other than mCRC have been treated with ^{90}Y-RE. This is particularly the case for liver metastasized breast cancer, of which response rates of over 90% are reported [61, 62]. ^{90}Y-RE has been applied in patients with neuroendocrine liver metastases, too, albeit in small numbers [11, 63]. Reported response rates were 100%, and it would therefore be worthwhile to further explore the use of ^{90}Y-RE for this indication.

Fortunately, ^{90}Y-RE is not the only novel and effective treatment option offered to patients with unresectable HCC. Recently, a breakthrough has been reported in the field of biological agents. For sorafenib (Nexavar®, Bayer Healtcare AG, Leverkusen, Germany), an oral multikinase inhibitor, a statistically significant and clinically meaningful improvement in survival has been shown in HCC patients with advanced disease: 10.7 months in the sorafenib group versus 7.9 months in the placebo group (p=0.0006) [64]. Recently, a phase I/II trial has started in which patients with unresectable HCC are treated with the resin microspheres plus sorafenib [60].

The clinical efficacy of other promising molecular agents, e.g., bevacizumab, erlotinib, is currently being investigated as well. When added to FOLFOX or XELOX (capecitabine + oxaliplatin), the angiogenesis inhibitor bevacizumab (Avastin®, Genentech Inc., South San Francisco, CA, USA) has been proven to prolong survival of patients with colorectal cancer by approximately 6 months compared with FOLFOX or XELOX alone [65, 66]. In fact, in an ongoing multicenter study, the "FAST" trial, patients with unresectable colorectal liver metastases are treated concurrently with FOLFOX or FOLFIRI, bevacizumab, and ^{90}Y-RE (resin microspheres) [67].

In conclusion, ^{90}Y-RE is associated with high response rates, both in a salvage and in a first-line setting. The true impact on survival will only become known after publication of several ongoing and/or to be initiated phase III studies. The results of trials in which ^{90}Y-RE and modern chemotherapy agents are combined with novel biological agents are awaited with interest as well.

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Clinical Policy Bulletin:
Liver and Other Neoplasms - Treatment Approaches
Number: 0268
(Replaces CPB 338)

Policy

1. Percutaneous Ethanol Injection

   Aetna considers percutaneous ethanol injection (PEI) medically necessary for the treatment of hepatocellular cancers (HCC) without extra-hepatic spread.

   Aetna considers PEI for liver neoplasms experimental and investigational when criteria are not met. There is inadequate information to document the effectiveness of PEI as an alternative to surgical resection for the treatment of hepatic metastases.

   Aetna considers *combined* radiofrequency ablation and PEI experimental and investigational for the treatment of HCC because of insufficient evidence in the peer-reviewed literature.

2. Chemoembolization

   Aetna considers chemoembolization (CE) medically necessary for *any* of the following:

   1. For treatment of neuroendocrine cancers (i.e., carcinoid tumors and pancreatic endocrine tumors) involving the liver. For carcinoid tumors, CE is considered medically necessary only in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea); *or*
   2. For unresectable, primary HCC; *or*
   3. For liver-only metastasis from uveal (ocular) melanoma; *or*
   4. Pre-operative hepatic artery chemoembolization followed by orthotopic liver transplantation for HCC.

   Aetna considers CE experimental and investigational for other indications including palliative treatment of liver metastases from other non-neuroendocrine primaries (e.g., breast cancer, cervical cancer, colon cancer, melanoma, rhabdomyosarcoma, or unknown primaries) and chemoembolization of the pancreas for pancreatic cancer because there is inadequate evidence in the medical literature of the

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effectiveness of CE for these indications.

3. Intra-Hepatic Chemotherapy

Aetna considers intra-hepatic chemotherapy (infusion) medically necessary for members with liver metastases from colorectal cancer.

Aetna considers intra-hepatic chemotherapy experimental and investigational for other indications, including treatment of liver primaries or metastases from other primaries besides colorectal cancer because of insufficient evidence in the peer-reviewed literature.

Aetna considers "one-shot" arterial chemotherapy for members with liver metastases from colorectal cancer experimental and investigational because of insufficient evidence in the peer-reviewed literature.

Aetna considers transarterially administered gene therapy experimental and investigational for primary and secondary liver malignancies because of insufficient evidence in the peer-reviewed literature.

4. Intra-Hepatic Microspheres

Aetna considers intra-hepatic microspheres (e.g., TheraSphere, MDS Nordion Inc.; SIR-Spheres, Sirtex Medical Inc.) medically necessary for any of the following:

1. For treatment of neuroendocrine cancers (i.e., carcinoid tumors and pancreatic endocrine tumors) involving the liver. For carcinoid tumors, intra-hepatic microspheres are considered medically necessary only in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea); *or*
2. For unresectable, primary HCC; *or*
3. For unresectable liver tumors from primary colorectal cancer; *or*
4. Pre-operative use as a bridge to orthotopic liver transplantation for HCC.

Aetna considers intra-hepatic microspheres experimental and investigational for metastases from esophageal cancer and gallbladder cancer and other indications because of insufficient evidence in the peer-reviewed literature.

5. Drug-Eluting Beads Trans-Arterial Chemoembolization

Aetna considers drug-eluting beads trans-arterial chemoembolization experimental and investigational for leiomyosarcoma, and for primary and liver-dominant metastatic disease of the liver because of insufficient evidence in the peer-reviewed literature.

See also CPB 0274 - Ablation of Hepatic Lesions.

Background

Chemoembolization (CE) involves the periodic injection of chemotherapy mixed with embolic material into selected branches of the hepatic arteries feeding liver tumors. Chemoembolization has been successfully used as a palliative treatment of symptoms associated with functioning neuroendocrine tumors involving the liver. The most

common such tumor is the carcinoid tumor whose hormone production is associated with the carcinoid syndrome, characterized by debilitating flushing, wheezing and diarrhea. Pancreatic endocrine tumors that produce gastrin, insulin or other pancreatic hormones are unusual types of neuroendocrine tumors. Pancreatic endocrine (i.e., islet cell) tumors must be distinguished from the more common pancreatic epithelial tumors that arise from the exocrine portion of the pancreas.

The prognosis for patients with unresectable hepatocellular carcinoma (HCC) tumors is extremely poor. Even in the case of small nodular lesions detected by US screening, patients receiving no treatment showed a mean 3-year survival rate of 12 %. Among non-surgical options, percutaneous ethanol injection (PEI) can be considered the treatment of choice for patients with small HCC tumors. Transcatheter arterial chemoembolization (TACE), most frequently performed by intra-arterially injecting an infusion of antineoplastic agents mixed with iodized oil (Lipiodol), has been extensively used in the treatment of large HCC tumors. However, although massive tumor necrosis can be demonstrated in most cases, a complete necrosis of the tumor has rarely been achieved with TACE, since residual tumor can be found in a non-negligible number of the treated lesions.

Transcatheter arterial chemoembolization was found mostly effective in nodules less than 4 cm in diameter, with a thick tumor capsule. In fact, small, encapsulated HCC are almost completely fed by hepatic arterial blood and therefore highly responsive to hepatic arterial embolization. On the contrary, in unencapsulated tumors or in tumors showing extracapsular invasion of neoplastic cells, TACE often fails to induce complete necrosis since tumor cells, either unimpeded by the absence of a capsule or spreading across the capsule itself, invade the adjacent liver parenchyma, thus obtaining additional blood supply from the sinusoidal portal system.

Large HCC lesions can be more effectively treated with combined TACE and PEI. In fact, alcohol diffusion is easier after the occurrence of the necrotic changes produced by TACE, thus allowing the intra-nodular injection of larger amounts of ethanol. Moreover, after arterial embolization, the normal wash-out of the injected ethanol is more difficult in the tumorous area, resulting in longer retention of the substance. The combination of TACE and PEI seems to be a highly effective treatment for large HCC also in the instances when daughter nodules are associated with a main tumor. The presence of the capsule significantly enhances the chances of success and should be considered an important requirement when selecting patients to be submitted to TACE and PEI.

According to available literature, TACE may be indicated for symptomatic treatment of functional neuroendocrine cancers (i.e., carcinoid tumors and pancreatic endocrine tumors) involving the liver, in persons with adequate hepatic function (bilirubin less than 2 mg/dL, absence of ascites; no portal vein occlusion; and tumor involvement of less than 65 % of liver). For carcinoid tumors, TACE is indicated only in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea). The safety and effectiveness of more than 4 TACE procedures is unknown.

For unresectable, primary HCC, TACE is indicated in persons with small encapsulated nodules (less than 4 cm in diameter), no evidence of extra-hepatic metastases, and with adequate hepatic (serum bilirubin concentration less than 2.9 mg/dL) and renal function (serum creatinine less than 2.0 mg/dL).

Pleguezuelo and colleagues (2008) stated that TACE improves survival in cirrhotic patients with HCC. The optimal schedule, best anti-cancer agent and best technique are

still unclear. Transcatheter arterial chemoembolization may not be better than transarterial embolization (TAE). Hepatocellular carcinoma is very chemoresistant, thus embolization may be more important than chemotherapy. Lipiodol can not be considered as an embolic agent and there are no data to show that it can release chemotherapeutic agents slowly. It can mask residual vascularity on CT imaging and its use is not recommended. Both TACE and TAE result in hypoxia, which stimulates angiogenesis, promoting tumor growth; thus combination of TACE with anti-angiogenic agents may improve current results. To date, there is no evidence that TACE pre-liver transplantation or resection helps to expand current selection criteria for patients with HCC, nor results in less recurrence after surgery. Combination with other techniques, such as radiofrequency ablation (RFA) and drugs, may enhance the effect of TACE. New trials are being conducted to clarify these issues.

Biolato et al (2010) provided an overview on the loco-regional therapy performed by TACE in patients with HCC, either as sole, either as neoadjuvant to surgery or bridge therapy to orthotopic liver transplantation (OLT). Chemoembolization combines de-arterialization of the tumor and selective delivery of chemotherapeutic agents into tumor's feeding vessels during angiography. Tumor ischemia raises the drug concentration compared to infusion alone and extends the retention of the chemotherapeutic drug. As loco-regional therapy, TACE allows a complete local tumor control of 25 to 35 % and permits an increase of survival in patients with intermediate HCC according to Barcelona-Clinic Liver Cancer (BCLC) classification. Excellent results were also achieved by combined therapies, such as with PEI or RFA, as neoadjuvant therapy prior to liver resection and in some circumstances as a bridging tool before liver transplantation. Drug eluting beads are microspheres that can be loaded with doxorubicin and induce toxic and ischemic necrosis with the same device; that allows an increase of drug selectively exposed to tumor cells and simultaneously a reduction of systemic toxicity. Tumor embolization induces a neoangiogenic reaction with a significant growth of adjacent satellites, so the association with sorafenib has a strong rationale for a combined therapy and is currently under investigation. The authors concluded that TACE is the standard of care for treatment of intermediate HCC.

Percutaneous ethanol injection has been shown to be effective only in primary HCC with a limited number (fewer than 4) of small foci (less than 5 cm in diameter) and with no evidence of extra-hepatic metastasis. According to the medical literature, PEI is not suitable for persons with coagulopathy or ascites. The National Comprehensive Cancer Network practice guidelines (NCCN, 2010) on hepatobiliary cancers stated that the 2 most commonly used methods of ablation therapy are PEI and RFA.

In a randomized controlled study, Brunello and colleagues (2008) compared PEI and RFA for the treatment of early HCC. A total of 139 cirrhotic patients in Child-Pugh classes A/B with 1 to 3 nodes of HCC (diameter 15 to 30 mm), for a total of 177 lesions were included in this study. Patients were randomized to receive RFA (n = 70) or PEI (n = 69). The primary end-point was complete response (CR) 1 year after the percutaneous ablation of all HCC nodes identified at baseline. Secondary end-points were: early (30 to 50 days) CR, complications, survival and costs. In an intention-to-treat analysis, 1-year CR was achieved in 46/70 (65.7 %) and in 25/69 (36.2 %) patients treated by RFA and PEI, respectively (p = 0.0005). For lesions greater than 20 mm in diameter, there was a larger CR rate in the RFA-treated subjects (68.1 % versus 26.3 %). An early CR was obtained in 67/70 (95.7 %) patients treated by RFA compared with 42/64 (65.6 %) patients treated by PEI (p = 0.0001). Complications occurred in 10 and 12 patients treated by RFA and PEI, respectively. The overall survival (OS) rate was not significantly different in the RFA versus PEI arm (adjusted hazard ratio = 0.88, 95 % confidence interval [CI]: 0.50 to 1.53). There was an incremental health-care cost of

8,286 Euro for each additional patient successfully treated by RFA. The authors concluded that the 1-year CR rate after percutaneous treatment of early HCC was significantly better with RFA than with PEI, but did not provide a clear survival advantage in cirrhotic patients.

Wong et al (2008) examined if combining PEI with RFA in the management of HCC in high-risk locations improves treatment outcomes. These researchers compared the outcome of management of high-risk tumors with PEI and RFA (n = 50) or RFA alone (n = 114) with the outcome of RFA of non-high-risk tumors (n = 44). They also compared the survival rates of patients with and those without high-risk HCC. Percutaneous ethanol injection was performed into the part of the tumor closest to a blood vessel or vital structure before RFA. The study included 142 patients with 208 HCCs managed with RFA. Despite larger tumor sizes (2.8 +/- 1 cm versus 1.9 +/- 0.7 cm versus 2.5 +/- 0.1 cm for the high-risk RFA plus PEI, non-high-risk RFA, and high-risk RFA groups, respectively; $p < 0.001$), the primary effectiveness rate of high-risk RFA and PEI (92 %) was similar to that of non-high-risk RFA (96 %). The primary effectiveness rate of high-risk RFA and PEI was slightly higher ($p = 0.1$) than that of high-risk RFA (85 %). The local tumor progression rates (21 % versus 33 % versus 24 % at 18 months) of the 3 respective groups were not statistically different ($p = 0.91$). Patients with and those without high-risk tumors had equal survival rates ($p = 0.42$) after 12 (87 % versus 100 %) and 24 (77 % versus 80 %) months of follow-up. Independent predictors of primary effectiveness were a tumor size of 3 cm or less ($p = 0.01$) and distinct tumor borders ($p = 0.009$). Indistinct borders ($p = 0.033$) and non-treatment-naive status of HCC ($p = 0.002$) were associated with higher local tumor progression rates. The only predictor of survival was complete ablation of all index tumors ($p = 0.001$). The authors concluded that the combination of RFA and PEI in the management of HCC in high-risk locations has a slightly higher primary effectiveness rate than does RFA alone. They stated that a randomized controlled study is warranted.

In a Cochrane review, Schoppmeyer (2009) evaluated the beneficial and harmful effects of PEI or percutaneous acetic acid injection (PAI) in adults with early HCC. A systematic search was performed in the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, EMBASE, and ISI Web of Science in May 2009. Meeting abstracts of 6 oncological and hepatological societies (ASCO, ESMO, ECCO, AASLD, EASL, APASL) and references of articles were hand-searched. Researchers in the field were contacted. Randomized trials comparing PEI or PAI with no intervention, sham intervention, other percutaneous interventions or surgery for the treatment of early HCC were considered regardless of blinding, publication status, or language. Studies comparing RFA or combination treatments were excluded. Two authors independently selected trials for inclusion, and extracted and analyzed data. The hazard ratios (HRs) for median OS and recurrence-free survival were calculated using the Cox regression model with Parmar's method. Type and number of adverse events were reported descriptively. Three randomized trials with a total of 261 patients were eligible for inclusion. The risk of bias was high in all trials. Two of the trials compared PEI with PAI. Overall survival (HR 1.47; 95 % CI: 0.68 to 3.19) and recurrence-free survival (HR 1.42; 95 % CI: 0.68 to 2.94) were not significantly different. Data on the duration of hospital stay were inconclusive. Data on quality of life were not available. There were only mild adverse events in both treatment modalities. The other trial compared PEI with surgery. There was no significant difference in overall survival (HR 1.57; 95 % CI: 0.53 to 4.61) and recurrence-free survival (HR 1.35; 95 % CI: 0.69 to 2.63). No serious adverse events were reported in the PEI group. Three post-operative deaths occurred in the surgery group. The authors concluded that PEI and PAI does not differ significantly regarding benefits and harms in patients with early HCC, but only a limited number of patients have

been examined and the bias risk was high in all trials. There is also insufficient evidence to determine whether PEI or segmental liver resection is more effective, although PEI may seem safer.

In a meta-analysis, Wang et al (2010) identified the survival benefits of TACE combined with percutaneous ablation (PA) therapy (RFA or PEI) for unresectable HCC compared with those of TACE or PA alone. Randomized-controlled trials (RCTs) published as full papers or abstracts were searched to assess the survival benefit or tumor recurrence for patients with unresectable HCC on electronic databases. The primary outcome was survival. The secondary outcomes were response to therapy and tumor recurrence. A total of 10 RCTs met the criteria to perform a meta-analysis including 595 participants. Transcatheter arterial chemoembolization combined with PA therapy, respectively improved, 1-, 2-, and 3-year OS compared with that of monotherapy [odds ratio (OR) = 2.28, 95 % CI: 1.14 to 4.57; p = 0.020], (OR = 4.53, 95 % CI: 2.62 to 7.82, p < 0.00001) and (OR = 3.50, 95 % CI: 1.75 to 7.02, p = 0.0004). Sensitivity analysis demonstrated a significant benefit in 1-, 2- and 3-year OS of TACE plus PEI compared with that of TACE alone for patients with large HCC lesions, but not in TACE plus RFA versus RFA for patients with small HCCs. The pooled result of 5 RCTs showed that combination therapy decreased tumor recurrence compared with that of monotherapy (OR = 0.45, 95 % CI: 0.26 to 0.78, p = 0.004). The authors concluded that TACE combined with PA therapy especially PEI improved the OS status for large HCCs.

Hepatic arterial infusion (HAI) of chemotherapy involves the use of an implanted subcutaneous pump to deliver continuous chemotherapy into the hepatic artery. Controlled trials have shown that this therapy is associated with higher tumor response rates and this approach is considered a potentially curative treatment of patients with colorectal cancer (CRC) with isolated liver metastases. Other applications of intra-hepatic chemotherapy are unproven.

Mocellin et al (2007) stated that the treatment of unresectable liver-confined metastatic disease from CRC is a challenging issue. Although loco-regional treatments such as HAI claim the advantage of delivering higher doses of anti-cancer agents directly into the affected organ, the benefit in terms of OS is unclear. These investigators quantitatively summarized the results of RCTs comparing HAI with systemic chemotherapy (SCT). They reported that 10 RCTs have been published for a total of 1,277 patients. For tumor response rates, relative risks (RR) and their 95 % CIs were obtained from raw data; for OS, HRs and their 95 % CIs were extrapolated from the Kaplan-Meier survival curves. These researchers noted that HAI regimens were based on floxuridine (FUDR) in 9 of 10 RCTs, whereas in 1 RCT, fluorouracil (FU) + leucovorin was used. Systemic chemotherapy consisted of FUDR, FU, FU + leucovorin, or a miscellany of FU and best supportive care in 3, 1, 4, and 2 studies, respectively. Pooling the data, tumor response rate was 42.9 % and 18.4 % for HAI and SCT, respectively (RR = 2.26; 95 % CI, 1.80 to 2.84; p < 0.0001). Mean weighted median OS times were 15.9 and 12.4 months for HAI and SCT, respectively; the meta-risk of death was not statistically different between the 2 study groups (HR = 0.90; 95 % CI, 0.76 to 1.07; p = 0.24). The authors concluded that currently available evidence does not support the clinical or investigational use of fluoropyrimidine-based HAI alone for the treatment of patients with unresectable CRC liver metastases, at least as a first-line therapy.

In a review on recent advances in transarterial therapy of primary and secondary liver malignancies, Kalva and colleagues (2008) stated that transarterially administered gene therapy holds promise but is still in the early stages of investigation.

Despite various modalities available for the treatment of non-resectable HCC, such

therapies have not resulted in marked impact on OS. A new approach in treating these patients is administration of microspheres via hepatic artery branches with subsequent deposition in the tumor terminal vasculature. This method could provide an approximately 3-fold or greater radiation dose in tumor nodules relative to normal liver. Previous studies have demonstrated that yttrium-90 embedded into non-biodegradable glass microspheres (TheraSphere, MDS Nordion Inc., Kanata, Ontario, Canada) can be administered safely by intra-hepatic arterial injection to patients with HCC and underlying cirrhosis at a dose of 100 Gy. A recent study (Dancey et al, 2000) reported that intra-hepatic yttrium-90 microspheres appears to be beneficial for patients with non-resectable HCC with less toxicity than systemic or hepatic arterial chemotherapy or hepatic arterial chemoembolization.

Dancey et al (2000) indicated that the following criteria be used to select appropriate patients for administration of intra-hepatic microspheres as an adjuvant to chemotherapy, surgery or transplantation for persons with unresectable HCC. These criteria are based on the selection criteria for clinical studies of the TheraSphere submitted for FDA approval, and contraindications to use of TheraSphere in the FDA-approved product labeling. These criteria may also be applied to persons with metastatic liver tumors from primary CRC (see discussion of SIR-Spheres below):

1. Histologically confirmed non-resectable lesion confined to the liver and at least 1 measurable lesion; and
2. Eastern Cooperative Oncology Group (ECOG) performance status score less than or equal to 3

    1. Absolute granulocyte count greater than or equal to 2.0 x 10 9/L
    2. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) less than 5 x upper normal limit [AST = 5 to 40 IU/L, ALT = 5 to 35 IU/L, ALP = 42 to 128 U/L]
    3. Bilirubin less than 1.5 x upper normal limit [total bilirubin = 0.1 to 1.0 mg/dL or 5.1 to 17.0 mmol/L]
    4. Estimated life expectancy greater than or equal to 12 weeks
    5. Normal pulmonary function defined as within 30 % of the expected values for each parameter (e.g., forced vital capacity, forced expiratory volume in 1 second, maximal mid-expiratory flow, maximal voluntary ventilation, and arterial blood gases);
    6. Platelet count greater than or equal to 100 x 109/L
    7. Prothrombin time (PT) and activated partial prothrombin time (APTT) within normal limits [PT = 11.0 to 12.5 seconds; APTT = 30 to 40 seconds]; *and*

3. Adequate bone marrow and hepatic function; and
4. No contraindications to hepatic artery catheterization (e.g., vascular abnormalities, bleeding diathesis, allergy to contrast dye, or portal vein thrombosis); and
5. No other concurrently planned oncotherapy; and
6. At least 1 month post other chemotherapy or surgery.

The following exclusion criteria apply:

1. Previous chemotherapy or radiation therapy for hepatoma; or
2. Potential absorbed dose to lungs greater than 30 Gy; or
3. Any uncorrectable angiographic flow to the gastrointestinal tract; or
4. Co-morbid disease that would preclude safe delivery of intra-hepatic microspheres treatment and place the member at undue risk.

Diagnostic work-up prior to the use of intra-hepatic microspheres includes (i) hepatic angiogram which entails placement of intra-hepatic catheter to assess vasculature and TheraSphere delivery route, and (ii) technetium-99 macroaggregated albumin (Tc-99 MAA) study to evaluate hepatic flow to gastrointestinal tract and/or pulmonary shunting. These studies are medically necessary and thus are eligible for coverage.

In the United States, SIR-Spheres are indicated for the treatment of unresectable metastatic liver tumors from primary CRC with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (floxuridine). The Food and Drug Administration (FDA) approval of SIR-Spheres was based on the results of a RCT involving 70 persons with CRC metastatic to the liver, 34 of whom received FUDR chemotherapy (control group), and 36 of whom received FUDR plus SIR-Spheres. Two of the patients receiving FUDR plus SIR-Spheres had a CR, and 16 had a partial response (PR). By comparison, 1 patient receiving FUDR alone achieved a CR and 7 had a PR. There is a statistically significant delay of time to progression of the disease in the group treated with FUDR plus SIR-Spheres, when compared with the group treated with FUDR only.

The FDA-approved product labeling for SIR-Spheres states that treatment with SIR-Spheres may be indicated when the metastatic CRC in the liver is considered unresectable. According to the FDA-approved labeling, metastatic CRC may be considered non-resectable in any of the following circumstances:

1. Multiple liver metastases together with involvement of both lobes; or
2. Tumor invasion of the hepatic confluence where the 3 hepatic veins enter the inferior vena cava (IVC) such that none of the hepatic veins could be preserved if the metastases were resected; or
3. Tumor invasion of the porta hepatis such that neither origin of the right or left portal veins could be preserved if resection were undertaken; or
4. Widespread metastases such that resection would require removal of more liver than is necessary to maintain life.

The FDA-approved product labeling for SIR-Sphere's states that resectability may be evaluated via imaging with a triple phase contrast angio-portal CT scan or MRI.

The FDA-approved labeling for SIR-Sphere states that the following tests are recommended before treatment.

1. A hepatic angiogram should be performed to establish arterial anatomy of the liver.
2. A nuclear medicine break-through scan (intra-hepatic technetium MAA Scan) to determine the percent lung shunting. If a port has been inserted, this test can be performed through the port.
3. Serologic tests of liver function should be performed to determine the extent of liver function/damage.

The FDA-approved product labeling for SIR-Spheres states that appropriate imaging studies are recommended to determine the extent of disease. These may include chest x-ray, CT scan of chest and abdomen, abdominal ultrasound and a bone scan.

The product labeling states that SIR-Spheres are contraindicated in patients who have

- Ascites or are in clinical liver failure, or
- Been treated with capecitabine within the 2 previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres, or
- Disseminated extra-hepatic malignant disease, or
- Greater than 20 % lung shunting of the hepatic artery blood flow determined by

technetium MAA scan, or
- Had previous external beam radiation therapy to the liver, or
- Markedly abnormal synthetic and excretory liver function tests (LTFs), or
- Portal vein thrombosis; or
- Pre-assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel.

The manufacturer of SIR-Spheres recommends a SPECT scan of the upper abdomen be performed immediately after implantation of SIR-Spheres to confirm placement of the microspheres in the liver.

An assessment by the California Technology Assessment Forum (Tice, 2009) on selective internal radiation therapy or radioembolization for inoperable liver metastases from colorectal cancer reported that 22 case series with data on patients with metastatic CRC have demonstrated that it is feasible to deliver radiation therapy to liver tumors and achieve at least partial remission in a substantial proportion of patients with relatively few serious adverse events. The assessment stated that procedure-specific adverse events such as radiation pneumonitis, gastrointestinal ulceration and radiation-induced liver disease have been characterized and pre-treatment planning strategies have been developed to limit their frequency and severity. The CTAF assessment (Tice, 2009) reported that results of 2 RCTs (citing Gray et al, 2001; van Hazel et al, 2004) are encouraging, but not definitive. Both trials demonstrated improvements in disease-free survival and a trend towards longer OS. However, the trials were very small (less than 100 patients in total) and the response rates in the control groups were lower than expected. Furthermore, the assessment noted, the control groups did not use the standard first-line therapy for CRC metastatic only to the liver. The assessment stated that ongoing clinical trials that are randomizing over 800 newly diagnosed patients to first line chemotherapy with or without radioembolization should define the efficacy of combined therapy and the associated additional toxicity. Similarly, the data on the utility of radioembolization as salvage therapy for patients who have failed multiple rounds of chemotherapy is limited and immature.

Guidelines from the National Comprehensive Cancer Network (NCCN, 2009) state that radioembolization is an acceptable alternative for management of unresectable liver only or liver dominant metastases from carcinoids or islet cell tumors.

Guidance from the National Institute for Health and Clinical Excellence (2011) concluded that current evidence on the safety of selective internal radiation therapy for non-resectableccolorectal metastases in the liver is adequate. The report concluded, however, that the evidence on its efficacy in chemotherapy-naive patients is inadequate in quantity. The report found that, for patients who have previously been treated with chemotherapy, there is evidence that selective internal radiation therapy can prolong time to progression of hepatic metastases, but more evidence is required on survival and quality of life. Therefore for patients who have been previously treated with chemotherapy this procedure should be used with special arrangements for clinical governance, consent and audit. The NICE Committee considered selective internal radiation therapy a potentially beneficial treatment for patients with non-resectable colorectal metastases in the liver, but concluded that more research and data collection are required to demonstrate its efficacy. The Committee noted that observational studies report large numbers of patients previously treated by chemotherapy who have received selective internal radiation therapy, but that the number of these patients reported in comparative trials was very small. For patients who have previously been treated with chemotherapy, comparative trials are needed to determine whether selective internal radiation therapy prolongs

survival compared with best standard treatment, and to determine its effect on quality of life. There is also a need to identify which subgroups of patients are likely to derive clinical benefit from selective internal radiation therapy. The NICE Committee noted that there have been a small number of reports of SIRT downstaging colorectal metastases to the extent that treatment by resection or ablation became possible. However, it considered that there was insufficient evidence to comment on the potential use of the procedure with this intent.

The advantage of chemoembolization of the liver as an anti-neoplastic treatment for HCC is that it achieves high intra-tumoral concentrations of the chemotherapeutic agent locally that can not be reached with systemic chemotherapy in non-toxic doses. However, chemotherapeutic release and local concentrations can not be standardized by this technique. Drug-eluting beads (DEB) are believed to have predictable pharmacokinetics and can achieve higher doses of the chemotherapeutic and prolonged contact time with cancer cells.

In a phase I/II clinical trial, Poon and colleagues (2007) assessed the safety and efficacy of TACE using doxorubicin-eluting beads (DC Beads) for HCC. Patients with incurable HCC and Child-Pugh class A cirrhosis were considered eligible. Two courses of TACE using DC Beads were given at an interval of 2 months, and tumor response was assessed by computerized tomography scan. The phase I trial was a dose-escalating study starting from 25 mg to 150 mg doxorubicin in cohorts of 3 patients. The 150-mg doxorubicin dose was used for the phase II study. Primary end points were treatment-related complications and deaths. Secondary end points included tumor response and pharmacokinetics of doxorubicin. In the phase I study involving 15 patients, no dose-limiting toxicity was observed for up to 150 mg doxorubicin, which was used for 20 patients in the phase II study. The pharmacokinetic study showed a low peak plasma doxorubicin concentration (49.4 +/- 23.7 ng/ml), and no systemic toxicity was observed. The treatment-related complication rate was 11.4 %. There was no treatment-related death. Among 30 patients who completed 2 courses of TACE, the PR rate and the CR rates were 50 % and 0 %, respectively, by response evaluation criteria in solid tumors (RECIST) criteria at computerized tomography scan 1 month after the second TACE. By modified RECIST criteria, taking into account the extent of tumor necrosis, 19 (63.3 %) patients had a PR and 2 (6.7 %) had a CR. The authors concluded that these findings showed that TACE using DC Beads is a safe and effective treatment for HCC, supporting a phase III randomized trial to compare this novel treatment with conventional TACE using doxorubicin-lipiodol emulsion.

In an open-label, single-center, single-arm study, Malagari et al (2008) evaluated the safety and efficacy of DC Beads delivered by TACE for the treatment of unresectable HCC. A total of 62 cirrhotic patients with documented single unresectable HCC were included in this study. Mean tumor diameter was 5.6 cm (range of 3 to 9 cm) classified as Okuda stages 1 (n = 53) and 2 (n = 9). Patients received repeat embolizations with DC Beads every 3 months (maximum of 3). The maximum doxorubicin dose was 150 mg per embolization, loaded in DC Beads of 100 to 300 or 300 to 500 microm. Regarding efficacy, overall, an objective response according to the European Association for the Study of the Liver (EASL) criteria was observed in 59.6 %, 81.8 %, and 70.8 % across 3 treatments. A CR was observed in 4.8 % after the first procedure and 3.6 % and 8.3 % after the second and third procedures, respectively. At 9 months a CR was seen in 12.2 %, an objective response in 80.7 %, progressive disease in 6.8 %, and 12.2 % showed stable disease. Mean tumor necrosis ranged from 77.4 % to 83.9 % (range of 28.6 % to 100 %) across 3 treatments. Alpha-fetoprotein levels showed a mean decrease of 1,123 ng/ml (95 % CI: 846 to 1399; p = 3 x 10(-11)) after the first session and remained stable after the second and third embolizations (42 and 70 ng/ml decrease, respectively).

Regarding safety, bilirubin, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase showed only transient increases during the study period. Severe procedure-related complications were seen in 3.2 % (cholecystitis, n = 1; liver abscess, n = 1). Post-embolization syndrome was observed in all patients. The authors concluded that CE using doxorubicin-loaded DC Beads is a safe and effective treatment of HCC as demonstrated by the low complication rate, increased tumor response, and sustained reduction of alpha-fetoprotein levels.

Carter and Martin (2009) stated that DEB-TACE is a novel therapy for the treatment of hyper-vascuarized tumors. Through the intra-arterial delivery of microspheres, DEB-TACE allows for embolization as well as local release of chemotherapy in the treatment of hepatic malignancy, providing an alternative therapeutic option in unresectable tumors. Its role as an adjunct to surgical resection or RFA is less clear. These researchers summarized recent studies investigating DEB-TACE in order to better define safety, efficacy and outcomes associated with its use. A systematic review of all published articles and trials identified 9 clinical trials and 23 abstracts. These were reviewed for tumor histology, stage of treatment, delivery technique, outcome at follow-up, complications and mortality rates. Publications involved treatment of HCC, metastatic colorectal carcinoma (MCRC), metastatic neuroendocrine (MNE) disease and cholangiocarcinoma (CCA). Using RECIST or EASL criteria, studies treating HCC reported CR rates of 5 % (5/101) at 1 month, 9 % (8/91) at 4 months, 14 % (19/138) at 6 months and 25 % (2/8) at 10 months; PR was reported as 58 % (76/131) at 1 month, 50 % (67/119) at 4 months, 57 % (62/108) at 6-7 months and 63 % (5/8) at 10 months. Studies involving MCRC, CCA and MNE disease were less valuable in terms of response rate because there is a lack of comparative data. The most common procedure-associated complications included fever (46 to 72 %), nausea and vomiting (42 to 47 %), abdominal pain (44 to 80 %) and liver abscess (2 to 3 %). Rather than reporting individual symptoms, 2 studies reported rates of post-embolic syndrome, consisting of fever, abdominal pain, and nausea and vomiting, at 82 % (75/91). Six of 8 studies reported length of hospital stay, which averaged 2.3 days per procedure. Mortality was reported as occurring in 10 of 456 (2 %) procedures, or 10 of 214 (5 %) patients. The authors concluded that drug-eluting bead TACE is becoming more widely utilized in primary and liver-dominant metastatic disease of the liver. Outcomes of success must be expanded beyond response rates because these are not a reliable surrogate for progression-free survival or OS. Ongoing clinical trials will further clarify the optimal timing and strategy of this technology.

In a phase II clinical trial, Fiorentini et al (2009) evaluated the safety and efficacy of TACE. A total of 10 patients with liver metastases (LM) from uveal melanoma (UM) were treated with TACE-containing beads pre-loaded with irinotecan (IRI, 100 mg). All patients had an objective response, 3 presented a very good PR and 7 obtained a PR. The median follow-up time from the beginning of therapy was 6.5 months (range of 4 to 9 months); 8 patients were alive at the time of this analysis. The most important adverse event was abdominal pain during the procedure. Adequate supportive treatment with antibiotic and anti-emetic prophylaxis, desametazone and intravenous hydration is strictly necessary until stabilization of serum levels of transaminases and to prevent infections. A major analgesic such as morphine must be used before and after the procedure. The authors concluded that TACE containing beads pre-loaded with IRI is effective in the treatment of LM from UM. This approach seems to have better efficacy than previous TACE regimens adopted.

In an open-label, multi-center, single-arm study, Martin et al (2009) examined the value of DEB in patients with unresectable colorectal hepatic metastasis who had failed standard therapy. Patients received repeat embolizations with IRI-loaded beads (max 100 mg per

embolization) per treating physician's discretion. A total of 55 patients underwent 99 treatments using IRI-DEB. The median number of total treatments per patient was 2 (range of 1 to 5). Median length of hospital stay was 23 hours (range of 23 hours to 10 days). There were 30 (30 %) sessions associated with adverse reactions during or after the treatment. The median disease free and OS from the time of first treatment was 247 days and 343 days. Six patients (10 %) were down-staged from their original disease status. Of these, 4 were treated with surgery and 2 with RFA. Neither number of liver lesions, size of liver lesions or extent of liver replacement (less than or equal to 25 % versus greater than 25 %) were predictors of OS. Only the presence of extra-hepatic disease (p = 0.001), extent of prior chemotherapy (failed 1st and 2nd line versus greater than 2 line failure) (p = 0,007) were predictors of OS in multi-variate analysis. The authors concluded that the findings in this interim report indicated that CE using IRI-loaded beads was safe and effective in the treatment of patients as demonstrated by a minimal complication rate and acceptable tumor response.

In a pilot study, Guiu et al (2009) evaluated efficacy and toxicity of a TACE procedure using a combination of pirarubicin, amiodarone, lipiodol, and gelatin sponge. A total of 43 patients were included in this study and they underwent TACE for unresectable HCC. Computed tomography scans were performed to assess tumor response (RECIST) and lipiodol uptake after the first session. Median follow-up lasted 30 months. Endpoints were OS and progression-free survival. Survival was estimated using Kaplan Meier estimations and compared using log-rank tests. Uni-variate and multi-variate Cox analyses were used to calculate HRs with their 95 % CI. Twenty-seven (67.5 %) patients had alcoholic cirrhosis. Mean tumor size was 9.5 cm (1 to 20 cm) and 37/43 were multi-focal or diffuse. Cancer of the liver Italian program score was 0 in 7/40 and 1 in 16/40. Mean number of TACE sessions was 3.5 (1 to 11). There were 3 treatment-related deaths (2 severe sepsis, 1 bowel perforation). A PR and a stable disease were observed in 12 (28 %) and 29 (67 %) patients, respectively. Median OS and progression-free survival were 29 months (95 % CI: 13.8 to 45) and 15 months (95 % CI: 11.5 to 20.8), respectively. Cancer of the liver Italian program score less than or equal to 1 (p = 0.042) and lipiodol uptake greater than 25 % (p = 0.003) were independent prognostic factors for better OS. The authors concluded that this new TACE procedure is safe with a high OS rate and certainly deserves phase III investigation to compare it with classic treatments such as doxorubicin-lipiodol TACE.

Tokh et al (2010) noted that conventional TACE uses a combination of chemotherapy, lipiodol, and an embolic agent. Drug-eluting bead therapy is a potentially less toxic and therapeutically equivalent form of intra-arterial drug delivery. These researchers assessed the safety, efficacy and survival among patients with HCC treated with DEB after a long experience with traditional TACE. A total of 63 sequential patients with unresectable HCC were treated over an 18-month period. Subjects received 2 courses of DEB-CE, using 100 mg doxorubicin in DEB ranging from 300 to 700 microns in diameter. They retrospectively analyzed patient demographics, etiologies of liver disease, Child Pugh status, CLIP scores, size of largest tumor, baseline alpha-fetoprotein (AFP), toxicity, change in size of largest tumor, change in AFP, and survival from first treatment. A total of 63 patients (51 men; median age of 62 years) were treated; 53 had cirrhosis (30 Hepatitis C, 12 from alcohol); 6 had portal vein thrombosis; median tumor size was 4.8 cm (range of 2 to 12 cm); 37 had elevated AFP (median 471 ng/ml, range of 21 to 54,860). 37 were Child's A and 26 B; 9 had CLIP scores greater than 2. 51 remain alive, and 30-day mortality was zero. Most common adverse reactions were abdominal pain (71 %), nausea (52 %), and fatigue (18 %). Overall, 81 % of evaluable patients had tumor regression; AFP decreased in 79 % of patients with elevated levels, with a median fall of 78.5 %. Poor prognostic indicators for survival following the procedure included cirrhosis, elevated bilirubin and elevated AFP; CLIP score, Child's status, etiology and

size did not significantly impact outcome. Actuarial survival was 18.2 months. The authors concluded that outcomes following treatment of HCC using DEB compare favorably with historic results using conventional CE. Patients experience substantially less fever, a shorter duration of pain, but more nausea within 24 hours. There were no early deaths. Survival appears to be at least equivalent, with milder toxicity, compared with the authors' historic experience. They noted that RCTs of the 2 modalities of CE are currently under way.

Malagari et al (2010) evaluated the added role of a chemotherapeutic in TACE of intermediate-stage HCC. The issue is of major importance since, as suggested by recent evidence, hypoxia or incomplete de-vascularization of the tumor is a potent stimulator of angiogenesis, and there are not many papers supplying level one evidence confirming the value of a chemotherapeutic. The hypothesis was that since DEB-TACE is standardized and reproducible, a comparison with bland TACE can readily reveal the potential value of the chemotherapeutic. In this prospective study, 2 groups were randomized : group A (n = 41) was treated with doxorubicin DEB-TACE, and group B (n = 43) with bland embolization. Patients were randomized for tumor diameter; they were embolized at set time intervals (2 months), with a maximum of 3 embolizations. Tumor response was evaluated using the EASL criteria and AFP levels. At 6 months a CR was seen in 11 patients (26.8 %) in the DEB-TACE group and in 6 patients (14 %) in the bland embolization group; a PR was achieved in 19 patients (46.3 %) and 18 (41.9 %) patients in the DEB-TACE and bland embolization groups, respectively. Recurrences at 9 and 12 months were higher for bland embolization (78.3 % versus 45.7 %) at 12 months. Time to progression (TTP) was longer for the DEB-TACE group (42.4 +/- 9.5 and 36.2 +/- 9.0 weeks), at a statistically significant level (p = 0.008). The authors concluded that DEB-TACE presents a better local response, fewer recurrences, and a longer TTP than bland embolization with BeadBlock. However, survival benefit and bland embolization with smaller particles must be addressed in future papers to better assess the clinical value.

Nicolini et al (2010) retrospectively compared radiological tumor response and degree of necrosis in explanted livers after CE with epirubicin-loaded DC Bead versus bland embolization in patients on a transplant waiting list. From 2003 to 2007, 49 patients with HCC underwent transplantation at a single center. Sixteen patients were treated with bland embolization (n = 8) with 100-300-microm Embosphere particles or CE with epirubicin-loaded 100-300-microm DC Bead particles (n = 8) every other month until complete tumor de-vascularization. Computed tomography was performed every 3 months until recurrence. Explanted livers were analyzed to evaluate the degree of necrosis in the nodules. After orthotopic liver transplantation (OLT), patients were followed-up for survival and disease status. The groups were comparable for baseline characteristics. Most patients had Child-Pugh class A disease. Solitary HCC was found in 75 % of patients. Mean target lesion size was 32 mm +/- 15.4. Chemoembolization with DEB achieved complete necrosis in 77 % of lesions whereas bland embolization achieved complete necrosis in 27.2 % of lesions. There was a significant difference between bland embolization and CE with DEB with regard to histological necrosis (p = 0.043). No significant treatment-related complications were observed for either group. Fifteen patients are alive with no tumor recurrence. The authors concluded that CE with DEB before OLT achieved higher rates of complete histological response than bland embolization, with no serious adverse events observed. Because of the retrospective data analyses and small sample size, further studies are warranted to confirm these promising results.

Current NCCN guidelines on cervical cancer include no recommendation to use chemoembolization for cervical cancer, including cervical cancers metastatic to the liver. In addition, National Cancer Institute (PDQ) guidance includes no recommendation for

chemoembolization for liver cancer. ClinicalTrials.gov lists dozens of trials of chemoembolization, primarily for hepatocellular carcinoma and for colorectal cancers metastatic to the liver. However, there are no trials listed in ClinicalTrials.gov for chemoembolization for persons with cervical cancer. Peer-reviewed published evidence for chemoembolization for cervical cancer consists of 3 retrospective case-series studies (in Chinese – Liu et al, 2009; Yu et al, 2009; and Tian et al, 2010). The largest of these (Tian et al, 2010) found no improvements in survival with the addition of chemoembolization to radiotherapy for cervical cancer. The study concluded that "Compared with the simple radiotherapy, there are a similar short-term survival rate and significant poor 5-year, 8-year survival rate in the patients treated with the uterine arterial interventional chemoembolization combined with radiotherapy, which also may be strong dangerous factor for the occurrence of tardive bladder injury. The results shown that the uterine arterial interventional chemoembolization do not recommend to be routine adjuvant therapy for the radical radiotherapy of cervical cancer".

Cannon et al (2012) assessed the safety and effectiveness of chemoembolization with doxorubicin-eluting beads (DEBDOX) in the treatment of multi-nodular (greater than or equal to 10 lesions) HCC. A 503-patient prospective multi-national DC Bead registry database from 6/2007 to 2/2010 identified 176 patients treated for HCC with DEBDOX. There were 42 patients with multi-nodular HCC compared to 134 with non-multinodular HCC. After a median follow-up of 12 months, the multi-nodular group response rate according to modified RECIST criteria was 56 % and median overall survival was 7.6 months, compared to 57 % and 15 months in the non-multi-nodular group ($p = 0.08$). The authors concluded that multi-nodular HCC represents a more advanced stage of disease; however, DEBDOX treatment is safe and effective when compared to historical controls and current best systemic therapy. They stated that continued hepatic arterial therapy and evaluation is needed in this clinical subset to further confirm these results.

Lencioni et al (2013) stated that TACE is the current standard of care for patients with intermediate-stage HCC and relatively preserved liver function. In a meta-analysis of RCTs comparing conventional TACE regimens including the administration of an anticancer-in-oil emulsion followed by embolic agents versus best supportive care, TACE was shown to improve median survival from 16 to 20 months. Various strategies to improve outcomes for this patient group have become the subject of much ongoing clinical research. The introduction of an embolic DEB has been shown to substantially improve the pharmacokinetic profile of TACE, providing levels of consistency and repeatability not available with conventional regimens while concomitantly significantly diminishing systemic drug exposure. In randomized trials, DEB-TACE significantly reduced liver toxicity and drug-related adverse events compared with conventional TACE. These investigators reviewed technique, indications and contraindications, and clinical outcomes of conventional and DEB-TACE in the management of HCC. In addition, scientific background and early clinical experience with the use of combination regimens including TACE and systemically active molecular-targeted agents with anti-angiogenic properties were discussed. The authors concluded that the combination of DEB-TACE and anti-angiogenic therapy represents a potentially powerful approach that is currently undergoing clinical investigation in a phase III setting.

In a meta-analysis, Gao and associates (2013) evaluated the effectiveness of DEB-TACE compared with conventional TACE (cTACE). These researchers included 7 studies (a total of 693 patients) to compare DEB-TACE with cTACE. The pooled (OR were calculated using a random or fixed effects model. MEDLINE, EMBASE and the Cochrane Database were searched for articles published from dates of inceptions up to February 20, 2012. Sensitivity analysis and publication bias estimate were also performed to evaluate the potential risk bias in the overall results of pooled analysis. The

pooled estimates for tumor response of DEB-TACE were not significantly different from those of cTACE, with CR (OR: 1.18; 95 % CI: 0.81 to 1.71; p = 0.394), PR (OR: 1.37; 95 % CI: 0.94 to 1.99; p = 0.101), SD (OR: 0.88; 95 % CI: 0.51 to 1.51; p = 0.637), PD (OR: 0.85; 95 % CI: 0.52 to 1.38; p = 0.512), DC (OR: 1.37, 95 % CI: 0.95 to 1.98; p = 0.089) and OR (OR: 1.40; 95 % CI: 0.97 to 2.000; p = 0.070). The authors concluded that the current evidence suggests that DEB-TACE is able to accomplish the same tumor response as cTACE. Moreover, they stated that although this analysis provided a comprehensive look at published data involving the clinical effectiveness of DEB-TACE compared with conventional TACE, additional large scale of RCTs are still needed.

An UpToDate review on "Nonsurgical therapies for localized hepatocellular carcinoma: Transarterial embolization, radiotherapy, and radioembolization" (Curley et al, 2013) states that "A newer approach to TACE uses drug-eluting beads (DEBs) that slowly release chemotherapy, thus diminishing systemic toxicity. Early results from retrospective reports and several small prospective randomized trials suggest similar rates of tumor control as with conventional TACE, with lower rates of serious hepatobiliary toxicity, although follow-up is short in most series:

- A meta-analysis of seven studies comparing conventional TACE versus DEB-TACE (five prospective randomized trials and two retrospective comparative reports, totaling 693 patients) concluded that the pooled estimates for tumor response with DEB-TACE were not significantly different from those of conventional TACE (odds ratio [OR] for disease control 1.37, 95 % CI 0.95-1.98).
- Comparative toxicity was addressed in the largest randomized trial, the PRECISION V trial, in which conventional TACE using doxorubicin (50 to 75 mg/m2) was directly compared to DEB-TACE (150 mg doxorubicin per procedure) in 212 patients with Child-Pugh A/B cirrhosis and unresectable HCC. The DEB group had lower rates of treatment-emergent adverse events in the hepatobiliary system (16 versus 25 percent). The mean maximum postchemoembolization alanine transaminase increase with DEB-TACE was 50 percent less than in the conventional TACE group (p < 0.001), and the mean maximum aspartate transaminase increase was 41 percent lower. Furthermore, despite a higher mean total dose of doxorubicin in the DEB-TACE group (295 versus 233 mg), there was a small but statistically significant difference in mean change from baseline in left ventricular ejection fraction (LVEF) of 4 percentage points that favored DEB-TACE group. The incidence of postembolization syndrome was similar between both groups (25 versus 26 percent for DEB-TACE and conventional TACE). On the other hand, treatment-emergent gastrointestinal adverse events occurred more often in patients treated with DEB-TACE (61 versus 45 percent).

The authors noted that "Where available, TACE using drug-eluting beads may be preferred, although long-term experience with this modality is limited".

Furthermore, the NCCN clinical practice guideline on "Hepatobiliary cancers" (Version 1.2013) notes that "Recent studies have evaluated TACE with drug-eluting beads in patients with unresectable HCC …. These results need to be confirmed in larger prospective studies".

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

36245

36260

37242

37243

75894

75896

77750

77776 - 77778

96446

Other CPT codes related to the CPB:

96522

HCPCS codes covered if selection criteria are met:

C2616	Brachytherapy source, nonstranded, yttrium-90, per source [microspheres]
Q3001	Radioelements for brachytherapy, any type, each
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

Other HCPCS codes related to the CPB:

J2353	Injections, octreotide, depot form for intramuscular injection, 1 mg
J2354	Injections, octreotide, non-depot form for subcutaneous intravenous injection, 25 mcg

Percutaneous Ethanol Injection:

ICD-9 codes covered if selection criteria are met:

155.0	Malignant neoplasm of the liver, primary [hepatocellular cancers (HCC) without extrahepatic spread]

ICD-9 codes not covered for indications listed in the CPB:

155.2	Malignant neoplasm of the liver, not specified as primary or secondary
197.7	Secondary malignant neoplasm of liver, specified as secondary

Chemoembolization:

ICD-9 codes covered if selection criteria are met:

155.0 - 155.2	Malignant neoplasm of the liver and intrahepatic bile ducts [unresectable]
157.0 - 157.9	Malignant neoplasm of pancreas [endocrine involving the liver] [in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing, and diarrhea)]
190.0	Malignant neoplasm of eyeball except conjunctiva, cornea, retina, and choroid [with liver-only metastases]
209.00 - 209.29	Malignant carcinoid tumors

209.72	Secondary neuroendocrine tumor of liver
V49.83	Awaiting organ transplant status [Preoperative hepatic artery chemoembolization followed by orthotopic liver transplantation for HCC}

ICD-9 codes not covered for indications listed in the CPB:

153.0 - 153.9	Malignant neoplasm of colon
171.0 - 171.9	Malignant neoplasm of connective tissue and other soft tissue [rhabdomyosarcoma]
172.0 - 172.9	Malignant melanoma of skin
174.1-174.9	Malignant Neoplasm of Female Breast
175.0-175.9	Malignant Neoplasm of Male Breast
197.7	Secondary malignant neoplasm of liver, specified as secondary [palliative treatment of liver metastases from other non-neuroendocrine primaries (e.g., colon cancer, melanoma, or unknown primaries)]
199.1	Other malignant neoplasm without specification of site [unknown primary]
V10.3	Personal history of malignant neoplasm of breast

Intra-hepatic chemotherapy:

ICD-9 codes covered if selection criteria are met:

153.0 - 154.8	Malignant neoplasm of colon, rectum, rectosigmoid junction, and anus [not covered for "one-shot" arterial chemotherapy or transarterial gene therapy]

ICD-9 codes not covered for indications listed in the CPB:

155.0 - 155.2	Malignant neoplasm of the liver and intrahepatic bile ducts [liver primary]

Intra-hepatic microspheres:

ICD-9 codes covered if selection criteria are met:

153.0 - 154.8	Malignant neoplasm of colon, rectum, rectosigmoid junction, and anus [unresectable liver tumors from primary colorectal cancer]
155.0 - 155.2	Malignant neoplasm of the liver and intrahepatic bile ducts [unresectable primary HCC}
156.0	Malignant neoplasm of gallbladder
157.0 - 157.9	Malignant neoplasm of pancreas [endocrine tumors involving the liver and functional neuroendocrine cancers] [carcinoid tumors in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea)]
197.8	Secondary malignant neoplasm of other digestive organs and spleen
209.00 - 209.29	Malignant carcinoid tumors [functional neuroendocrine cancers in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and

	diarrhea)]
209.72	Secondary neuroendocrine tumor of liver

***Drug-Eluting Beads Trans-Arterial Chemoembolization**:*

ICD-9 codes not covered for indications listed in the CPB:

155.0 - 155.2	Malignant neoplasm of the liver and intrahepatic bile ducts
171.0 - 171.9	Malignant neoplasm of connective tissue and other soft tissue [leiomyosarcoma]
197.7	Secondary malignant neoplasm of liver, specified as secondary [liver dominant]

Other ICD-9 codes related to the CPB:

259.2	Carcinoid syndrome
782.62	Flushing
786.07	Wheezing
787.91	Diarrhea

The above policy is based on the following references:

Percutaneous Ethanol Injection

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Intra-hepatic Chemotherapy (Infusion) for Liver Malignancies

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CIGNA HEALTHCARE COVERAGE POSITION

Subject **Selective Internal Radiation Therapy (SIRT)**

Revised Date **7/15/2006**
Original Effective Date **6/15/2004**
Coverage Position Number **0081**

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INSTRUCTIONS FOR USE

*Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines.*

Coverage Position

CIGNA HealthCare covers selective internal radiation therapy (SIRT) using SIR-Spheres® as medically necessary for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) with Floxuridine (FUDR).

CIGNA HealthCare covers selective internal radiation therapy (SIRT) using Thera-Spheres® as medically necessary when provided in accordance with the Humanitarian Device Exemption (HDE) specifications of the U.S. Food and Drug Administration (FDA) for use in irradiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC).

General Background

Hepatocellular carcinoma (HCC) is a cancer that is relatively uncommon in the United States, although its incidence is becoming more frequent, due to an increase in the spread of hepatitis C infection. Hepatitis B and hepatitis C infection appear to be the most significant causes of HCC worldwide. Having a first-degree relative with hepatitis B plus HCC is also associated with an increased risk for family members who are hepatitis B carriers. The biologic marker alpha-fetoprotein (AFP) is useful for the diagnosis of this neoplasm. It has been reported that 50-70% of patients in the United States who have HCC have elevated AFP levels.

HCC, if found at an early stage, is potentially curable by surgical resection. Approximately 10% of all patients diagnosed with primary HCC have tumors that are amenable to resection. Five-year survival rates for patients with nonresectable liver cancer are about 7% (American Cancer Society [ACS], 2005). Once the diagnosis of HCC is confirmed, a patient's prognosis is dependent on the size of the tumor, the extent of liver functional impairment, the presence or absence of metastases and cirrhosis. Patients with primary HCC that has metastasized may not be candidates for liver resection or transplant surgery.

The liver is also the dominate site of metastatic disease for a number of malignancies, including neuroendocrine, ocular melanoma and colorectal cancer. Colorectal cancer accounts for approximately 50% of patients with metastatic disease. If left untreated, these patients have a poor prognosis with a median survival of 4-21 months, a three-year survival rate of three percent, and virtually no five-year survival. Although liver resection is not the primary treatment for most patients with hepatic colorectal metastases, appropriate liver resection is the standard of care for treatment of isolated hepatic colorectal metastases (Society for Surgery of the Alimentary Tract [SSAT], 2004). Treatment alternatives for these patients may include; systemic or infused chemotherapy, hepatic artery ligation or embolization, percutaneous ethanol injection, radiofrequency ablation, cryotherapy, or radiolabeled antibodies. These treatments, in conjunction with surgical resection and/or radiation therapy are best handled in the clinical trial setting (ACS, 2005; National Cancer Institute [NCI], 2006).

Traditional external whole-beam radiation therapy is of limited use for patients diagnosed with liver cancer, as the liver can only tolerate 30 to 35 Grays (Gy) before radiation-induced disease occurs. This low radiation dosage is non-tumoricidal and may not improve patient mortality. The need for focused treatment that decreases the risk of destroying healthy liver cells, decreases patients' pain and improves patients' mortality has led to the development of alternative treatments (i.e., systemic chemotherapy, hepatic artery ligation, hepatic artery embolization, or selective intrahepatic radiation therapy [SIRT]).

Selective Internal Radiation Therapy (SIRT)
When tumors arise in the liver, their blood supply is derived from the hepatic artery; in contrast, normal liver tissue receives 80% of its blood supply from the portal vein. Researchers have recently taken advantage of this knowledge by attempting to deliver Yttrium-90 radiation microspheres directly into liver tumors. By selectively infusing radioactive material into the left, right or common hepatic artery, a concentrated dosage of radiation can be delivered directly into the tumor bed, while conserving the normal liver tissue that surrounds the tumor. The size of the microspheres causes them to become entrapped within the tumor vasculature and retained within the tumor.

Access to the hepatic artery may be accomplished via a percutaneous femoral or gastroduodenal arterial catheter or a porta-cath that is radiologically guided into the liver. The total radioactivity required by a patient will be dependent on the extent and presentation of the tumor tissue. SIRT is the therapeutic process of infusing patient-specific tumoricidal doses of radioactive microspheres selectively through these catheters into the left, right, or common hepatic artery. SIRT can usually be performed in an outpatient setting, as there is no radiation exposure to others once the microspheres have been infused. Yttrium-90 is a beta emitter which decays to stable zirconium-90, to which hepatic tumors and healthy liver tissue are sensitive. It has a short half-life of 64.2 hours (i.e., 2.67 days) that limits radiation hazard, while providing a clinically appropriate dose of radiotherapy.

U.S. Food and Drug Administration (FDA)
There are currently two types of Yttrium-90 microspheres (i.e., glass and resin) that have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of HCC. SIR-Spheres®, yttrium resin microspheres, are manufactured and distributed by SIRETEX, (Paragon Medical, Perth, Australia).

SIR-Spheres® was granted pre-market approval for use by the FDA in March 2002 for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of Floxuridine (FUDR). SIR-Spheres should not be implanted into patients with seriously compromised liver function or who have liver failure. Sir-Spheres are infused over a 10-minute period to provide an average radiation dose of 200 to 300 Gy to the tumor with an average of 15-50 Gy to the normal liver parenchyma. No studies have been done on the safety and effectiveness of this device in pregnant women, nursing mothers or children.

TheraSpheres®, glass microspheres are manufactured and distributed by MDS Nordion, Ottawa, ON. These microspheres are injected via the hepatic artery, under direct monitoring, into either the right or left lobe of the liver. They are not biodegradable and should not redistribute to other organs of the body. Patients typically receive only two treatments to each lobe of the liver, given at approximately two-month intervals. No studies have been done on the safety and effectiveness of this device in pregnant women, nursing mothers or children.

In 1988, the FDA approved the use of TheraSphere® Yttrium-90 glass as a Humanitarian Device Exemption (HDE). This device is approved for use in irradiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately positioned hepatic arterial catheters.

Contraindications to the use of Yttrium-90 include patients:

- with a Tc-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy that shows any deposition to the gastrointestinal tract that can not be corrected by angiographic techniques
- with shunting of blood to the lungs that could result in delivery of greater than 16.5 milliCurie (mCi) of yttrium-90 to the lungs. Radiation pneumonitis has been seen in patients receiving doses of yttrium-90 greater than 30 Grays (Gy) in a single treatment
- with vascular abnormalities, bleeding diathesis, or portal vein thrombosis thus making catheterization of the hepatic artery a contraindication
- with severe liver dysfunction, pulmonary insufficiency, or any prior intrahepatic chemotherapy; or
- who are currently pregnant or nursing

Patients with severe underlying liver diseases are not candidates for this type of therapy. Patients must have good performance status, no extrahepatic tumors and relatively good hepatic function without severe portal hypertension (FDA, 1988).

Literature Review: Selective Internal Radiation (SIR)-Spheres®
The first study conducted in Europe on the efficacy of using SIR-Spheres in the treatment of 23 patients with advanced hepatic metastases and HCC was reported in 2005 by Pöpperl and colleagues. The patients within this study had cancer that was non-responsive to polychemotherapy and/or local therapy. Side effects after SIR-Sphere treatment included nausea, abdominal pain, fever, mild pancreatitis and peptic ulceration. At three months follow-up, 13 of the 23 patients had decreased fluorodeoxyglucose - positron emission tomography (FDG-PET) uptake with a decrease in tumor markers; while radiographic studies showed minimal or no change in tumor size in 10 of these 13 patients. Two additional patients showed stable findings, while one additional patient showed progressive disease. Long-term follow-up was available on two patients, and both showed signs of hepatic and extrahepatic progression six and nine months after SIRT therapy. The researchers concluded that additional studies are needed to determine if this therapy should be used as a stand-alone or as an adjunct to other treatments. After determining the best treatment combination then long-term survival for these patients may be improved.

To prospectively review the safety and efficacy of using SIR-Spheres in patients with unresectable primary or secondary hepatic malignancies, Lim and colleagues (2005) enrolled 46 patients in a multicentered study. These patients had to have documented existence of liver metastases from their primary tumor; patients with HCC were allowed to participate if their liver lesions histologically or radiologically resembled hepatoma with an alpha-fetaprotein level of at least 500. Patients with extra-hepatic disease were also enrolled if the liver was the primary site of tumor origin. Two treatment protocols were used during this study; patients with CRC that had not received prior treatment with chemotherapy were given systemic 5-floxuridine (FU) together with SIR. A concurrent bolus of 5-fluorouracil (5FU) chemotherapy as a radiosensitiser was used for those who had already received chemotherapy. This second protocol was used at the investigator's discretion. Overall there were 12 partial responses to SIR treatment, with all of these occurring in patients with disease confined to the liver. Toxicities that were clearly related to treatment with SIR included: severe gastric/duodenal ulceration, hematemesis, and bleeding esophageal varices from portal hypertension not present prior to SIR therapy. This study involved the use of a mixed population, and two varying treatment protocols. The

researchers concluded that additional studies are needed to stratify exactly which patients these therapies may be appropriate for use with, as it may be useful for treatment in patients who have exhausted chemotherapeutic options. The researchers continue to collect data on these patients.

Hazel et al. (2004) conducted a randomized phase II study in several centers to compare response rates and toxicity levels of 10 patients receiving systemic chemotherapy (i.e., control arm) versus 11 patients receiving SIRT plus systemic chemotherapy. The systemic chemolytic agents used were fluorouracil and leucovorin delivered for five consecutive days and repeated at four week intervals. The patients, randomized to receive SIRT and systemic chemotherapy, were administered Sir-Spheres on the 3rd or 4th day of their second round of chemotherapy. Prior to the administration of the microspheres, these patients were given an injection of Angiotension 2, with the Sir-Spheres being injected after a 30-second delay. Neither arm of this study had patients who responded completely. Response rates were determined by follow-up computerized tomography (CT) scans that were compared to pretreatment films. This post-treatment scan was read by a radiologist who was blinded to the treatment that the patient had received. Ten patients were recorded as having a partial response in the combined therapy group with a median progression of their disease occurring at 18.6 months, versus progression of disease noted in the control arm occurring at 3.6 months. Survival rates for each of these groups were 29.4 months (i.e., combined therapy group) versus 12.8 months (i.e., control group). The researchers reported that there are limited conclusions that can be determined from this study. Not all patients returned for follow-up scanning or continued rounds of chemotherapy. They did conclude that it appears the addition of SIRT to a protocol of systemic chemotherapy does increase survival and delay the progression of liver cancer. The authors have requested that additional, randomized trials be conducted.

Kennedy et al. (2004) conducted a study to determine the pathological response of liver tumors to the use of microsphere therapy. These results were documented through the analysis of four explanted livers previously treated with yttrium-90 microspheres. Tumor vasculature plays an important part in the delivery of microsphere therapy; tumoricidal doses of radiation must be patient specific to protect the viability of the surrounding normal liver tissue. The differences, between these microsphere agents, is the amount of radiation delivered per microsphere. Glass microspheres can deliver 2500 Giga-Becquerel (GBq) per sphere while resin microspheres deliver 50 GBq per sphere. During micosphere therapy it is vital that lung shunting is kept at a minimum of 30 Gy or below, to prevent radiation pneumonitis. This restricts patient selection for microsphere therapy to those with ≤ 10 % shunt fraction if using glass spheres and ≤ 20% shunt fraction if using resin microspheres. This study is small, but does document the significance of patient pretreatment selection and scanning, to possibly calculate the appropriate dosing, and to select the appropriate radioactive agent to deliver.

SIRETeX conducted a phase III randomized controlled trial to assess whether a single injection of SIR-Spheres could increase tumor response rate, time to disease progression in the liver, patient survival and to measure treatment-related toxicity or changes in quality of life. This trial was originally designed to enroll 95 patients, but was closed for accrual in 1997 after entering 74 patients. The decision to cease accrual was made due to:

- increasing reluctance of both patients and their referring medical practitioners to have patients randomized,
- absence of ongoing funding for the trial, and
- a statement in 1996 by the FDA that treatment related response and time to disease progression were acceptable criteria to support a Pre Market Application to the FDA for registration of SIR-Spheres in the United States.

During the SIRTeX trial, patients were randomized using a blinded envelope batch method controlled by an independent person. Patients were also stratified before randomization into three groups depending on the percentage of liver involved with the tumor (viz; <25%, 25% - 50%, >50%). All patients had undergone complete surgical resection of a primary adenocarcinoma of the large bowel and only those patients with non-resectable metastases limited to the liver and lymph nodes in the porta hepatic were included in the study. Carcinoembryonic antigen (CEA) levels were obtained. Laporatomy was performed to document non-resectable status of the liver, and to rule out evidence of intra-abdominal spread of the tumor. Patients were then randomized (one patient was excluded due to metastasis found during surgery). Only those patients (N=35, investigational arm) selected to receive SIR-Spheres underwent a

nuclear scan to determine the percentage of lung breakthrough, for appropriate dosing. Tumor size and liver volume were then documented on all patients using serial computerized tomography (CT) scans. Thirty-four patients (control arm) received hepatic artery chemotherapy only. SIRT and hepatic artery chemotherapy (HAC) impacted tumor volume with a similar difference of 24% versus 50%, p= 0.03 and CEA levels were also decreased 47% versus 72%, p=0.004. Survival using the Kaplan-Meier analysis showed a non-significant trend towards increased survival for patients treated with SIRT and HAC, compared to those receiving HAC alone. Though this study looks promising, patients were not totally blinded to the treatment they were to receive, as those assigned to SIRT and HAC also had nuclear scans done. Outcome measurements were not reported according to the standard Response Evaluation Criteria in Solid Tumors developed by the NCI Cancer Therapy Evaluation Program. The study was also small in sample size.

Stubbs et al. (February 1997 to June 1999) conducted a case series review on 50 patients with advanced, nonresectable, colorectal liver metastases. Estimated liver involvement was less than 25% in 30 patients, 25% to 50% in 13, and greater than 50% in seven. All patients received injections of SIR-Spheres and then followed, at four-week intervals, regional chemotherapy of 5FU. Treatment-related morbidity did occur including a 12% incidence of duodenal ulceration. Patients were then assigned to two groups based on whether or not extrahepatic disease (EHD) developed within six months of SIRT. Median survival of group one (n=26) was 6.9 months from the time of SIRT to the development of EHD and for group two (n=24) 17.5 months from the time of SIRT to the development of EHD. Stubbs reported that survival times for those who did not develop extrahepatic metastases for some time appeared to be extended but further studies of this treatment are needed.

Summary of SIR-Spheres®: Studies conducted have been small with varying treatment protocols being used; there was also minimal randomization and short follow-up durations. The efficacy of SIR-Spheres therapy appears promising as an alternative treatment for patients diagnosed with unresectable HCC. Specific patient selection criteria, dosage calculations and therapeutic combinations that may be safely used have yet to be determined.

Literature Review: TheraSpheres®

Sato et al. (2006) conducted prospective review of 30 patients within their institution to determine the efficacy of TheraSpheres treatment in producing response rates that are due to radiation and microscopic embolization rather than flow-related macroscopic embolization and ischemia. During this study 420 independent angiograms were assessed by a team of seven radiology specialists who were blinded to the pre or post-procedure timing of the angiograms. Patients were evaluated using the humanitarian device exemption criteria in accordance with the FDA for TheraSpheres treatment. Baseline angiograms were conducted to measure shunting to the lungs and gastrointestinal tract. All patients had the right gastric artery and the gastroduodenal arteries embolized as a precautionary measure and those patients with portal vein thrombosis were allowed to remain in the study of they met entrance criteria. The World Health Organization (WHO), the Response Evaluation Criteria in Solid Tumors (RECIST), and European Association for the Study of Liver (EASL) tumor response criteria were used to determine tumor response. Postprocedural arterial patency was measured at 100%. The objective tumor response rates for all patients were 24%, 31%, and 72% for the WHO, RECIST, and EASL criteria, respectively. The angiograms could not be identified as pre- or post-treatment 43% of the time by the radiologists. The researchers concluded that although their study was small, the use of TheraSpheres does promote favorable response rates that are due to radiation and microscopic embolization rather than follow-related macroscopic embolization and ischemia. The researchers also concluded that although TACE is clearly the worldwide gold standard of treatment for HCC, with the addition of positive tumor response to TheraSpheres injections, additional studies are needed that compare this therapy to other conventional methods of treatment for patients with hepatic neoplasia.

Forty-three consecutive patients with HCC were prospectively treated in a Phase II study of TheraSpheres injections. The patients were then followed over a four-year period of time by Salem and colleagues (2005). These patients all had unresectable HCC and SIRT therapy was being used as first or second-line treatment. All patients were evaluated prior to receiving SIRT injections by selective visceral angiography to document their vascular and tumor anatomy as a result of their HCC. During this study both lung and gastric shunting measures were also determined in order to tailor each injection to each patient's specific anatomical need as determined by a multidisciplinary tumor board. During this study

there were no reports of gastrointestinal or pulmonary adverse events. The researchers contributed this outcome to a very careful approach to treatment and adherence to the accepted warnings and contraindications. Of the 87 lesions that were treated, 44 (51%) had greater than a 50% reduction in size. When tumor necrosis was also measured an additional 28% response rate was noted, with 69 lesions (79%) responded to SIRT treatment. The researchers concluded that although this is a small, heterogenous sample size, all patients were allowed to participate regardless of age, stage or type of HCC, bilirubin levels or portal vein thrombosis. Due to these outcomes, the researchers also concluded that SIRT represents a promising therapeutic agent that should be included in the transarterial treatment armamentarium for patients with HCC. Randomized controlled trials should be undertaken that compare survival with ^{90}Y microspheres to survival with the use of other forms of liver-directed treatment to the use of supportive care alone.

Goin et al. (2005) reported risk stratification data from a combination of prospective and retrospective reviews of 121 patients with HCC. This stratification data was later reviewed by the FDA for the HDE approval of TheraSpheres. The first study began July, 1986, and included 13 patients (five high-risk and eight low-risk) these patients received a median liver dose of 74 Gy. The second study began April, 1992, and included 22 patients (five high-risk and 17 low-risk) these patients received median doses of 104 Gy. The third study began after the HDE approval and included 86 patients (23 at high risk and 63 at low risk); these patients were treated with doses up to 150 Gy. Within three months of treatment, 22 (18%) deaths had occurred. Of these patients, only one had received a follow-up treatment on the opposite lobe for bilobular disease. Median survival for the low-risk group was 466 days compared to the high-risk group of 108 days (hazard ratio, 6.0; 95% CI, 3.6-10.1; p<.0001). The authors concluded that survival could not be linked to a specific method of treatment, whole liver or lobar.

These stratification studies are lacking the complete data analysis of all patients and treatment protocols varied. Enrollment time for these studies was long (1986-2002), treatment techniques were modified during this time that could have influenced the outcomes and study parameters varied.

Geschwind et al. (2004) reported on a multi-center, outcome study of 80 patients with HCC who underwent TheraSpheres treatment. These patients were divided into two treatment groups with 17 (Group 1) receiving a nominal fixed dose of 100 Gy and 63 patients (Group 2) receiving a nominal dose of 135-150 Gy. The patients in Group 1 with bilobar disease received whole-liver treatment, while the patients in Group 2 with bilobar disease were treated according to the lobe with the dominant tumor burden. When the HCC was classified, 54 patients (68%) were classified as Okuda stage I, and 26 (32%) were classified with Cancer of the Liver Italian Program (CLIP) scores <3. As of November 30, 2003 survival according to each patient group was:

- 15 patients were living (median follow-up days after treatment = 727),
- 48 patients had expired (median follow-up days after treatment = 326),
- four patients had received liver transplantation (median follow-up days after treatment = 274),
- nine patients had received trans-arterial chemoembolization (TACE) or trans-arterial embolization (TAE) (median follow-up days after treatment = 168), and
- four had received systemic chemotherapy (median follow-up days after treatment = 705)

CLIP scores results for these patients were:

- Child-Pugh A: 72 patients (median follow-up days, 567 after treatment)
- Child-Pugh B: 8 patients (median follow-up days, 245 after treatment)

Tumor replacement (%):

- ≤ 50: 67 patients (median follow-up days, 492 after treatment)
- > 50: 13 patients (median follow-up days, 471 after treatment)

The authors concluded this study provided some guidance for the appropriate selection criteria for use with individuals with HCC who are likely to benefit from liver-directed treatment. However, this database study included two different treatment protocols with results reported in a cumulative manner, it is difficult

to determine if TheraSpheres treatment led to better outcomes or if its combination with TACE or TAE led to better outcomes.

Salem et al. (2004) conducted a retrospective review of 15 patients with HCC and portal vein thrombosis (PVT) of one or both main, or segments of the portal vein branches. Liver toxicity was determined using the National Institutes of Health (NIH), NCI toxicity criteria. Adverse events were determined by established standards of the Society of Interventional Radiology. Thirty-five patients were evaluated for this study, while 15 (43%) met the eligibility criteria. PVT was found by lobe: 31%, 6%, and 6% for the right, left and both lobes, respectively. All patients were treated regardless of lung shunt fractions with TheraSpheres infusion. Median survival from the date of treatment to death or last known contact was 216 days (95% CI: 126-423 days). Median survival from date of diagnosis was 496 days (95% CI: 383-853 days). There was no report of late radiation-induced hepatitis (i.e., anicetric ascites). The authors concluded that although the findings of this study appear promising in a select population of patients, the sample size is small and retrospective in nature.

Carr (2004) reported the interim safety and survival results of a cohort of 65 patients all biopsy-proven unresectable HCC that were treated with hepatic arterial 90 Yttrium microspheres (TheraSpheres). Forty-two patients had a substantial decrease in tumor size and 25 patients had a partial response as documented on CT scan. Median survival of Okuda stage 1 patients (n=42) was 649 days (historical comparison 244) and for Okuda stage II patients (n=23) was 302 days (historical comparison 64 days). All patients were followed for six months with 42 deaths, 21 due to liver failure, six from HCC progression, and three from metastases. The researchers concluded that TheraSpheres appears to be a relatively safe and effective therapy for advanced-stage nonresectable HCC.

This study is of a mixed population of therapy sessions single versus multiple doses, with a short follow-up time and was part of a quality of life assessment study of microsphere outcome versus trans-arterial chemoembilization (TACE) therapy.

Dancey et al. (2000) reported on a case series of 22 patients with histologically confirmed nonresectable HCC confined to the liver and at least one measureable lesion. Nine patients were Okuda stage I and 11 were Okuda stage II. All 22 patients experienced one adverse event during this therapy time. The most common serious adverse events were elevations in liver enzymes, bilirubin and upper gastrointestinal (GI) ulceration. The response rate was 20%, median duration of the response was 127 weeks, and the median survival time was 54 weeks. The researchers concluded that although promising this study was focused on determining dose safety in an Okuda stage I or II type patient and numerous adverse events occurred during this time.

Summary of Thera-Sphere®: Although studies conducted to date have shown promise for the use of internal radiation patient selection criteria, radiation dosimetry and the overall impact on patient safety have yet to be determined.

Professional Societies/Organizations
In 2006, the National Comprehensive Cancer Network (NCCN) published practice guidelines for the treatment of unresectable and inoperable hepatobiliary cancers, alternative therapies include: ablative therapy (e.g., radiofrequency, alcohol, cryotherapy, and microwave), chemoembolization, chemotherapy plus radiation, conformal radiation, radiotherapeutic microspheres, supportive care, and systemic, intra-arterial chemotherapy or clinical trials. All of these modalities have limitations, such as the size and number of lesions, potential toxicities, and a questionable effect on long-term survival. For patients without cancer-related symptoms, options include participation in a clinical trial or ablation of small-volume disease. Patients with metastastic disease may be offered supportive care or therapy as part of a clinical trial (NCCN, 2006).

The Society of Interventional Radiology (SIR) Standards of Practice Committee published guidance on quality improvement guidelines for the interventional treatment of hepatic malignancies. In the treatment of HCC, based on the size, number and location of the tumor(s) chemoembolization and tumor ablation may be appropriate alone or in combination. Neuroendocrine malignancies that do not respond to short- or long-acting somatostatin agents, may respond to chemoembolization. For hepatic metastasis originating from colorectal cancer, systemic chemotherapy or chemotherapy with chemoembolization may

be considered as a salvage option when other systemic chemotherapy options have been exhausted. Other treatment methods, such as yttrium Y90 sphere infusion, are being investigated and may play an interesting role over time (Brown, 2006).

In September 2004, the National Institute of Clinical Excellence (NICE) published an interventional procedure guide concerning the use of SIRT for colorectal metastases in the liver. The standard treatment option for patients with colorectal metastases in the liver is surgical resection. However, there are a limited number of patients (i.e., 10%) with conditions that are amenable to resection. Other treatment options include systemic chemotherapy, radiotherapy, radiofrequency ablation, cryotherapy, alcohol injection and laser photocoagulation. SIRT is used to treat non-resectable liver metastases secondary to colorectal cancer, usually in combination with hepatic arterial chemotherapy. This procedure does carry risk of radiation injury to the liver, gastrointestinal ulceration or hemorrhage and radiation pneumonitis.

The National Cancer Institute (NCI) is currently recruiting patients with unresectable hepatocellular carcinoma to participate in a Phase II trial that will measure the treatment efficacy of TheraSpheres infusion. This study will measure tumor response rates, patient survival and adverse effects of this treatment. Recruitment for this study began in 2002 and the expected completion date is October 2009 (NCI, 2005).

Summary
There is evidence within the published, peer-reviewed literature and textbooks that support the use of Yttrium-90 microspheres in the treatment of unresectable hepatocellular cancer (HCC). Studies have shown that SIR-Spheres® may be useful in the treatment of patients with unresectable metastatic liver tumors from primary colorectal cancer when used with adjuvant intra-hepatic artery chemotherapy (IHAC) of floxuridine (FUDR). As a means of radiation therapy or as a neoadjunct to surgery or transplantation in patients with unresectable HCC, the use of TheraSphere® may be appropriate National Comprehensive Cancer Network (NCCN), 2006; Alexander, 2005).

Parameters have yet to be determined that would define the deliverance of single, or multiple doses. Patient selection criteria are still under investigation, as well as patient response to microsphere therapy as a standalone treatment or in combination with embolization (TAE) or chemotherapy (TACE) (Alexander, 2005; Kemeny, 2004; ACS, 2005; NCI, 2006). Treatment alternatives for these patients may include; systemic or infused chemotherapy, hepatic artery ligation or embolization, percutaneous ethanol injection, radiofrequency ablation, cryotherapy, or radiolabeled antibodies. Treatments other than surgical resection or transplant are best handled in the clinical trial setting (ACOR, 2004; ACS, 2005; NCI, 2006).

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT* Codes	Description
	No specific codes

HCPCS Codes	Description
C2616	Brachytherapy source, yttrium-90, per source
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

ICD-9-CM Diagnosis Codes	Description
155.0	Malignant neoplasm of liver and intrahepatic bile ducts. Liver; primary

155.1	Malignant neoplasm of liver and intrahepatic bile ducts. Intrahepatic bile ducts
197.7	Secondary malignant neoplasm of respiratory and digestive systems, Liver; secondary

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Left Ventricular Assist Devices as Destination Therapy

Question: should destination therapy be added as an indication for left ventricular assist devices (LVADs) on the Prioritized List?

Question source: HERC staff

Issue: LVADs are currently covered on the Prioritized List as a bridge to heart transplantation and as a bridge to recovery for severe heart failure. LVADs can also be used as destination therapy—treatment for severe heart failure when transplant is not an option for a patient. This indication for LVADs was discussed at two HOSC/HSC meetings in 2010, and destination therapy was not added as an indication due to concerns about the increased cost to the health plans from both increased patient demand/eligible patients and longer utilization. DMAP estimated that addition of LVADs as destination therapy would increase costs more than 1%.

Testimony was heard from Dr. Howard Song, cardiothoracic surgeon at OHSU, that LVADs are placed for patients with serious heart failure, and then the decision regarding heart transplant is addressed. At times, the patients with LVADs are not eligible for transplant and therefore the LVAD is used for destination therapy regardless of the OHP guidelines. He also felt that there was strong evidence that LVADs were much superior to optimal medical management of Class IV heart failure in terms of reducing mortality. Dr. Song argued that LVADs were more cost effective than indicated in the studies, as the newer generation models were more effective and the cost savings from avoiding hospitalization and other care for end stage heart failure patients on medical management is substantial.

In 2010, the HSC determined that more experience with LVADs should be obtained and better cost-effectiveness data should be published prior to adoption of LVADs as destination therapy on the Prioritized List.

In March, 2015, NICE published a new coverage guidance based on a December 2014 evidence review which recommended coverage of LVADs as destination therapy. This change in NICE policy was driven mainly by the substantive decreased in mortality seen in end stage heart failure patients with LVADs as compared to medical management.

Left Ventricular Assist Devices as Destination Therapy

Current Prioritized List status:

CPT code	Code description	Current Line(s)
33979	Insertion of ventricular assist device, implantable intracorporeal, single ventricle	**86** MYOCARDITIS, PERICARDITIS, AND ENDOCARDITIS **102** HEART FAILURE **267** ARDIOMYOPATHY, MALIGNANT ARRHYTHMIAS, AND COMPLEX CONGENITAL HEART DISEASE Treatment: CARDIAC TRANSPLANT
33980	Removal of ventricular assist device, implantable intracorporeal, single ventricle	**86,102,267**
33981-33983	Replacement of ventricular assist device pump(s), implantable intracorporeal,	**86,102,267**
93750	Interrogation of ventricular assist device (VAD), in person, with physician or other qualified health care professional analysis of device parameters	**86,102,267**

GUIDELINE NOTE 18, VENTRICULAR ASSIST DEVICES

Lines 102,267

Ventricular assist devices are covered only in the following circumstances:

1) as a bridge to cardiac transplant;
2) as treatment for pulmonary hypertension when pulmonary hypertension is the only contraindication to cardiac transplant and the anticipated outcome is cardiac transplant; or,
3) as a bridge to recovery.

Ventricular assist devices are not covered for destination therapy.

Ventricular assist devices are covered for cardiomyopathy only when the intention is bridge to cardiac transplant.

Long-term VADs are covered for indications 1 and 2. Long-term VADs are defined as a VAD that is implanted in a patient with the intent for the patient to be supported for greater than a month with the potential for discharge from the hospital with the device. Temporary or short term VADs are covered for indications 1 and 3. Short-term VADs are defined as a VAD that is implanted in a patient with the intent for the patient to be supported for days or weeks with no potential for discharge from the hospital with the device.

Left Ventricular Assist Devices as Destination Therapy

HOSC minutes October, 2010

LVAD as destination therapy

Dr. Howard Song from OHSU Heart Transplantation Program gave a presentation on left ventricular assist devices (LVAD) as destination therapy. A patient, Jean Knospe from Salem, spoke on her experiences with long term LVAD therapy. The discussion centered around cost savings from the device. Saha was concerned about the newness of the technology. There is currently only 1 certified VAD program in Oregon (OHSU). Dodson was concerned about access for rural patients. Song and McKelvey reported that there are rural patients receiving VADs and that the rural physicians are able to care for this device. The device costs the same as a heart transplant. Olson pointed out that our current coverage is twice as expensive (payment for VAD and transplant).

Olson suggested having only CMS certified centers provide this treatment for OHP patients. Song stated that CMS has criteria for when patients should be given a VAD.

Saha suggested having the HRC look at this technology and bring a report to the HSC. Shaffer reported that the MED project reviewed VADs recently. Only one study has been done to date on the new generation of VAD devices with 120 patients. No children or adolescents were included in that trial. No cost-effectiveness data was found. McKelvey felt that the HSC already pays for this technology and therefore further research does not need to be done. There is not a huge group of patients who will demand this therapy if it becomes covered. Song indicated that there will be some newer studies published soon.

The decision was to have HSC staff review CMS criteria and the MED report and cost info and possible cost savings from rehospitalizations, etc. and come up with criteria/guideline to discuss in December.

Action:
HSC staff to review CMS coverage criteria and the MED report and any additional information found on cost information/possible cost savings. Staff to develop criteria/guideline for LVAD as destination therapy to discuss at the December meeting

HOSC minutes December, 2010

LVADs as destination therapy

Smits introduced the summary document reviewing the possible expansion of left ventricular assist devices (LVADs) for use as destination therapy. Dr. Howard Song from OHSU provided testimony.

Dr. Song noted that not covering LVADs for destination therapy created problems when patients are unable to receive a heart transplant due to donor shortages or when patients decide to simply keep the LVAD rather than pursue transplant.

There was discussion about whether LVADs as destination therapy was new technology. Coffman noted that CMS has covered LVADs for this indication since 2003, which included older LVAD technology which was less effective.

Concern was expressed on the part of the OHP health plans and DMAP that expanding the indications for LVAD use to destination therapy would greatly increase the number of patients receiving this expensive technology and therefore increase costs considerably.

Song stated that including Joint Commission certification as a qualification in the guideline would restrict the number of centers that would be available to place LVADs in the future. He did not think that this would lead to a "growth industry." Concern was raised that such restricted access could be problematic for rural patients. Song replied that the OHSU program (currently the only accredited program in Oregon) tries to ensure outreach to rural areas to train local providers/make sure support is there to allow access. Olson wondered which patients would not qualify for LVAD. Song replied that patients with right ventricular failure or other major organ failure or lack of social support would not qualify. Olson also wondered how many patients would access LVAD technology through Medicaid, given that many would end up on disability (Medicare). Song noted that many younger patients with LVADs are not disabled, and in fact are able to return to work. McKelvey stated that she felt that LVAD use would not increase much with allowing destination therapy, as OHP already covers LVADs for bridge to transplant, which frequently turns into destination therapy. She noted that the population that qualifies for LVADs given the proposed guideline would be quite small. Olson pointed out that the patients who would become eligible for LVADs as destination therapy are already costing the health plans a considerable amount of money in other health care costs.

Song was asked whether his program has any projected numbers for OHP patients who would receive LVADs if destination therapy was allowed. Song would anticipate possibly a 50% increase (7-8 total patients per year).

Price reported that 5 OHP patients a year have received LVADs as bridge to transplant in the past 2 years. Of the 5 patients given LVADs in 2010, 1 has elected to not be transplanted, 2 have not been listed for transplant yet, 1 is listed for transplant, and 1 died before transplant. In 2009, 5 patients received LVADs, and all were transplanted.

Shaffer expressed DMAPs concern with how much expansion there would be with destination therapy, the cost associated with this technology, and the limited evidence of effectiveness in current published literature for destination therapy. Dodson also indicated concern about lack of cost effectiveness data.

DMAP indicated that adding LVADs as destination therapy would lead to cost increases in the current contracts with the health plans. These rate increase estimates would not be ready until January, 2012. Therefore, DMAP could not implement coverage of LVADs as destination therapy until that time.

In terms of current knowledge of costs, Song indicated that after the initial hospitalization and procedure, the patient has costs for dressing changes ($100/mo out of pocket), medications, and Coumadin monitoring. Price indicated that DMAP has paid for LVAD placement/hospital stay, as well as $11,000 to set up at home. She did not have information on ongoing costs.

The group felt that there was not enough data on cost effectiveness, possible cost increases for OHP and anticipated numbers of patients who would use this technology.

The group felt that waiting until the August meeting to readdress this issue would not affect the implementation date of this technology if the decision was for coverage, given that DMAP cannot cover until January, 2012. Song will try to obtain cost data on patients who would qualify who do not receive LVADs (hospital costs, medications, etc.) to help the

HSC look at overall cost. He will also try to obtain overall health care costs after LVAD placement

Action:
Dr. Song and DMAP will try to obtain better cost figures for coverage of LVADs for destination therapy as well as medical care of patients who would qualify but do not receive LVADs. The HOSC will reconsider LVADs as destination therapy at their August, 2011 meeting.

Evidence review

1) **NICE 2014,** evidence review for LVADs for destination therapy (Available at http://www.nice.org.uk/guidance/ipg516/evidence/ipg516-implantation-of-a-left-ventricular-assist-device-for-destination-therapy-in-people-ineligible-for-heart-transplantation-overview2)
    a. N=9 studies
        i. 2795 patients from 1 registry, 2 randomised controlled trials, 1 non-randomised comparative study and 3 case series.
        ii. Some possible overlap of patients between studies
        iii. Longest follow up period was 4 yrs
    b. Survival
        i. RCT of 129 patients (68 LVAD, 61 medical management), survival rates were 23% and 8% respectively at 2-year follow-up (p=0.09). In a longer follow-up of the same study, survival rates were 16% in the pulsatile-flow LVAD group and 8% in the optimal medical management group at 4-year follow-up (no p value reported).
        ii. In a registry of 1287 patients treated by continuous-flow (n=1160) or pulsatile-flow (n=127) LVADs survival rates were 76% and 68% respectively at 1-year follow-up (p<0.0001). At 2-year follow-up, survival rates were 67% in the continuous-flow group and 45% in the pulsatile-flow group (p<0.0001). In the same study, survival to device exchange or death secondary to device malfunction was 96% in the continuous-flow group and 83% in the pulsatile-flow group at 1-year follow-up (no p value reported).
    c. Quality of life
        i. RCT of 200 patients, mean MLWHF scores (scores range from 0 to 105 with lower scores indicating better quality of life) improved from 75.4 to 34.1 (p<0.001) and 76.1 to 44.4 (p<0.001) respectively at 1-year follow-up (p value between groups=0.03). In the same study, mean overall KCCQ scores (scores range from 0 to 100 with higher scores indicating better quality of life) improved from 27.4 to 65.9 (p<0.001) in the continuous-flow group and from 46.5 to 59.1 (p<0.001) in the pulsatile-flow group at 1-year follow-up (p value between groups=0.06).
        ii. RCT of 129 patients treated by pulsatile-flow LVAD destination therapy or optimal medical management, mean MLWHF scores (scores range from 0 to 105 with lower scores indicating better quality of life) improved from 75 to 41 and 75 to 58 respectively at 1-year follow-up (p value between groups=0.11).

d. Adverse events
   i. Death due to device failure or malfunction: ranged from less than 1% to 2% of patients
   ii. LVAD related infection: reported in 28-36% of patients
   iii. Local infection: reported in 46-49% of patients
   iv. Pump replacement: reported in 9-34% of patients at 2 yrs
   v. Pump thrombosis: reported in 4-5% of patients
   vi. Bleeding that needed blood transfusion: reported in 23-76% of patients at 2 years
   vii. Neurologic events: Stoke was reported in 7-12% of patients with up to 2 yrs of follow up
   viii. Right heart failure: reported in 20-27% of patients with LVADs
   ix. Respiratory failure: Reported in 38-41% of patients
   x. Renal failure: reported in 16-24 % of patients
   xi. Cardiac arrhythmia: reported in 56-59% of patients
   xii. Sepsis: reported in 36-44% of patients

2) **Rector 2012,** VA meta-analysis of LVADs for destination therapy
   a. Found moderate strength evidence that the newer generation LVAD devices provided better patient outcomes than older devices
   b. Insufficient evidence was found to refine patient or site criteria for best outcomes from LVAD devices
   c. Based on a single industry funded analysis, the cost effectiveness of the current generation LVAD as destination therapy was found to be approximately $200,000 per QALY, with strength of evidence for this estimate found to be low

3) **MED 2010, review of VADs**
   a. Results based mainly on one RCT (N=129) and two registry based studies (N=377, 100)
   b. Moderate quality evidence that LVAD improves survival when used as destination therapy (DT). A statistically significant reduction in the risk of death attributable to the use of LVAD in patients who are ineligible for transplantation was found in the one good quality RCT. Median survival was 408 days in the LVAD arm and 150 days in the OMM arm, a difference of 258 days. A poor-quality nonrandomized trial and analysis of two registries reported survival results consistent with the RCT.
   c. Moderate-quality evidence has shown LVAD to substantially improve disease-specific and generic functional status and suggests small improvements in other QOL measures.
   d. Serious adverse events, both medical events and device failure, are common in patients undergoing chronic support with LVAD and are at least partially attributable to the device according to moderate-quality evidence from the randomized controlled trial (RCT). Device failure or malfunction is also common, but reported experiences suggest that it does not contribute substantially to mortality. According to the best available evidence, patients experience on average approximately six serious adverse events per year.
   e. Evidence of cost-effectiveness is of low quality and included two disparate ICERs.
      i. According to two U.S. cost-consequence studies, the cost for initial hospital care associated with LVAD implantation for DT is $137,000 to $164,000, and lifetime hospital costs for readmission, according to one of the studies, is $126,000 (2009 values).
      ii. A cost-effectiveness study from the British payer perspective, comparing LVAD with OMM, reported an ICER of £170,161/QALY over a five-year time horizon.

iii. An older Canadian study reported ICERs of $46,000/QALY to $55,000/QALY (2006 U.S. values) for a 12-year time horizon.
f. There was no evidence pertaining to LVAD as DT in children or adolescents.
80-92% of patients in the included studies were men

Cost effectiveness studies

1) **Long 2014**
   a. model for life expectancy and cost effectiveness of medical management vs heart transplant vs LVAD as bridge to transplant vs LVAD as destination therapy
      i. Medical management: life expectancy: 1.1 yrs (39% survival to 1 yr)
      ii. Heart transplant after medical therapy: life expectancy 8.5 yrs, cost $97,000/QALY
      iii. LVAD followed by heart transplant: life expectancy 12.3 years, cost $226,000/QALY (authors note cost/QALY much reduced with longer anticipated wait times prior to transplant)
      iv. LVAD as destination therapy: life expectancy 4.4 yrs, $202,000/QALY
      v. LVAD intended for heart transplant but converted to destination therapy: $175,000/QALY (no survival mentioned)
      vi. Projected 5 yr survival is essentially the same for heart transplant vs LVAD as destination therapy (see figure 2)
      i. ***Conclusions***—Under most scenarios, orthotopic heart transplantation (OHT) prolongs life and is cost effective in eligible patients. Bridge to transplant-LVAD is estimated to offer >3.8 additional life-years for patients waiting ≥6 months, but does not meet conventional cost-effectiveness thresholds. Destination therapy-LVAD significantly improves life expectancy in OHT-ineligible patients. However, further reductions in adverse events or improved quality of life are needed for destination therapy-LVAD to be cost effective.

2) **Rogers 2012**
   a. Modeling study for continuous flow LVAD vs optimal medical management
   b. Compared with medically managed patients, continuous-flow LVAD patients had higher 5-year costs ($360,407 versus $62,856), quality-adjusted life years (1.87 versus 0.37), and life years (2.42 versus 0.64). The incremental cost-effectiveness ratio of the continuous-flow device was $198 184 per quality-adjusted life year and $167 208 per life year. This equates to a 75% reduction in incremental cost-effectiveness ratio compared with the $802 700 per quality-adjusted life year for the pulsatile-flow device.
   c. ***Conclusions***—The cost-effectiveness associated with continuous-flow LVADs for destination therapy has improved significantly relative to the pulsatile flow devices. This change is explained by significant improvements in survival and functional status and reduction in implantation costs.

Coverage guidances

1) **NICE 2015**, LVADs for destination therapy
   a. Current evidence on the efficacy and safety of the implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation is adequate to support the use of this procedure

Other policies

1) **CMS 2010:** The evidence is adequate to conclude that VAD implantation as destination therapy improves health outcomes and is reasonable and necessary when the device has received FDA approval for a destination therapy indication and only for patients with New York Heart Association (NYHA) Class IV end-stage ventricular heart failure who are not candidates for heart transplant and who meet all of the following conditions:
    a. Have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and,
    b. Have a left ventricular ejection fraction (LVEF) < 25%; and,
    c. Have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.
2) Aetna and Regence and Anthem BCBS cover LVAD as destination therapy with Medicare criteria

HERC staff summary:

LVAD as destination therapy prolongs survival for patients with end stage heart failure compared to optimal medical management by a factor of approximately 4 (0.64 to 1.1 yr→2.4 to 4.4 yr). Quality of life measures are significantly better with LVAD as destination therapy compared to optimal medical management for end stage heart failure. Heart transplantation is significantly better than LVAD for both survival length and quality of life; however, the supply of donor hearts is limited.

The cost/QALY of LVAD as destination therapy is approximately $200,000. However, the anticipated cost/QALY of LVAD followed by heart transplant is actually higher, explained by the cost/complications of two major surgical procedures vs one. The cost/QALY of LVAD as a destination therapy has been significantly reduced with newer versions of the technology.

Left Ventricular Assist Devices as Destination Therapy

HERC Staff Recommendations:

1) Adopt LVADs for destination therapy
    a. Modify GN1 as shown below

GUIDELINE NOTE 18, VENTRICULAR ASSIST DEVICES

Lines 86,102,267

Ventricular assist devices are covered ~~only in the following circumstances: 1)~~ as a bridge to cardiac transplant; ~~2) as treatment for pulmonary hypertension when pulmonary hypertension is the only contraindication to cardiac transplant and the anticipated outcome is cardiac transplant; or, 3)~~ as a bridge to recovery~~.~~, and as destination therapy.

~~Ventricular assist devices are not covered for destination therapy.~~

~~Ventricular assist devices are covered for cardiomyopathy only when the intention is bridge to cardiac transplant.~~

~~Long-term VADs are covered for indications 1 and 2. Long-term VADs are defined as a VAD that is implanted in a patient with the intent for the patient to be supported for greater than a month with the potential for discharge from the hospital with the device. Temporary or short term VADs are covered for indications 1 and 3. Short-term VADs are defined as a VAD that is implanted in a patient with the intent for the patient to be supported for days or weeks with no potential for discharge from the hospital with the device.~~

When used as destination therapy, patients must

1) have chronic end-stage heart failure (New York Heart Association Class IV end-stage left ventricular failure), AND
2) not be candidates for heart transplantation, AND
3) meet all of the following conditions:
    a. Have failed to respond to optimal medical management, including beta-blockers and ACE inhibitors (if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and
    b. Have a left ventricular ejection fraction (LVEF) <25%; and
    c. Have demonstrated functional limitation with a peak oxygen consumption of <14 ml/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.

QUERI

Use of Left Ventricular Assist Devices as Destination Therapy in End-Stage Congestive Heart Failure: A Systematic Review

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

Recommended citation: Rector TS, Taylor BC, Greer N, Rutks I, and Wilt TJ. Use of Left Ventricular Assist Devices as Destination Therapy in End-Stage Congestive Heart Failure: A Systematic Review. VA-ESP Project #09-009; 2012.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the Minneapolis VA Medical Center, Minneapolis, MN funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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BACKGROUND

Heart failure is defined as reduced ability of the heart to pump blood and maintain normal bodily function. Heart transplantation is currently the preferred treatment for end-stage heart failure but the supply of donor hearts is insufficient to meet the need and many patients are not eligible for transplantation due to age or comorbid conditions.

Implantable mechanical pumps can assist the circulation of blood by the ventricles. Left ventricular assist devices (LVADs) have been approved by the U.S. Food and Drug Administration (FDA) for use in patients awaiting transplant (a bridge to transplant) and as a last resort in patients with refractory heart failure who are not eligible for a heart transplant (destination therapy). In January 2010, the first newer generation, rotary continuous flow ventricular assist device (HeartMate II) was approved by the FDA for destination therapy. Eligibility criteria are essentially the same as those used to select patients for the pivotal clinical trial that included patients with shortness of breath and/or fatigue at rest or during minimal exertion despite treatment with optimal therapy for heart failure associated with a low ejection fraction (< 25%) who were not candidates for heart transplantation due to their age or co-morbid conditions. The purpose of this report is to review the scientific evidence for use of the current generation of left ventricular assist devices as destination therapy.

The key questions were:

Key Question #1. How does use of an FDA-approved, current generation LVAD as destination therapy (i.e., the HeartMate II left ventricular assist device) effect patient outcomes?

Key Question #2. What patient or site characteristics have been associated with patient benefits or harms when the FDA-approved, current generation LVAD is used as destination therapy?

Key Question #3. What is the range of cost-effectiveness estimates of using the FDA-approved, current generation LVAD as destination therapy in end-stage heart failure and what explains variation in these estimates?

METHODS

We searched MEDLINE using standard search terms (Appendix B). The search was limited to articles involving human subjects and published in the English language from 1995 to October 2011. We also searched the Cochrane Database of Systematic Reviews, the Translating Research into Practice (TRIP) database for systematic reviews and technology assessments, the Center for Medicare and Medicaid Services (CMS) Web site and the NIH Clinical Trials Web site. Reference lists of articles and reports were reviewed to identify additional references. Information was extracted from eligible articles by the investigators. Study quality was assessed using criteria appropriate for the design of the studies identified to address the three key questions (comparison studies, prognostic studies or cost-effectiveness analyses).

DATA SYNTHESIS

Evidence tables were constructed for each key question to summarize each study included in the review including patient and intervention characteristics, patient outcomes (benefits and harms) and methodological quality. Qualitative syntheses of the available data were done to answer each of the 3 key questions. There were not enough similar studies to pool data using formal meta-analysis in an effort to get more precise estimates. Any findings, or lack thereof, representing the Departments of Veterans Affairs or Defense (DoD) populations were noted.

PEER REVIEW

A draft version of this report was reviewed by the technical expert panel, as well as other expert health care providers. Reviewer comments and our responses are summarized in Appendix C.

RESULTS

The electronic search identified 1,637 citations. Preliminary review of the titles and abstracts excluded 1,491 from further review; 146 were retained for more in-depth review. From these, we identified 3 articles for Key Question #1, 3 articles for Key Question #2 and no articles for Key Question #3. A search of reference lists and identification of recently published studies added one article for each key question.

Key Question #1. How does use of an FDA-approved, current generation LVAD as destination therapy (i.e., the HeartMate II left ventricular assist device) effect patient outcomes?

Conclusion

- A single study provides moderate strength evidence that use of the HeartMate II as a destination left ventricular assist device produces better patient outcomes, including patient survival, with fewer harms and hospitalizations than the HeartMate XVE, the only other ventricular assist device approved by the FDA for destination therapy.

We found one good quality randomized clinical trial of the HeartMate II used as a left ventricular assist device for destination therapy.[1] Patients enrolled in this study met the general criteria for destination therapy that were largely based on enrollment criteria in a previous study of an older generation device[2] including being ineligible for a heart transplant, being symptomatic at rest or with minimal exertion (New York Heart Association [NYHA] class IV heart failure) despite optimization of other therapies for heart failure, and a left ventricular ejection fraction less than 25%. Thus the findings are likely applicable to current candidates for destination therapy. The subjects' (n=200) mean age was 62 years and 84% were male. Compared to the older generation HeartMate XVE left ventricular assist device, use of the HeartMate II had better patient outcomes (See Appendix D, Table 1). After 24 months, the primary endpoint of survival free of disabling stroke or reoperation to remove the device was 46% versus 11% ($p < 0.0001$). Survival in the HeartMate II group was significantly better (58% versus 24% after 2 years) and subjects spent a greater percentage of their follow-up time outside of a hospital (88% versus 74%) largely due to a lower readmission rate. During follow-up survivors with

the HeartMate II also had fewer functional limitations due to heart failure as measured by the NYHA class, Minnesota Living with Heart Failure Questionnaire and clinical component of the Kansas City Cardiomyopathy Questionnaire. The incidences of several adverse events were lower as well including right heart failure, cardiac arrhythmias, device-related infections, sepsis, respiratory failure, renal failure, and device replacement. None of the adverse events rates were higher in the HeartMate II group than the HeartMate XVE group including major bleeding and strokes.

Currently all cases of destination therapy being registered in a national data base are being treated with the HeartMate II device.[3] Since patient characteristics and outcomes in the HeartMate XVE arm of this randomized comparison of devices were similar to those in the previous clinical trial that demonstrated the HeartMate VE provided superior outcomes compared to optimal medical therapy,[2] one might infer that the HeartMate II would also be superior to optimal medical therapy. Clinical trials of other newer generation continuous flow ventricular assist devices for destination therapy are ongoing, however, results are not expected for several years.

Key Question #2. What patient or site characteristics have been associated with patient benefits or harms when the FDA-approved, current generation LVAD is used as destination therapy?

Conclusion

- The available evidence is insufficient to refine patient or site selection criteria for use of the HeartMate II as destination therapy.

A few studies have identified risk factors for mortality and complications and developed or applied mortality prediction models to this particular patient population. Further studies are needed to validate use of different criteria to improve patient outcomes. An ongoing clinical trial is selecting less severely ill patients and may expand the criteria for use of a newer generation continuous flow device (HeartWare) as destination therapy.[4,5] In the meantime, the approved FDA indication and CMS criteria for coverage are available to guide patient selection.

Key Question #3. What is the range of cost-effectiveness estimates of using the FDA-approved, current generation LVAD as destination therapy in end-stage heart failure and what explains variation in these estimates?

Conclusion

- A single industry funded analysis has estimated that the cost-effectiveness of using the FDA-approved, current generation LVAD as destination therapy in patients with end-stage heart disease is approximately $200,000 per quality-adjusted life year. The strength of the evidence for this estimate is low.

Even with favorable assumptions regarding the cost and effectiveness of treatment, destination therapy using the current generation, continuous flow ventricular assist device appears to be relatively cost-ineffective compared with traditional standards and other Medicare approved interventions.[6] However, large improvements in cost-effectiveness have occurred in the past decade. If improvements continue to be made, destination therapy in end-stage heart disease with an LVAD may become more cost-effective in the future.

RECOMMENDATIONS FOR FUTURE RESEARCH

Additional high-quality data are needed to inform clinical practices and policies regarding the use of ventricular assist devices to treat patients with end-stage heart failure who are not eligible for a heart transplant. Investigators suggest the following recommendations regarding future research:

- Create or participate in a registry of all Veterans that receive an LVAD as destination therapy, and support enrollment of Veterans in ongoing, randomized controlled clinical trials.
- Develop decision aids to help providers communicate information about the benefits, risks and care needed when patients are considering an approved ventricular assist device as destination therapy and to help providers elicit patients' values and preferences.
- Update cost-effectiveness models as better data become available and incorporate probabilistic sensitivity analyses to assess uncertainty in the cost-effectiveness estimates.
- Conduct a budget impact analysis that specifically addresses the potential impact within the Veterans Health Administration of use of the currently approved continuous flow ventricular assist devices as destination therapy.

Comparative Survival and Cost-Effectiveness of Advanced Therapies for End-Stage Heart Failure

Elisa F. Long, PhD; Gary W. Swain, MD, MBA; Abeel A. Mangi, MD

Background—Treatment options for end-stage heart failure include inotrope-dependent medical therapy, orthotopic heart transplantation (OHT), left ventricular assist device (LVAD) as destination therapy or bridge to transplant.

Methods and Results—We developed a state-transition model to simulate 4 treatment options and associated morbidity and mortality. Transition probabilities, costs, and utilities were estimated from published sources. Calculated outcomes included survival, quality-adjusted life-years, and incremental cost-effectiveness. Sensitivity analyses were performed on model parameters to test robustness. Average life expectancy for OHT-eligible patients is estimated at 1.1 years, with 39% surviving to 1 year. OHT with a median wait time of 5.6 months is estimated to increase life expectancy to 8.5 years, and costs <$100 000/quality-adjusted life-year gained, relative to inotrope-dependent medical therapy. Bridge to transplant-LVAD followed by OHT further is estimated to increase life expectancy to 12.3 years, for $226 000/quality-adjusted life-year gained versus OHT. Among OHT-ineligible patients, mean life expectancy with inotrope-dependent medical therapy is estimated at 9.4 months, with 26% surviving to 1 year. Patients who instead received destination therapy-LVAD are estimated to live 4.4 years on average from extrapolation of recent constant hazard rates beyond the first year. This strategy costs $202 000/quality-adjusted life-year gained, relative to inotrope-dependent medical therapy. Patient's age, time on wait list, and costs associated with care influence outcomes.

Conclusions—Under most scenarios, OHT prolongs life and is cost effective in eligible patients. Bridge to transplant-LVAD is estimated to offer >3.8 additional life-years for patients waiting ≥6 months, but does not meet conventional cost-effectiveness thresholds. Destination therapy-LVAD significantly improves life expectancy in OHT-ineligible patients. However, further reductions in adverse events or improved quality of life are needed for destination therapy-LVAD to be cost effective. **(*Circ Heart Fail*. 2014;7:470-478.)**

Key Words: cost-benefit analysis ■ transplantation

Heart failure afflicts >5 million Americans,[1] with 700 000 people newly diagnosed each year.[2] In 2013, heart failure cost our healthcare system >$32 billion and is expected to double by 2030.[2] A considerable proportion of hospitalized patients with heart failure have inotrope-dependent stage D heart failure[3–5] and experience a 1-year survival rate of only 25%.[6–8] The nationwide cost of index hospitalizations alone for orthotopic heart transplantation (OHT) and left ventricular assist device (LVAD) implantation approached $1 billion in 2009.[9]

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OHT is considered the definitive therapy for patients with inotrope-dependent stage D heart failure, with 1-year survival exceeding 85%.[10,11] Median survival for all OHT recipients is currently 10 years, increasing to 13 years conditional on surviving the first year.[10] More than 3500 people are currently listed for OHT, with a median wait-list time of 5 to 6 months,[12] although only 2200 OHT operations are performed annually in the United States, in part attributable to limited donor availability.[10,13]

Randomized clinical trials involving patients with stage D heart failure have demonstrated improvements in survival among transplant-ineligible patients undergoing LVAD implantation as destination therapy (DT). The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial showed a 48% reduction in risk of death in LVAD patients when compared with patients receiving inotrope-dependent medical therapy (IDMT).[6] Heartmate-II investigators subsequently showed that patients implanted with continuous-flow LVADs achieved a 54% reduction in risk of death when compared with patients implanted with earlier LVADs used in the REMATCH trial.[14] Further analysis has shown a 1-year survival approaching 80% among patients receiving DT-LVAD.[15] Patients who undergo LVAD implantation as a bridge to transplant (BTT) obtain 1-year survival rates nearly as high as OHT.[16] The presence

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The Data Supplement is available at http://circheartfailure.ahajournals.org/lookup/suppl/doi:10.1161/CIRCHEARTFAILURE.113.000807/-/DC1.

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Cost-Effectiveness Analysis of Continuous-Flow Left Ventricular Assist Devices as Destination Therapy

Joseph G. Rogers, MD; Robin R. Bostic, BS; Kuo B. Tong, MS; Rob Adamson, MD; Mark Russo, MD; Mark S. Slaughter, MD

Background—Continuous-flow left ventricular assist devices (LVADs) have become the dominant devices for mechanical circulatory support, but their cost-effectiveness is undetermined. This study assessed the cost-effectiveness of continuous-flow devices for destination therapy versus optimal medical management in advanced heart failure and compared the results with previous estimates for pulsatile devices.

Methods and Results—A Markov model was developed to assess cost-effectiveness. Survival, hospitalization rates, quality of life, and cost data were obtained for advanced heart failure patients treated medically or with a continuous-flow LVAD. Rates of clinical outcomes for all patients were obtained from clinical trial databases. Medicare prospective payments were used to estimate the cost of heart failure admissions. The cost of LVAD implantation was obtained prospectively from hospital claims within a clinical trial. Compared with medically managed patients, continuous-flow LVAD patients had higher 5-year costs ($360 407 versus $62 856), quality-adjusted life years (1.87 versus 0.37), and life years (2.42 versus 0.64). The incremental cost-effectiveness ratio of the continuous-flow device was $198 184 per quality-adjusted life year and $167 208 per life year. This equates to a 75% reduction in incremental cost-effectiveness ratio compared with the $802 700 per quality-adjusted life year for the pulsatile-flow device. The results were most sensitive to the cost of device implantation, long-term survival, cost per rehospitalization, and utility associated with patients' functional status.

Conclusions—The cost-effectiveness associated with continuous-flow LVADs for destination therapy has improved significantly relative to the pulsatile flow devices. This change is explained by significant improvements in survival and functional status and reduction in implantation costs. **(*Circ Heart Fail*. 2012;5:10-16.)**

Key Words: cost-effectiveness ■ heart failure ■ heart-assist device

The burden of advanced heart failure is characterized by excessive morbidity and mortality, poor quality of life, high treatment costs, and limited treatment options. Nearly 6 million Americans have heart failure, and approximately 10% of those have advanced disease.[1,2] The estimated total annual cost for heart failure in the United States is $39 billion in 2010, with the advanced heart failure population consuming a disproportionate amount of these healthcare resources.[1,3] After failing evidence-based medical and electric therapies, these patients have extremely limited treatment options. Heart transplant is considered epidemiologically insignificant as most patients are ineligible for transplant or are unlikely to receive a donor heart resulting from the shortage of suitable organs. Technological innovations and the clinical application of alternative therapies such as mechanical circulatory support devices, including left ventricular assist devices (LVADs), may help bridge this gap of available and effective therapy.

Clinical Perspective on p 16

Several studies have evaluated the long-term outcomes and costs associated with LVAD therapy. Nearly 10 years ago, the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study randomly assigned patients ineligible for transplant to treatment with an LVAD or optimal medical management (OMM). The LVAD patients had survival rates of 52% at 1 year and 23% at 2 years compared with 25% and 8% in the OMM arm.[4] The mean cost for the implant-related hospitalization was $210 187.[5] A follow-up cost-effectiveness analysis based on the REMATCH trial published in 2004 concluded that the incremental cost-effectiveness ratio (ICER) was $802 700 per quality-adjusted life year (QALY).[6] As centers gained more experience with patient selection, device implantation, and postoperative management, costs for the initial implant hospitalization decreased. Miller et al presented

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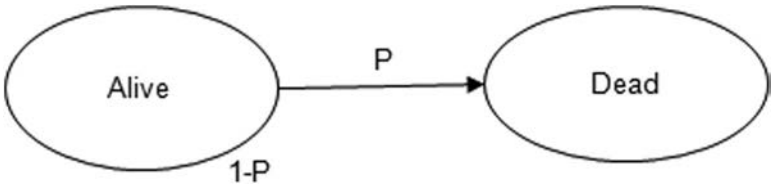

Figure 1. Health state transition model. This model included only 2 health states, alive and dead, with a time-dependent probability of transitioning from alive to dead.

cost data from a cohort of patients implanted with a pulsatile flow LVAD after completion of the REMATCH trial in select high-volume centers and demonstrated that the mean cost for implantation decreased to $128 048.[7] In a contemporary review of 6 pulsatile LVAD studies, Clegg et al reported a cost per QALY of $341 573 and cited a potential improvement in LVAD cost-effectiveness with the introduction of continuous-flow devices.[8]

The HeartMate II Destination Therapy trial randomly assigned patients with advanced heart failure to receive the older pulsatile LVAD used in REMATCH or a new generation continuous-flow LVAD.[9] Patients who received the continuous-flow device had 1- and 2-year survival rates of 68% and 58%, compared with 55% and 24% with the pulsatile device. The continuous-flow LVAD patients experienced similar long-term improvements in quality of life, exercise performance, and end-organ function to patients supported with pulsatile flow devices.[10,11] Furthermore, fewer continuous-flow devices required replacement for mechanical failure.

Given the improvement in survival, the reduced need for device replacement, improved quality of life, and a decrease in hospitalization costs associated with newer devices, the cost-effectiveness of LVAD therapy would reasonably be expected to improve. The objective of the current study was to perform a cost-effectiveness analysis of continuous-flow LVADs for destination therapy versus OMM from a third-party payer perspective based on the latest clinical and cost data available and to compare these data to previous estimates of the ICER for pulsatile LVADs.

Methods

Data Sources

Clinical outcomes and costs for this analysis were obtained from several sources. Clinical outcomes for optimal medical therapy were derived from the REMATCH trial (n=61, 1998–2001)[4] and the clinical outcomes of continuous-flow LVADs (n=134, 2005–2007) were obtained from the HeartMate II Destination Therapy Trial.[9]

Enrollment criteria in these trials distinguished a high risk patient population. Patients had predominantly New York Heart Association (NYHA) functional class IV symptoms and a left ventricular ejection fraction of ≤25%. They also had a peak oxygen consumption of <14 mL/kg/min or required treatment with continuous infusion of positive inotropic agents. These patients were ineligible for heart transplantation because of advanced age or comorbidities that were thought by the investigative site to preclude successful transplant.

The current analysis captured patient-specific clinical events and costs from the time of randomization in a clinical trial through a maximum of 5 years. In REMATCH, the 2-year survival rate was 0.08 for patients receiving OMM and 0.25 for the pulsatile LVAD.[4] In the HeartMate II Destination Therapy trial, the 2-year survival rate was 0.58 for patients receiving the continuous-flow device.[9] An indirect comparison of OMM and continuous-flow LVAD outcomes was required using data from REMATCH and the HeartMate II Destination Therapy trial because no trial has directly compared these treatments. Treatment strategies and protocols for OMM and LVAD destination therapy have been described previously.[4,9] Baseline patient characteristics were similar between the OMM and continuous-flow LVAD treatment groups except that those in the continuous-flow LVAD group were on average 6 years younger and 25% were classified by investigators as NYHA functional class III, whereas all OMM patients had NYHA class IV disease.[4,9]

Cost data were obtained from multiple sources, including prospectively collected hospital billing data, Medicare payments for professional services related to LVAD implantation, and Medicare prospective payments for rehospitalizations. A detailed description for each source is provided in later sections.

Model Design and Structure

A decision analytic model was adapted from the Blue Cross Blue Shield Technology Evaluation Center assessment.[6] After receiving an LVAD for destination therapy or being assigned to OMM, patients were evaluated through a Markov process containing 2 health states: alive or dead. Patients in the OMM and LVAD arms followed the same Markov process with monthly probabilities of transition between health states specific to each treatment group (Figure 1). Costs, QALYs, and life years (LYs) accrued during a patient's model-based lifetime were based on assumptions relating to monthly hospitalization rates and costs, outpatient costs, and the distribution of NYHA Functional Classification (I–IV) health states over time. These parameters and the monthly transition probabilities were informed using data from the REMATCH and HeartMate II Destination Therapy trials, as described below.

Calculation of QALYs and LYs

Cycle-specific survival probabilities were estimated from the Kaplan-Meier survival curves for the OMM cohort in the REMATCH trial and for the continuous-flow LVAD cohort in the HeartMate II Destination Therapy trial. Follow-up in both trials was completed at 24 months, thus requiring survival assumptions beyond this time point. In REMATCH, the survival probability of the OMM cohort at 24 months was 8%.[4] Extrapolation of survival past 24 months was based on an exponential survival curve using the constant hazard rate observed within 24 months (0.105 per month). For the LVAD treated patients, 3 different methods for survival extrapolation beyond 24 months were used. For the base case analysis, an exponential survival curve was fit to the 24-month data (0.023 per month) from the model. In the sensitivity analysis, the methods of stop and drop (ie, assuming that all patients surviving to 24 months die immediately thereafter) and a linear extrapolation between the observed survival at 24 months of 58% and 40% at 60 months were used (Figure 2).

For both the OMM and LVAD cohorts, QALYs were estimated based on survival adjusted for the cohort's average utility (ie, the preference that an individual or a society places on health outcomes, usually ranging from 0–1) in each cycle. Utility measurements were not collected in the HeartMate II Destination Therapy study or the REMATCH trial, so utility estimates were derived from health states based on NYHA classes.[12] The probability of belonging to a specific NYHA class varied over time. Monthly estimates of these probabilities were obtained from the REMATCH and HeartMate II Destination Therapy trials for the OMM and LVAD arms, respectively (Table 1). When the NYHA classes were not reported, data were interpolated from the immediately preceding month and the month after. The distribution at 24 months was used to estimate NYHA classes beyond 24 months. For the OMM cohort, only the distribution of patients in NYHA classes I/II or classes III/IV were

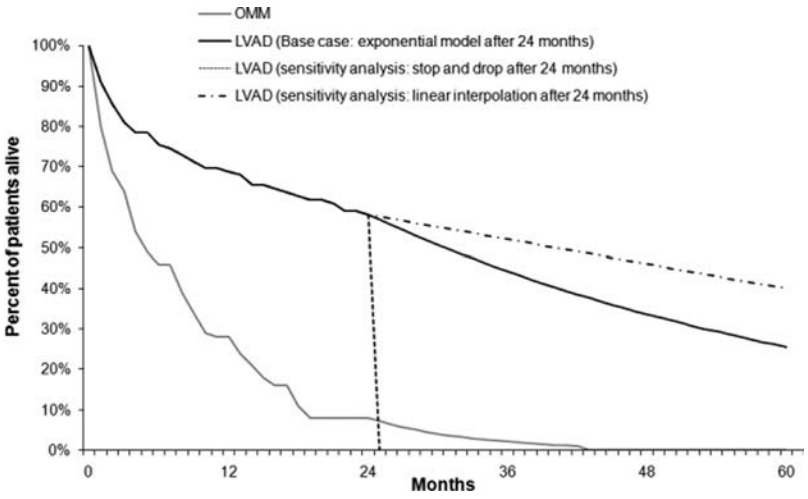

Figure 2. Survival curves for base case and sensitivity analyses. The survival curves for the base case analysis and the 2 sensitivity analyses—stop and drop and linear extrapolation—from 24 to 60 months are shown. OMM indicates optimal medical management; LVAD, left ventricular assist device.

available.[6] Patients were predominantly classified as classes III/IV during the 24-month trial period, so we assumed that 25% of those had class III and 75% had class IV heart failure. The few patients classified into classes I/II at 3 (3%) and 6 months (9%) were all assumed to have class II disease.[6] At the 24-month assessment in REMATCH, 1 of the 3 patients who remained alive in the OMM cohort reported NYHA class I/II symptoms. For the purposes of this analysis, the number of OMM patients with NYHA class I/II symptoms at ≥24 months was considered to be 0% to be consistent with the observed rates throughout the entire REMATCH trial. Mean utility values of 0.855, 0.771, 0.673, and 0.532 were assigned to NYHA classes I, II, III, and IV, respectively,[12] suggesting that patients with NYHA classes I heart failure were willing to trade, on average, 15% of their remaining years in return for perfect health, and those with NYHA classes IV disease were willing to trade 47% of their remaining life. It was assumed that the utilities for NYHA categories did not differ between the LVAD and OMM patients.

The total LYs and QALYs for the OMM and LVAD cohort in the study period were calculated as the sum of LYs and QALYs accumulated in each cycle and were discounted at 3% per year per recommendation from the Panel on Cost-Effectiveness in Health and Medicine.[13]

Table 1. Probability of Being in NYHA Classes I to IV

	OMM*[6]				LVAD†[9]			
NYHA	Class I	Class II	Class III	Class IV	Class I	Class II	Class III	Class IV
Baseline	0%	0%	25%	75%	0%	0%	25%	100%
Mo 1	0%	0%	25%	75%	NR	NR	NR	55%
Mo 3	0%	3%	24%	73%	33%	42%	23%	2%
Mo 6	0%	9%	23%	68%	NR	NR	NR	21%
Mo 9	0%	0%	25%	75%	NR	NR	NR	21%
Mo 12	0%	0%	25%	75%	42%	35%	24%	23%
Mo 18	0%	0%	25%	75%	NR	NR	NR	NR
Mo 24	0%‡	0%‡	25%‡	75%‡	42%	38%	14%	6%

NYHA indicates New York Heart Association; OMM, optimal medical management; LVAD, left ventricular assist device; NR, not reported.

*In the REMATCH trial, only the percentage of OMM cohort in NYHA classes I/II or classes III/IV were reported. In the model, the percentage of patients in classes I/II was assigned to class II, and 25% of those in classes III/IV were assumed in class III and 75% were assumed in class IV.

†For months with missing data, linear interpolation was used in the model.

‡In the REMATCH trial, 33% and 67% of OMM cohort reported NYHA classes I/II and III/IV, respectively. Because of the small sample size (n=3) for OMM patients at 24 mo, the data were reset to 0% and 100% in the model.

Calculation of Costs

Costs were assessed from the perspective of a third-party payer. Three main categories of costs were included: LVAD implantation and replacement costs, rehospitalization costs, and outpatient costs. Implantation and replacement costs applied only to LVAD recipients, whereas rehospitalization costs and outpatient costs applied to all patients.

LVAD implantation costs included hospital and professional service costs. Hospital costs encompassed the entire hospitalization from implantation to discharge, including the cost of the device, intensive care days, medical/surgical days, operating room, diagnostics, laboratory tests, blood products, drugs, and miscellaneous services. Although patients may incur costs during the preimplantation phase of the hospitalization for heart failure therapy or management of their comorbidities, these costs were not included. Hospital costs were estimated from hospital claims data collected from a subset of patients (83 out of 134) who were representative of all patients receiving a continuous-flow device in the HeartMate II trial.[14] The costs of professional services were obtained from an analysis of Medicare claims submitted by physicians for patients selected from a random sample of Medicare beneficiaries who underwent an LVAD implantation procedure in 2008.[15] The costs included the surgical procedure and follow-up evaluation and management from cardiologists and other physicians in the same quarter that the LVAD was implanted.

The frequency of rehospitalizations for the LVAD cohort was based on data from the HeartMate II Destination Therapy trial in which an annual rehospitalization (including LVAD pump replacement) rate of 2.64 per person and LVAD replacement rate of 0.06 per person was reported.[9] As hospitalizations for LVAD replacement versus a typical heart failure management are associated with markedly different payments, rates for these hospitalizations were estimated separately. A monthly rehospitalization rate, excluding rehospitalization for LVAD replacement, was estimated at 0.215 per person, and a monthly LVAD replacement rate was estimated at 0.005 per person. For the OMM cohort, the readmission rate in the base case analysis was based on the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, which compared patients with advanced heart failure who received cardiac resynchronization therapy with patients who received optimal pharmacological therapy.[16] In this study, the patients were all in NYHA class III or IV, and the average age was 66 years. For the OMM group, 65% of patients were hospitalized during follow-up, and the average number of hospital admissions per patient-year of follow-up was 1.59. In terms of admissions per month, this equates to 0.1325. The sensitivity analysis tested the assumption based on the 30-day rehospitalization rates for a cohort

Table 2. Model Parameters, Values, and Data Sources in the Base Case and Sensitivity Analysis

	Base Case	Range
24-mo survival for LVAD[9]	KM curve	NA
24-mo survival for OMM[4]	KM curve	NA
Long-term survival extrapolation for LVAD	Exponential	Stop and drop, linear (40% at 60 mo)
Long-term survival extrapolation for OMM[6]	Exponential	NA
LVAD implantation hospital cost[14]	$193,812	$122,785–$264,839*
LVAD implantation professional service cost[15]	$8,841	NA
LVAD replacement cost[18]	$131,430	NA
Monthly LVAD replacement rate[9]	0.005	NA
Rehospitalization cost (per event)[5,16]	$6,850	$6,850–$30,627
Monthly rehospitalization rate for LVAD[9]	0.21	NA
Monthly rehospitalization rate for OMM[16]	0.1325	0.1325–0.26
Monthly outpatient costs[20,21]	$2,331	NA
End-of-life cost[19]	$44,211	NA
Utility for NYHA Class I[12]	0.855	0.641–1.0
Utility for NYHA Class II[12]	0.771	0.578–0.964
Utility for NYHA Class III[12]	0.673	0.505–0.841
Utility for NYHA Class IV[12]	0.532	0.399–0.665

LVAD indicates left ventricular assist device; KM, Kaplan-Meier; OMM, optimal medical management; NA, not applicable; OMM, optimal medical management; NYHA, New York Heart Association.

*One standard deviation from the mean cost ($193,812).

of medically managed heart failure patients in the Medicare fee-for-service program.[17] The cost per rehospitalization was estimated from the average Medicare reimbursement rates for medical severity diagnosis-related group (MS-DRG) 291 (heart failure and shock with major complications and comorbidities) and MS-DRG 292 (heart failure and shock with complications and comorbidities).[18] The cost for LVAD replacement was estimated from the average Medicare reimbursement rates for MS-DRG 1 (heart transplant or implant of heart assist system with major complications and comorbidities).[18] The cost per rehospitalization was assumed to be the same for patients with an LVAD and those receiving OMM, consistent with the prior cost-effectiveness analysis of LVADs.[6] For patients who died, a 1-time end-of-life cost was added, which was based on the cost of medical management for patients with end-stage heart failure during the last quarter of their lives.[19]

Outpatient costs included professional services, laboratory tests, and drugs. In a study of bridge-to-transplant patients, the average weekly outpatient cost was $352, yielding a monthly cost of $1531 (1995 US dollars).[20,21] This amount was revalued in 2009 US dollars using the consumer price index for medical care services.[22] Consistent with the prior cost-effectiveness analysis of LVADs,[6] outpatient costs were assumed to be the same for LVAD and OMM patients. Although these costs were based on a small cohort of bridge-to-transplant patients who were treated more than a decade ago, as these costs were a small fraction of the costs for initial implantation and subsequent hospitalizations, this estimate was unlikely to affect the cost-effectiveness findings.

All costs are in 2009 US dollars. Costs incurred beyond the first year were discounted at 3% per year. Detailed cost parameter values used in the base-case analysis are presented in Table 2.

Table 3. Costs, QALYs, and Life Year Results for the Base Case Analysis

Parameters	OMM	LVAD
Total cost ($)	$62,856	$360,407
Total QALYs (y)	0.37	1.87
Total LYs (y)	0.64	2.42

QALY indicates quality-adjusted life year; OMM, optimal medical management; LVAD, left ventricular assist device; LY, life year.

Base-Case Analysis

The costs and outcomes for the OMM and LVAD cohorts were forecasted over 5 years. The incremental cost-effectiveness ratio (ICER) was calculated comparing the difference in average total costs and the difference in average QALYs or LYs between the OMM and LVAD cohorts. The model was constructed with TreeAge Pro 2006 software (TreeAge Software, Inc, Williamstown, MA).

Sensitivity Analysis

The Blue Cross Blue Shield technology assessment, which used data from the REMATCH study, suggested that the model results were more sensitive to the cost of LVAD implantation and variations in utility for NYHA classes than other parameters. The same model structure was applied in our analysis, and the parameters driving the results remained the same. In addition, alternative assumptions for rehospitalization costs and long-term survival for the LVAD cohort were tested. Alternative costs of rehospitalizations for both LVAD and OMM patients were estimated from the average cost per rehospitalization for the pulsatile device cohort in the REMATCH trial.[5] Alternative assumptions for long-term survival extrapolation for LVAD patients, such as stop and drop and a linear survival curve, were included in the sensitivity analysis.

Results

Baseline Results

Using the values described for all parameters, at 5 years patients in the LVAD arm gained on average 1.87 QALYs or 2.42 LYs, at a total cost of $360 407. Medically treated patients gained 0.37 QALYs or 0.64 LYs, at a cost of $62 856 (Table 3). The ICER for the continuous-flow LVAD compared with OMM was $198 184 per QALY and $167 208 per LY.

The baseline results suggested a substantial improvement of continuous-flow devices compared with the previous cost-effectiveness analysis for pulsatile devices, where the total costs were estimated at $391 906 (2002 US dollars), total QALY at 0.76, and ICER at $802 674 (2002 US dollars).[6]

Sensitivity Analyses

Results were most sensitive to variations in long-term survival probabilities associated with the LVAD, the cost of LVAD implantation, cost per rehospitalization, and utility for NYHA classes I and II (Figure 3). However, ICERs of $300 000 or more depended on the improbable assumption that all patients implanted with an LVAD who survived 24 months would die immediately thereafter. In other scenarios, where a wide range of values for the selected parameters were tested, the ICERs for LVAD relative to OMM remained below $300 000 per QALY.

Discussion

This study demonstrates a meaningful improvement in the cost-effectiveness of mechanical circulatory support in the

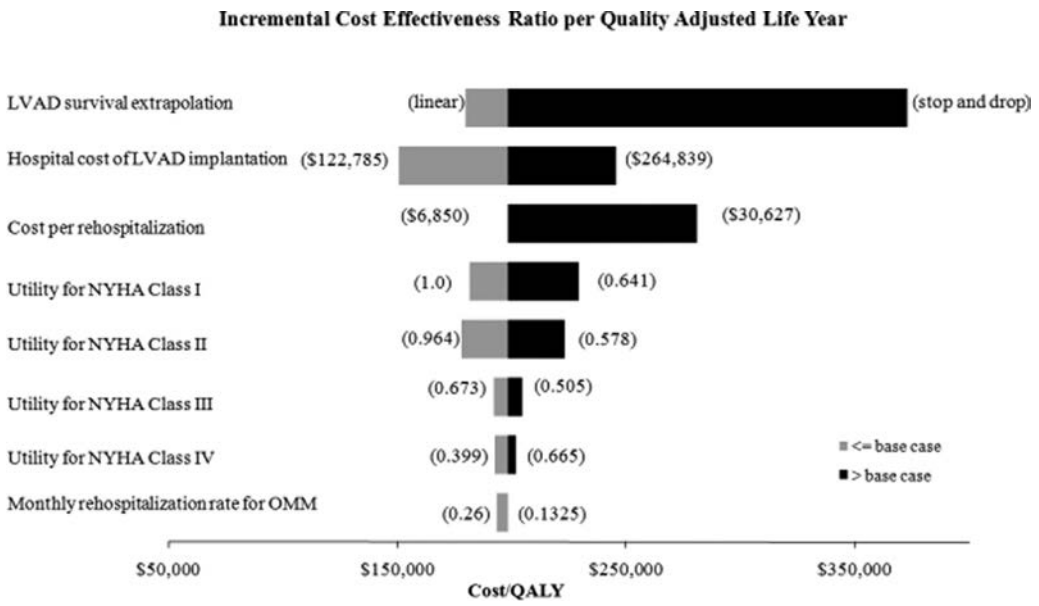

Figure 3. Results of the 1-way sensitivity analyses. In the left ventricular assist device (LVAD) arm, the methods of stop and drop (assuming that all patients surviving to 24 months die immediately thereafter) and a linear extrapolation (assuming a 60-month survival rate of 40%) were used. Utility values for patients with New York Heart Association (NYHA) I to IV heart failure were ranged by plus or minus 25% of the base case estimates. The initial hospital cost of LVAD implantation is varied by 1 standard deviation below or above the mean. The cost per rehospitalization for patients receiving an LVAD from the REMATCH trial ($30 267) is used in the LVAD and optimal medical management (OMM) arms. The monthly rehospitalization rate for the OMM arm is assumed to be between the rate for the LVAD arm (0.215) and 0.1325.

recent era. These favorable outcomes are largely related to improved survival with continuous-flow LVADs coupled with reductions in implant costs and a persistent improvement in functional abilities in patients treated with mechanically supported circulation. The relative 75% reduction in cost/QALY during the past decade suggests that LVAD therapy continues to evolve in to a mainstream therapy for advanced heart failure.

Advanced heart failure is associated with high residual mortality. For those patients who meet indications, heart transplant remains the gold standard and preferred therapy. However, the shortage of suitable donor organs has limited this option to fewer than 2500 patients each year. A durable and cost-effective mechanical circulatory support treatment option could narrow the chasm that exists between the number of patients with advanced heart failure and the scare resources for transplantation.

Mechanical circulatory support devices were initially designed as pulsatile pumps requiring sufficient size to hold a normal cardiac stroke volume and a complex mechanism to propel the blood that included multiple moving parts. Although these devices were hemodynamically successful, device size and durability, as well as significant adverse events, limited their clinical applicability. Newer pump designs based on continuous flow have permitted miniaturization and design simplification, which has resulted in improved durability and less surgical trauma for implantation. Improved patient-centric care has accompanied these engineering advances. In the latest randomized trial of continuous-flow versus pulsatile LVADs for destination therapy, there was a significant improvement in 2-year survival and reduction in adverse events.[23] LVADs are emerging as the treatment of choice for patients with advanced heart failure who are ineligible for heart transplantation. However, the relatively high cost of this therapy raises the lingering issue of cost-effectiveness.

In the Medicare population ineligible for transplant, the average cost of treating advanced heart failure with OMM is approximately $180 000, with the majority being spent in the last 6 months of life.[3] In the initial evaluation of costs for pulsatile LVADs, the average cost of LVAD implantation was $210 187, and an independent technology assessment determined an ICER of $802 700.[5,6] In comparison with the pulsatile devices, the hospital costs for continuous-flow device implantation decreased by 50%.[14] Despite the increased survival and quality of life improvements, high treatment costs restricted the adoption of LVAD therapy to a highly selected, extremely sick patient population. Our current cost analysis of patients treated with the new continuous-flow LVADs reveals a significant reduction in the ICER/QALY, from $802 700 to $198 184. This ICER/QALY is still significantly higher than the traditionally used threshold of $50 000 when considering therapies to be cost-effective, but the incremental cost reduction in a relatively short time period is encouraging.

ICERs, as calculated in cost-effectiveness analyses, represent the opportunity cost of resources at margin. However, when applied to orphan disease or other end-of-life treatments, ICERs can be challenged, as the evaluation does not consider the innovative nature of medicine or availability of alternative treatment.[24] Although the notion of an ICER threshold value as a guiding principle for resource allocation is subject to debate, cost-effectiveness guided by ICERs continues to be the most commonly used tool in the evaluation of health care practices and new medical technologies.

ICERs less than $50 000 per QALY are considered cost-effective and those between $50 000 and $100 000 are regarded as acceptable. Thus, the use of LVADs for the treatment of advanced heart failure has not yet achieved the currently accepted benchmark. Ongoing improvements in patient survival, reduction in long term complications and readmission rates, and a focus on inpatient and outpatient processes of care would reasonably be expected to result in further declines in the ICER, with the goal of ultimately achieving the current standard for cost-effectiveness.

A number of potential limitations of this study are worth noting. The clinical and economic data for LVADs and OMM were obtained on the basis of reports from different time periods. Survival data for OMM were based on REMATCH performed nearly 10 years ago, whereas the continuous-flow LVAD data were based on the recently completed HeartMate II Destination Therapy trial. Similar to the progress seen with LVADs, one would expect advances in medical management and its outcomes; for example, earlier referral to hospice may have reduced the hospitalization costs, which may lead to a reduction in the overall costs. Furthermore, patients randomly assigned to the OMM arm in REMATCH OMM were older than those treated with continuous-flow LVADs in HeartMate II Destination Therapy trial. If the data on a more recent OMM cohort with a similar age distribution were used, one may anticipate a better survival than currently estimated for the OMM patients. However, given the marked difference in survival and the lack of novel treatments demonstrated to improve the outcomes of patients with this severity of illness, it is reasonable to believe that the results would have been similar if more recent data for OMM were used. Another consideration in the interpretation of this study is the anticipation that long-term mechanical circulatory support will be applied in an older patient population than studied in the HeartMate II Destination Therapy trial. The overall impact of ventricular assist devices on survival, functionality, hospital days, and cost in the elderly may negatively affect the cost-effectiveness of mechanically assisted circulation and should be systematically evaluated. Second, costs of rehospitalizations were not collected in the HeartMate II Destination Therapy trial and were derived by estimation from other sources. The Medicare inpatient prospective payment system uses diagnosis-related groups, which are linked to payment rates for an acute hospital stay based on a patient's clinical condition and treatment strategy, and these were used in this study. As the causes for hospital admissions were unavailable, the analysis only included the payment for a typical episode of heart failure related admission during which medical management is provided. Using MS-DRG payments for heart failure and shock may have overstated the rehospitalization costs for the OMM cohort. It may also have under- or overstated the costs for the LVAD cohort. Although it is reasonable to believe that most admissions would fall under heart failure related MS-DRGs, a recent report from the Interagency Registry for Mechanically Assisted Circulatory Support showed that most readmissions were for nonheart failure reasons. This current estimate for the readmission ($6850) is substantially lower than the average readmission cost ($30 627) in the REMATCH trial. REMATCH was conducted 10 years ago, when the clinical experience with the LVADs remained extremely limited. With the growing clinical experience and the improvement of the device, the implantation cost and the adverse event rates were dramatically reduced. It is reasonable to believe that there was a similar trend for the rehospitalization cost. Furthermore, the REMATCH costing cohort included only 34 patients, and most of them died within 2 years. If we assume that most costs are incurred during the last 6 months of a patient's life, the higher mortality would lead to a higher estimate of average cost per hospitalization.

Utility estimates in the study were not validated for an LVAD population, and LVAD-specific utility estimates are currently not available from the literature. The use of functional class as a surrogate for utility has been used in other clinical heart failure trials and was used in the original cost-effectiveness assessment of LVAD therapy.[6] Analysis of functional and quality of life outcomes from the HeartMate II clinical trials program demonstrated early and sustained improvements in 6-minute walk distance, as well as Minnesota Living with Heart Failure and Kansas City Cardiomyopathy scores.[10] Thus, it may be anticipated that substitution of another functional or quality of life metric would have yielded similar utility to that observed with NYHA functional class. The Interagency Registry for Mechanically Assisted Circulatory Support registry is collecting the EQ-5D data for the LVAD population; the single-index utility estimates derived from the EQ-5D data, when they become available, can be used to validate the NYHA class–based utility estimates in this study.

Conclusion

Using methods similar to those of the original Blue Cross Blue Shield technology assessment, we have demonstrated a significant improvement in the ICER for LVADs used to treat advanced heart failure in patients who are not eligible for heart transplantation. On the basis of this assessment, it is anticipated that continued refinement of patient selection criteria, technological advances, and improvements in management strategies will converge and result in the demonstration of LVADs as an economically effective treatment option for patients with advanced heart failure.

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CLINICAL PERSPECTIVE

Mechanical circulatory support has become an accepted treatment for patients with advanced heart failure ineligible for transplantation. It is anticipated that the growing heart failure population coupled with the shortage of suitable donor organs will result in further increases in the use left ventricular assist devices (LVADs) as a means to enhance quality of life and survival. Critical evaluation of new and expanding technologies such as LVADs must include careful analysis of efficacy, safety, and cost-effectiveness. The most comprehensive study of LVAD cost-effectiveness was published 7 years ago based on very early clinical experience with mechanically assisted circulation and older generation devices. High device and implantation costs, as well as relatively modest survival benefits, resulted in an incremental cost effectiveness ratio/quality-adjusted life year of more than $800 000. To place this in perspective, the per-patient cost of advanced heart failure in a Medicare population treated with standard medical and electric therapies has been reported to be $180 000, with short anticipated life expectancy and limited likelihood for improvements in quality of life. Thus, the "utility" of standard therapies in these patients is poor. The rapid improvements in LVAD technology, patient selection, center experience, and management strategies would reasonably be anticipated to improve the cost-effectiveness of this therapy by reducing perioperative and long-term mortality, decreasing complications, and enhancing functionality and quality of life over prolonged periods of time.

NICE National Institute for Health and Care Excellence

Implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation

Issued: March 2015

NICE interventional procedure guidance 516

guidance.nice.org.uk/ipg516

Healthcare Improvement Scotland

NICE has accredited the process used by the NICE Interventional Procedures Programme to produce interventional procedures guidance. Accreditation is valid for 5 years from January 2010 and applies to guidance produced since January 2009 using the processes described in the 'Interventional Procedures Programme: Process guide, January 2009' and the 'Interventional Procedures Programme: Methods guide, June 2007'. More information on accreditation can be viewed at www.nice.org.uk/accreditation

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1 Recommendations

1.1 Current evidence on the efficacy and safety of the implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. For people who are eligible for heart transplantation, refer to NICE's interventional procedure guidance on short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery.

1.2 Patient selection should be done by a multidisciplinary team that includes a cardiologist with a specialist interest in heart failure, a cardiothoracic surgeon and a cardiac anaesthetist (see section 1.3).

1.3 Implantation of left ventricular assist devices for destination therapy should be done by surgeons, anaesthetists and intensive care specialists with special training and regular practice in performing this procedure and caring for these patients. Subsequent care should be provided by a multidisciplinary team including staff with the expertise to deal with patients' medical and psychological management, and with the maintenance of their left ventricular assist devices.

1.4 Clinicians should enter details on all patients who have a left ventricular assist device for destination therapy onto the UK Central Cardiac Audit Database.

2 Indications and current treatments

2.1 Heart failure is a complex clinical syndrome of symptoms that occur when the efficiency of the heart as a pump is impaired. It leads to reduced blood flow to the body tissues and increased filling pressure in the heart, which causes congestion and oedema in the lungs (causing breathlessness) or the body (causing swelling of the legs). Other symptoms include reduced exercise tolerance, fatigue and malaise.

2.2 Medical treatment of heart failure involves drugs such as diuretics and inotropic agents. Invasive therapies include electrophysiological interventions

such as pacemakers and implantable cardioverter defibrillators, revascularisation by percutaneous coronary angioplasty and stenting or coronary artery bypass grafting, valve replacement or repair, and temporary use of intra-aortic balloon pumps. In chronic heart failure, conventional treatment strategies may no longer work, resulting in the need for heart transplantation. Ventricular assist devices can be used to provide temporary circulatory support while a patient awaits heart transplantation (bridge-to-transplantation).

3 The procedure

3.1 'Destination therapy' is a term that refers to the implantation of a left ventricular assist device (LVAD) with the aim of providing permanent circulatory support to people with advanced heart failure who are ineligible for heart transplantation. This guidance is based on evidence from studies in which the intended treatment strategy was destination therapy, and not bridge-to-transplantation.

3.2 The LVAD is implanted with the patient under general anaesthesia and involves open heart surgery, usually with cardiopulmonary bypass. Initially, the pump component of the LVAD is placed in the pericardium. An inflow pipe is then inserted into the left side of the heart (usually the left ventricle) and an outflow pipe is inserted into the systemic arterial system (usually the aorta). Subsequently, a power cable, attached to the pump, is brought out of the abdominal wall to the outside of the body and attached to a control system and battery. Once the pump begins to work and support the heart, the cardiopulmonary bypass machine is removed and the chest incision is closed. The LVAD draws oxygenated blood from the failing left ventricle and pumps it into the systemic arterial system under pressure.

3.3 The first LVADs used pulsatile pumps that mimicked the natural pulsing action of the heart. Newer, more commonly used, devices use a rapidly spinning rotor to produce a continuous flow of blood into the systemic arterial system. Some people may also need simultaneous implantation of a second device to support right ventricular function.

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 randomised controlled trial of 129 patients treated by pulsatile-flow left ventricular assist device (LVAD) destination therapy (n=68) or optimal medical management (n=61), survival rates were 23% and 8% respectively at 2-year follow-up (p=0.09). At 4-year follow-up, survival rates were 16% in the pulsatile-flow LVAD group and 8% in the optimal medical management group (no p value reported).

4.2 In a registry of 1287 patients treated by continuous-flow (n=1160) or pulsatile-flow (n=127) LVADs, survival rates were 76% and 68% respectively at 1-year follow-up (p<0.0001). At 2-year follow-up, survival rates were 67% in the continuous-flow group and 45% in the pulsatile-flow group (p<0.0001).

4.3 In a randomised controlled trial of 200 patients treated by continuous-flow (n=134) or pulsatile-flow LVADs (n=66), 6-minute walking test distances improved from 182 m to 318 m (p<0.001) and 172 m to 306 m (p<0.001) respectively at 1-year follow-up (p value between groups=0.22).

4.4 In the randomised controlled trial of 200 patients treated by continuous-flow or pulsatile-flow LVADs, mean Minnesota Living with Heart Failure questionnaire scores (scores range from 0 to 105, with lower scores indicating better quality of life) improved from 75.4 to 34.1 (p<0.001) and 76.1 to 44.4 (p<0.001) respectively at 1-year follow-up (p value between groups=0.03). In the same study, mean overall Kansas City Cardiomyopathy questionnaire scores (scores range from 0 to 100, with higher scores indicating better quality of life) improved from 27.4 to 65.9 (p<0.001) in the continuous-flow group and from 46.5 to 59.1 (p<0.001) in the pulsatile-flow group at 1-year follow-up (p value between groups=0.06).

4.5 In the randomised controlled trial of 129 patients treated by pulsatile-flow LVAD destination therapy or optimal medical management, mean SF-36 emotional

domain scores (scores range from 0 to 100, with higher scores indicating better emotional outcomes) changed from 33 to 64 and from 25 to 17 respectively at 1-year follow-up (p value between groups<0.05).

4.6 Specialist advisers listed key efficacy outcomes as: event-free survival; cardiac output; exercise capacity; quality of life; and the 'potential for heart recovery'.

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 Death caused by device failure was reported in less than 1% (6/1160) of patients treated by continuous-flow left ventricular assist devices (LVADs) and 2% (3/127) of patients treated by pulsatile-flow LVADs in a registry of 1287 patients at 2-year follow-up. Death arising from loss of power to external components of LVADs was reported in 2% (9/414) of patients in a case series of 414 patients treated by continuous-flow LVADs, at a minimum follow-up of 2 years.

5.2 Ischaemic stroke was reported in 8% (11/133) of patients treated by continuous-flow LVADs and 7% (4/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in a randomised controlled trial of 200 patients (p=0.38). In the same study, haemorrhagic stroke was reported in 11% (15/133) of patients treated by continuous-flow LVADs and 8% (5/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up (p=0.33).

5.3 Right heart failure, managed by extended inotrope therapy, was reported in 20% (27/133) of patients treated by continuous-flow LVADs and 27% (16/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients (p<0.001). In the same study, right heart failure, treated by right ventricular assist devices, was reported in 4% (5/133) of patients treated by continuous-flow LVADs and 5% (3/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up (p=0.12).

5.4 Respiratory failure was reported in 38% (50/133) of patients treated by continuous-flow LVADs and 41% (24/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p<0.001$).

5.5 Renal failure was reported in 16% (21/133) of patients treated by continuous-flow LVADs and 24% (14/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p<0.001$).

5.6 Cardiac arrhythmia was reported in 56% (75/133) of patients treated by continuous-flow LVADs and 59% (35/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p=0.006$).

5.7 LVAD-related infection was reported in 35% (47/133) of patients treated by continuous-flow LVADs and 36% (21/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p=0.01$).

5.8 Pump replacement was needed for 9% (12/133) of patients treated by continuous-flow LVADs and 34% (20/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients ($p<0.001$).

5.9 Pump thrombosis was reported in 4% (5/133) of patients treated by continuous-flow LVADs and 0% of patients treated by pulsatile-flow LVADs at 2-year follow-up in the randomised controlled trial of 200 patients (no p value reported).

5.10 Bleeding that needed blood transfusion was reported in 76% (315/414) of patients in the case series of 414 patients treated by continuous-flow LVADs. In the same study, bleeding that needed surgical re-exploration was reported in 23% (95/414) of patients (no further details were provided).

5.11 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 list any anecdotal adverse events. They considered that aortic regurgitation was a theoretical adverse event.

6 Committee comments

6.1 The Committee noted that heart failure is very common. It considered that the use of left ventricular assist devices for destination therapy in people ineligible for heart transplantation needs very careful selection of patients who are likely to derive sustained benefit in terms of survival and quality of life.

6.2 The Committee recognised that this procedure is associated with a high incidence of complications, but it judged that the potential benefit for appropriately selected patients outweighed its potential for harm.

6.3 The Committee noted that technology for this procedure has evolved significantly in recent years and continues to do so.

7 Further information

7.1 For related NICE guidance, see the NICE website. For patients who are eligible for heart transplantation, see NICE's interventional procedure guidance on short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery.

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.

About this guidance

NICE interventional procedures guidance makes recommendations on the safety and efficacy of the procedure. It does not cover whether or not the NHS should fund a procedure. Funding decisions are taken by local NHS bodies after considering the clinical effectiveness of the procedure and whether it represents value for money for the NHS.

This guidance was developed using the NICE interventional procedures guidance process.

We have produced a summary of this guidance for patients and carers. Information about the evidence the guidance is based on is also available.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

Your responsibility

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

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to 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.

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Decision Memo for Ventricular Assist Devices as Destination Therapy (CAG-00119R2)

Decision Summary

The Centers for Medicare & Medicaid Services (CMS) is issuing the following decision:

The evidence is adequate to conclude that VAD implantation as destination therapy improves health outcomes and is reasonable and necessary when the device has received FDA approval for a destination therapy indication and only for patients with New York Heart Association (NYHA) Class IV end-stage ventricular heart failure who are not candidates for heart transplant and who meet all of the following conditions:

a. Have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and,
b. Have a left ventricular ejection fraction (LVEF) < 25%; and,
c. Have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.

CMS is not changing any other parts of Section 20.9 "Artificial Hearts and Related Devices" of the National Coverage Determinations Manual. The final policy in its entirety is available in Appendix A with changes appearing in Section 3.

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Decision Memo

To: Administrative File CAG-00119R2

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Subject: Coverage Decision Memorandum for Ventricular Assist Devices as Destination Therapy (VAD)

Date: November 9, 2010

I. Decision

The Centers for Medicare & Medicaid Services (CMS) is issuing the following decision:

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a. Have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and,
b. Have a left ventricular ejection fraction (LVEF) < 25%; and,
c. Have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.

CMS is not changing any other parts of Section 20.9 "Artificial Hearts and Related Devices" of the National Coverage Determinations Manual. The final policy in its entirety is available in Appendix A with changes appearing in Section 3.

II. Background

Heart failure is a condition in which the heart cannot pump enough blood to the body. The incidence of heart failure rises with advancing age and continues to be a significant cause of morbidity and mortality for elderly Medicare patients. According to the Centers for Disease Control and Prevention (www.cdc.gov/dhdsp/library/fs_heart_failure.htm), in the United States approximately 5.8 million people have heart failure with about 670,000 new cases diagnosed each year. About one in five patients with heart failure will die from the disease within one year of its diagnosis.

While heart failure is not caused by aging, the elderly are more likely to have had predisposing conditions such as long-standing hypertension (high blood pressure) or myocardial infarction (heart attack). Depending on the severity of heart failure, patients can be treated with several different types of drugs, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, digoxin, inotropes and others. Inotropes are drugs that increase the contractile force of the heart. These medications cannot reverse heart failure but may improve the symptoms of heart failure by reducing fluid, reducing strain on the heart by reducing blood pressure, slowing heart rate or making the heart beat stronger. Despite improvements in available medications and closer monitoring of patients, heart failure continues to be a progressive disease, which becomes refractory to medical management over time. Advanced or end-stage heart

failure can be cured by heart transplant. Unfortunately, elderly patients are not generally candidates for transplants due to age alone or comorbid conditions, which present unacceptable surgical risks. Only about 2300 heart transplants are performed annually in the United States with available organs generally allocated to younger patients most likely to survive surgery and have a prolonged benefit (www.medhelp.org/NIHlib/GF-270.html).

The functional limitations due to heart failure can be quantified using the New York Heart Association (NYHA) classification system, which was most recently updated by the American Heart Association (AHA). In 1994, the Criteria Committee of the New York City affiliate of AHA revised the classification to describe the following functional classes of heart failure

(http://www.americanheart.org/presenter.jhtml?identifier=4569):

Class I
Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.

Class II
Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.

Class III
Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.

Class IV
Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

It has been noted in the literature that the NYHA classification system is often subjective with physicians having difficulty assigning patients to any one class. Therefore, in an article published in the American Family Physician (Chavey et al, 2001), the authors offer a classification scheme that they believe will result in less ambiguous patient assignment to a class. The authors present new symptomatic definitions and link them to a corresponding NYHA class or classes. In this scheme, patients with a recent history of dyspnea at rest and patients with dyspnea at rest are assigned to different classes as the authors believe this to be indicative of prognosis.

Asymptomatic – NYHA Class I
Symptomatic – NYHA Class II/III
Symptomatic with recent history of dyspnea at rest – NYHA Class IIIB
Symptomatic with dyspnea at rest – NYHA Class IV

This proposal did not become a standard for clinical heart failure classification.

Ventricular assist devices (VADs) are mechanical pumps used to assist a damaged or weakened heart in pumping blood. These devices support a patient's weakened native heart but do not replace it, unlike heart transplant. VADs are surgically attached to a ventricle of the native heart and the mechanical pump is implanted in the abdomen or in the chest cavity. The device requires a driveline that goes from the pump inside the patient's body to an external power and control unit. Typically these external portions of the device are portable and the patient can carry them in a small bag along with extra batteries.The device also has a base unit that is not portable but can be used when the patient is at home or in the hospital.

Selection criteria for severe heart failure patients who may be considered for VAD implantation include clinical assessment (NYHA functional class, clinical history, management and duration of disease, cardiopulmonary stress testing) and cardiac and anatomic considerations (body size), as well as non-cardiac considerations and assessment of operative risk.

Mechanical circulatory support devices, including VADs, have been used to assist acutely injured hearts to recover from such things as infection or the effects of open heart surgery for a number of years. More recently, VADs have been used to support failing hearts over longer periods of time as a "bridge to transplant" until a suitable donor heart becomes available. Information from the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) states that at any one time 3500 to 4000 patients are listed for heart transplant but more than 25% of these patients may die before a donor heart is found (www.medhelp.org/NIHlib/GF-270.html). With the advent of improvements in the reliability and durability of VADs some patients on transplant waiting lists actually recovered cardiac function and were able to have their devices removed. Still other patients received newer smaller devices, which enabled them to leave the hospital and return home, sometimes for long periods, while awaiting transplant. Even patients with end-stage heart failure who are not transplant candidates have achieved improved survival with permanent VAD support through destination therapy (DT). As the number of patients attaining long-term survival with VADs continues to rise, new research seeks to expand the indications for VAD implantation to include patients in earlier stage heart failure to prevent development of unsurvivable comorbidities which could limit the clinical benefit of a VAD.

In November, 2002, based on the successful completion of the REMATCH clinical trial the FDA expanded the approved indications for a previously approved bridge device (HeartMate™ SNAP VE LVAS) for use by end-stage, non-transplantable patients as permanent or "destination therapy." That approval stated: "This device is now also indicated for use in patients with New York Heart Association Class IV end-stage left ventricular failure who have received optimal medical therapy for at least 60 of the last 90 days, who have a life expectancy of less than two years, and who are not eligible for cardiac transplantation."

On January 20, 2010, a second device (HeartMate II™) was approved by the FDA as destination therapy "for use

in patients with New York Heart Association (NYHA) Class III B or IV end-stage left ventricular failure, who have received optimal medical therapy for at least 45 of the last 60 days and are not candidates for cardiac transplantation." The HeartMate II is a continuous-flow device weighing approximately one pound. It is "implanted below the heart with its entrance attached to the left ventricle and its exit connected to the aorta... Blood flows from the heart into the pump. A small electric motor in the pump drives a rotor inside the pump which pushes blood into the aorta and out to the body. A flexible tube passes through the patient's skin and connects the implanted pump to a small controller worn outside the body. The controller is powered either by batteries or connected by means of a power supply to a standard household electrical power outlet." (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm201473.htm) The patient population on which the new device was studied was more diverse than that in the REMATCH trial, and had somewhat different patient selection criteria than the earlier destination patients.

III. History of Medicare Coverage

On October 1, 2003, Medicare began covering VAD implantation as destination therapy for beneficiaries with certain clinical indications. This decision was based primarily on the results of the REMATCH study which randomized end stage heart failure patients to receive either the HeartMate SNAP VE device or medical management.

In addition to limiting coverage to specified clinical indications, Medicare required that devices be used according to their FDA label and instituted requirements for hospitals in which the procedure takes place (e.g., surgeon experience, registry participation, hospital infrastructure, clinical expertise and patient support). These were efforts to ensure that the outcomes achieved in the REMATCH study would be replicated outside the study.

In 2007, with the patient clinical indications remaining unchanged, CMS updated the hospital criteria to require hospitals to be certified by the Joint Commission under the Disease Specific Certification Program, adjusted the minimum experience of the surgeon and identified the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) as the required registry.

Current Request

CMS received a request from Thoratec, Inc. to reconsider Section 20.9 of the National Coverage Determinations Manual related to VADs used as destination therapy, based on the outcomes of the HeartMate II Destination Therapy study. Specifically, Thoratec requested expanding coverage to include patients with NYHA Class IIIB symptoms, to reduce the required time on optimal medical management to 45 of the last 60 days, to include time on a balloon pump or inotrope therapy as indications for coverage, to increase the peak oxygen consumption to < 14 ml/kg/min and to remove the body size requirement. The request did not include changes to other portions of the NCD (facility criteria, post-cardiotomy or bridge to transplant indications).

CMS is focusing this review on the patient selection aspect of the policy and is not reviewing other portions of the NCD as part this analysis.

Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category under Part A or Part B as a prerequisite to Medicare coverage. VADs may fall within the Inpatient Hospital Services benefit category (section 1861(b)(2) of the Social Security Act (the Act)), which describes supplies, appliances, and equipment furnished by the hospital, for use in the hospital, for the care and treatment of inpatients. After a VAD has been surgically implanted into the patient and when the patient is not a hospital patient, the replacement of an external part or parts may be covered under Medicare Part B within the Prosthetic Device benefit category (section 1861(s)(8) of the Act). This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Date	Action
February 22, 2010	CMS opens a National Coverage Analysis to reconsider the patient population covered for the implantation of a VAD as destination therapy.
March 24, 2010	The initial 30-day public comment period closes.
August 19, 2010	CMS posts the proposed decision memorandum and begins a second 30-day public comment period.
September 18, 2010	The second 30-day public comment period closes.

V. FDA Status

HeartMate II LVAS

On January 20, 2010, Thoratec Inc. received FDA approval to expand the labeled indication for the HeartMate II Left Ventricular Assist System to include patients that are not candidates for heart transplantation. The device was approved in 2008 for a bridge to transplant indication. As stated in the FDA approval letter (http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040S005a.pdf), the device indication is as follows:

This device is indicated for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure. It is now also indicated for use in patients with New York Heart Association (NYHA) Class IIIB or IV end-stage left ventricular failure who have received optimal medical therapy for at least 45 of the last 60 days, and are not candidates for cardiac transplantation. The HeartMate II LVAS is intended for use both inside and outside the hospital, or for transportation of ventricular assist device patients via

ground ambulance, fixed-wing aircraft, or helicopter.

HeartMate II is a continuous-flow (non-pulsatile) ventricular assist device that is smaller in size than previously FDA approved devices.

HeartMate XVE LVAS

On April 4, 2003, Thoratec Inc. received FDA approval to expand the labeled indication for the HeartMate XVE to include patients that are not candidates for heart transplant.The device was previously approved for a bridge to transplant indication. As stated in the FDA approval order statement (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pmasimplesearch.cfm?db=pma&id=13984#aostatement), the device indication is as follows:

Approval for an expanded indication for use for the thoratec heartmate xve lvas. This device system is indicated for use as a bridge to cardiac transplantation in cardiac transplant candidates at risk of imminent death from nonreversible left ventricular failure. It is now also indicated for use in patients with new york heart association class iv end stage left ventricular failure who have received optimal medical therapy for at least 60 of the last 90 days, and who have a life expectancy of less than two years, and who are not eligible for cardiac transplantation. The device system is approved for use both inside and outside the hospital.

The HeartMate XVE is a pulsatile device that requires a minimum body surface area of 1.5m² for implantation.

VI. General Methodological Principles

When making national coverage decisions under section 1862(a)(1)(A) of the Social Security Act, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will not be made available to the public. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

Our review focuses on published evidence related to four patient selection criteria from the HeartMate II destination therapy study that Thoratec is requesting be reflected in Medicare coverage. Currently, the HeartMate II study entry criteria and the current destination therapy NCD differ in these areas: 1) heart failure classification, 2) time on optimal medical management, inotropes and balloon pump, 3) peak oxygen consumption, and 4) body surface area (BSA).

In this coverage analysis, we considered destination therapy studies and evidence that were published since the last reconsideration in 2007. It incorporates all evidence from prior decision memoranda regarding this issue. A summary of the body of evidence reviewed to date in developing this decision memorandum is available via the final decision memoranda released following the completion of each of the prior national coverage analyses (NCAs) for reconsiderations of the artificial heart and related devices NCD (http://www.cms.gov/mcd/viewdecisionmemo.asp?id=79 and http://www.cms.gov/mcd/viewdecisionmemo.asp?id=187).

The significant outcomes of interest related to VAD implantation are all-cause mortality, quality of life and adverse events. As discussed in the decision memorandum from 2003 when the REMATCH study was evaluated, an advantage in mortality as the result of this or any other therapy, however, must be weighed against the likelihood of adverse events or other negative consequences associated with its use, such as infection, prolonged hospitalization, or increased bleeding. In addition to these outcomes of interest, we are focusing on information related to patient selection criteria so patients can be appropriately and carefully selected for the procedure.

Literature Search

A PubMed search was performed with the search terms [destination therapy] AND [[ventricular assist device] or [HeartMate II]]. After reviewing abstracts, CMS limited the review to studies that involved the HeartMate II device and/or addressed one of our evidence questions (outlined below in B.1.). Two studies related to the HeartMate II destination therapy pivotal trial were selected for review (Slaughter, et al. 2009 and Rogers, et al. 2010). Focused searches were conducted on evidence question topics (VAD patient selection criteria, heart failure classification, peak oxygen consumption and body size) and the reference lists of full text articles were reviewed

for relevant articles. Articles by Lang et al. 2007, Musci et al. 2008, and Lietz et al. 2009 were identified.

In addition, CMS located the published FDA Summary of Safety and Effectiveness and includes that document in the body of evidence. The Summary of Safety and Effectiveness was located by searching the FDA website (www.fda.gov) using the search terms [HeartMateII] AND [destination therapy].

Searches of PubMed using the search terms [NYHA classification iiib, IIIB, iiib/iv and IIIB/IV] did not result in locating an accepted standard definition of NYHA Class IIIB heart failure.

B. Discussion of evidence reviewed

1. Question
Is the evidence adequate to conclude that VADs improve health outcomes of Medicare beneficiaries who are not candidates for transplant and who:

a. *are said to have NYHA Class IIIB symptoms?*
b. *have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or patient is balloon pump dependent for 7 days, or IV inotrope dependent for 14 days?*
c. *have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min if not contra-indicated?*
d. *have a body surface area of <1.5m²?*

2. External Technology Assessment

CMS did not locate nor commission an external technology assessment for this decision.

3. Internal Technology Assessment

Slaughter MS et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361:2241-51.

Methods: This pivotal trial had two arms with 134 patients randomized to receive the continuous flow HeartMate II and a 66 patient active control arm, whose patients were to receive the pulsatile HeartMate XVE. According to the publication, "Enrolled patients met the following criteria: a left ventricular ejection fraction [LVEF] of less than 25%; a peak oxygen consumption of less than 14 ml per kilogram of body weight per minute, or less than 50% of the predicted value; and New York Heart Association (NYHA) class IIIB or IV symptoms for at least 45 of the 60 days before enrollment or dependence on an intra-aortic balloon pump for a period of 7 days or inotropes for a period of at least 14 days before enrollment." Subsequent to randomization eight patients were not implanted with a device and four patients were implanted with a device outside their randomization assignment. Therefore 133 patients received a HeartMate II and 59 patients initially received the HeartMate XVE and their data were reported in an intention to treat and as-treated basis.

The primary composite endpoint of the study was 2 years post-implant survival, free of stroke resulting in a Modified Rankin Score > 3 or reoperation to repair or replace the device. The Modified Rankin Score is a functional assessment that ranges from zero (no symptoms at all) to six (dead). There were no stated goals for the number patients in either NYHA Class IIIB or Class IV in either arm. Definitions of Class IIIB or Class IV heart failure were not included in the published study or published supplemental material.

Thoratec provided CMS with the following unpublished definitions of Class IIIB and Class IV heart failure as utilized in the pivotal study protocol:

NYHA Class IIIB:
Cardiac disease resulting in marked limitations of physical activity. Patients are comfortable at rest. Mild physical activity causes fatigue, palpitation, dyspnea, or anginal pain.

NYHA Class IV:
Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Results: The patients in both arms had similar baseline characteristics (Table 1):

Table 1: Baseline characteristics of the study patients, according to treatment group (Slaughter et al., 2009).

Characteristic	**HeartMate II**	**HeartMate XVE**
Age—yr.		
Mean	62 ± 12	63 ± 12

Characteristic	HeartMate II	HeartMate XVE
Median(range)	64(26-79)	65 (29-81)
Male sex—no. (%)	108 (81)	61 (92)
LVEF	17.0 ± 5.5	16.8 ± 5.4
Ischemic heart failure—no. (%)	88 (66)	45 (68)
Intravenous inotrope—no.(%)	103 (77)	55 (83)
Biventricular pacemaker	85(63)	39 (59)
ICD	111(83)	52 (79)
Intra-aortic balloon pump	30(22)	15(23)

Among the 181 patients assessed for NYHA class at baseline, 5 were class IIIA (undefined in the study), 38 were class IIIB, and 138 were class IV. Neither the published study nor the published supplement accompanying it gave any breakdown by NYHA class of the patient characteristics or outcomes.

The primary endpoint (2-year post implant survival free of stroke) of the pivotal study reported on an intent to treat basis was met by 62 of the 134 patients (46%) in the continuous-flow device arm and 7 of the 66 patients (11%) the pulsatile device arm. The first occurring reason for failing to achieve the composite endpoint in the HeartMate II trial differed by device (Table 2).

Table 2. Primary endpoint according to treatment group (Slaughter, et al. 2009):

	HeartMate II	HeartMate XVE	P Value
Stroke (Rankin score > 3)	15(11%)	8 (12%)	0.56
Reoperation (pump/repair replace)	13 (10%)	24(24%)	< 0.001
Death within 2 yrs of implantation	44 (33%)	27(41%)	0.048
Any (primary endpoint)	72(54%)	59 (89%)	< 0.001

Table 3. Functional status and quality of life, reported on an as-treated basis, according to time since device implant (Slaughter et al., 2009).

HeartMate II

	Baseline	3Mo	12Mo	24Mo
NYHA class				
No.of patients tested (no./%)	126	91	72	50
Class I	0	30 (33)	30 (42)	21 (42)
Class II	0	38 (42)	25 (35)	19 (38)
Class IIIA	4 (3)	16 (18)	13 (18)	6 (12)
Class IIIB	27 (21)	5 (5)	4 (6)	1 (2)
Class IV	95 (75)	2 (2)	0	3 (6)

	Baseline	3Mo	12Mo	24Mo
Six Minute walk				
No. patients tested	50	77	61	36
Distance meters	182 ± 140	319 ± 191	318 ± 164	377 ± 191
Minnessota Living with Heart failure questionnaire				
No. patients tested	116	89	76	44
Score	75.4 ± 17.7	37.4 ± 22.2	34.1 ± 22.4	29.6 ± 22.4
Kansas City Cardiomyopathy questionnaire				
No. patients tested	115	89	76	47
Overall summary score	27.4±16.3	63.4 ± 18.5	65.9 ± 20.0	69.9 ± 18.7
Clinical summary score	35.1±18.5	47.2 ± 17.4	68.6 ± 21.8	72.9 ± 19.3

Data on functional status and quality of life for patients who received the pulsatile device demonstrate improvements over time (Table 3). We have not reproduced the data for the pulsatile device as it is not the subject of this decision. The entire table is included in the published article.

Adverse events and associated relative risks were reported on an as treated basis with results for the continuous-flow device patients showing lower risk in all measures (not all were statistically significant). Lowered risk reached statistical significance for pump replacement, sepsis, medical management (with inotropes) of right heart failure, respiratory failure and renal failure. While continuous-flow patients demonstrated lower risk, their absolute adverse event rates are important to note. Of the continuous-flow patients, 35% experienced an VAD related infection, 36% had sepsis, 16% had renal failure and 30% had bleeding requiring surgery and 18% had a stroke.

Authors' Conclusions: The investigators concluded that the "study shows improvements in the rate of survival, quality of life, functional capacity of patients, and device durability with the continuous-flow...device as compared to the pulsatile-flow...device" and support its use "to provide long-term hemodynamic support that is linked to improvements in longevity and quality of life."

FDA Summary of Safety and Effectiveness. PMA number P060040/S005. January 10, 2010.

This document describes the evidence considered by FDA in evaluating the HeartMate (HM) II for destination therapy. A central consideration is the pivotal trial which compared the HeartMate XVE to the HeartMate II for use in destination therapy, reported by Slaughter et al, 2009. but with independent FDA data analysis. Effectiveness of the HM II was evaluated using a composite endpoint including survival at 2 years, free of stroke resulting in a Modified Rankin Score > 3 or reoperation to repair or replace the device. Safety was documented by incidence of adverse events and device malfunctions and failures compared to the XVE. Secondary objectives evaluated included separate evaluations of each component of the endpoint, functional status (6-minute walk, patient activity score, and NYHA class), health status including quality of life (Minnesota Living with Heart Failure and Kansas City Cardiomyopathy Questionnaire), all adverse events, re-operations, re-hospitalizations, and neurocognative assessments (memory, language, visual/spatial perception, processing speed and abstract/executive function).

Methods: The study design was a prospective, randomized, unblinded, non-inferiority evaluation of HM II in end-stage left ventricular failure patients who were not candidates for heart transplant and were refractory to optimal medical therapy. The protocol's analysis plan specified testing for superiority once non-inferiority was established. Two patients were randomized to HM II for every patient randomized to XVE. Randomization was stratified by study center and blocked to maintain the 2:1 ratio over time. Two hundred patients were enrolled into the Primary Cohort (134 HM II and 66 XVE) at 38 sites from March 2005 to May 2007. All 200 patients in the Primary Cohort were followed for at least two years.

Four additional cohorts were considered by FDA in their evaluation:

- Small BSA Cohort: 24 patients with BSA < 1.5m² who could not be randomized to XVE due to its size.
- XVE Exchange Cohort: 123 failed XVE patients who received HM II as a replacement.
- Randomized Continued Access Protocol (CAP) Cohort: 187 patients enrolled under the primary cohort protocol after the primary cohort had been filled.
- Anatomic Deviation Cohort: 99 patients with BSA > 1.5m² who could not be randomized to XVE due to body habitus or other anatomic considerations.

Patients meeting the study endpoint were considered a success and a failure if not. Patients urgently transplanted due to device failure were study failures. Patients electively transplanted after reversal of a pre-enrollment co-morbidity were followed and considered a success if they ultimately achieved the composite endpoint within 2 years of VAD implant.

Results: Reasons for patient ineligibility for transplant included age (28%), recent cancer history (9%), obesity (7%), and substance abuse or insufficient social support (7%). Patient age range 26 to 81 yrs, median 64 yrs. No significant differences in age, BSA, body mass index (BMI), etiology or ethnicity between HM II and XVE groups. HM II group contained 19% females and XVE 8%, but, overall, males with ischemic disease predominated. Notable in patient history: 83% of patients entered the study with ICDs and 16% had a history of stroke; 79% of patients on inotrophs at baseline; 23% on intra-aortic balloon pump; and 8% on mechanical ventilation (indications of end-stage heart failure).

Table 4: As treated analysis of patient survival at 2 years by original implanted device. 62/134 HM II (46%) and 7/66 XVE (11%) patients achieved the composite endpoint:

	HM II (n 133)	**XVE (n 59)**
Ongoing on original device	50(38%)	0 (0%)
Ongoing with replacement same type device	12 (9%)	2 (3%)
	0 (0%)	14 (24%)

	HM II (n 133)	XVE (n 59)
Ongoing with replacement alternate type device		
Transplanted	13(10%)	8 (19%)
Explanted for recovery	1(1%)	1 (1%)
Total	76 (57%)	25 (42%)

The primary causes of death of the 57 HM II patients were: Stroke—13 pts (10%); right heart failure—8 pts (6%); device malfunction (loss of power, device thrombosis, VAD dysfunction)—10 pts (8%). In 34 XVE patients causes of death were: Stroke –11 pts (19%); right heart failure –5 pts (8%); infection—6 pts (10%); multi-system organ failure—4 pts (7%).

There is no discussion of nor data relating to NYHA class IIIB in this document. The only mention of NYHA class is found in a bar graph used to show surviving patients functioning at Class I or II functional level after implantation over the course of the study. According to the graph 98% of 58 evaluable HM II patients and 100% of 2 evaluable XVE patients achieved this level at 24 months.

FDA Conclusions: "The composite endpoint analysis showed the HeartMate II to be superior to the control HeartMate XVE device. In addition, both intent to treat and per protocol analyses demonstrated a Kaplan Meier survival advantage with the HeartMate II compared to control. No safety or engineering problems were detected that suggested that the increased benefit seen with the HeartMate II device was accompanied by significantly increased risk compared to the HeartMate XVE control. Hence, a favorable risk-benefit profile has been established for the HeartMate II device."

Data from the 24 patient Small Body Cohort are not included in the document, which concludes, "Because of its small size, the HeartMate II LVAS can be used in the treatment of smaller sized non-cardiac transplant patients. These smaller sized patients include mostly women and men of small stature. It can also be used in patients with anatomic features that preclude use of the larger HeartMate XVE device."

Rogers JG et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. J Am Coll Cardiol. 2010;55:1826-34.

Methods: This article discusses data on use of the HeartMate II in both bridge to transplant (BTT) and

destination therapy (DT) patients between 2005 and 2009 in studies sponsored by Thoratec at 38 U. S. centers. A total of 374 destination therapy patients in NYHA functional classes IIIB and IV heart failure, ineligible for transplant and refractory to optimal medical management are included in the report. This includes the trial data reported by Slaughter et al, 2009. and analyzed by FDA, as well as the additional cohorts analyzed by the FDA. There is no definition of NYHA class IIIB heart failure included in the paper and the results do not subdivide class III.

Results: Detailed baseline data for DT patients included mean age 63 ± 12, 27% female, 58% ischemic etiology of heart failure, LVEF 17.1% ± 5.8, 72% cardiac resynchronization therapy (CRT), 77% history of intravenous inotropes, 21% had been treated with intra-aortic balloon pump. There is no breakdown by functional class included in the baseline data, other than the comment that "most patients had NYHA functional class IV symptoms at baseline." At one month following implantation 47% of destination therapy patients are reported as improved to class I or II. "Approximately 80% of destination therapy patients remained in NYHA functional class I or II from 6 through 24 months."

Additional information about on-going destination therapy testing with HeartMate II is included in this article in bar graph format showing that of 353 patients receiving the device for destination therapy approximately 30% were in NYHA class III, but subclassification A or B was not specified. In summary the article reports that 80% of 245 destination therapy patients at 6 months and 79% of 99 destination therapy patients at 24 months had improved to NYHA class I or II. No information about overall survival or complications is reported in this article.

Authors' conclusions: "HeartMate II LVAD support in both the bridge to transplant and destination therapy applications result in early, sustained, and clinically meaningful improvements in functional capacity and heart failure-related quality of life."

Lang CC, Agostoni P, Mancini DM. Prognostic significance and measurement of exercise-derived hemodynamic variables in patients with heart failure. J of Cardiac Fail. 2007;12(8):672-9.

This review article discusses the need for reliable prognostic indicators for evaluation of candidates for heart transplant in view of the widening gap between number of surgical candidates and available organs. The authors note that the American Heart Association has recommended use of peak VO_2, specifically ≤14 ml/kg/min, as a criterion for acceptance of ambulatory patients for transplant.

Measurement of peak VO_2 in congestive heart failure patients can, however, be confounded by comorbidities and non-cardiac factors such that some other authors have questioned its usefulness. Various studies and methods tested for alternate measurements of hemodynamic dynamic response to exercise are briefly reviewed. The authors point out that VO_2 is an indirect measure of cardiac output (CO), which cannot be easily measured directly, and provides an index of cardiac reserve in CHF patients.

They conclude noninvasive methods of measuring cardiac output will require larger clinical trials to determine their prognostic value. In the mean time "the clinical usefulness of peak VO_2 was established by a large body of data acquired over two decades and is now widely used."

Lietz K, Miller LW. Patient selection for left ventricular assist devices. Curr Opin Cardiol. 2009;24:246-251.

This review article reviews indications for implantation of LVADs for both bridge to transplant and destination therapy and discusses in detail patient considerations that impact selection of appropriate candidates. Patients must be fully and carefully assessed to determine the severity of their heart failure and what benefits they are likely to derive from device use. Cardiogenic shock and worsening symptoms in inotrope-dependent patients are identified as accounting for 60% of implantations. Timing of device placement is important as heart failure is progressive and patients can become too severely compromised to derive survival benefit from it. In less ill patients, risk scoring may be helpful in determining the likely impact of a device on survival.

Specific considerations which should be evaluated in addition to cardiac function include right ventricular function, arrhythmias, anatomy and body habitus.Noncardiac considerations include patient age, comorbidities, psychiatric and social issues. Risk scoring guides can be used to assess the possibility of in-hospital mortality. The authors conclude: "Appropriate assessment of candidates for LVAD implantation is of paramount importance. As technology will continue to advance and new devices provide life-saving treatment, more research will be needed to better understand the key determinants of successful operative and long-term VAD outcomes."

Musci M, Loforte A, Potapov EV, et al. Body mass index and outcome after ventricular assist device placement. Ann Thorac Surg. 2008 Oct;86(4):1236-42.

Methods: A retrospective analysis of 590 consecutive patients with advanced heart failure who underwent VAD placement between 1996 and 2006 at Berlin. Patients were divided into five groups based on body-mass index (BMI, kg/m2) (< 20; 20-24; 25-29; 30-35; and > 35). Twenty patients comprised the group with BMI < 20. In a multivariate analysis adjusted for age, sex, diagnosis, emergency level, and type of device (left ventricular or biventricular assist device), procedural success (recovery, transplantation, or 30-day survival) and complications were analyzed. The best group was set as reference category for calculation of odds ratios.

Results: The groups with both extremes of BMI had the worst outcomes. The best procedural success was in the group with BMI 25 to 29 kg/m^2. Underweight patients had similar survival rates to patients with normal weight. The unadjusted odds ratio of 30-day mortality for BMI < 20 kg/m^2 was 2.1 (95% confidence interval 0.9-4.7, p = .05) compared with the 25-29 BMI group. Overweight and obese patients did not have decreased survival. Extreme obesity at the time of VAD implantation showed elevated risk for postoperative death. There was no significant difference for BMI groups in the type of complications and cause of death. Cumulative survival curves for BMI category and overall VAD patient survival showed no significant differences. There were no significant differences in cause of death by BMI group.

Authors' Conclusions:"Cardiac cachexia [muscle wasting and general debility that can occur during a chronic disease] need not be an exclusion criterion for VAD placement. Underweight patients appear to have benefit from mechanical support. Severely obese patients should be carefully selected before VAD placement."

4. MEDCAC

A meeting of the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) was not convened for this analysis.

5. Evidence-based guidelines

Evidence-based guidelines regarding the use of mechanically assisted circulatory support were not located. CMS also searched for guidelines regarding the treatment of heart failure and heart failure classification systems; one guideline and one guideline update was located.

Hunt SA et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web Site. Available at: http://www.acc.org/clinical/guidelines/failure//index.pdf.

Hunt SA et al. 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. Circulation. 2009;119:e391-e479.

The American College of Cardiology (ACC) and the American Heart Association (AHA) first published guidelines for the evaluation and management of heart failure (HF) in 1995. Those guidelines were updated in 2001 and 2005 and a focused update was published in 2009. The 2001 document introduced a new classification system for describing the development and progression of heart failure. In this four stage system the first two stages (A and B) are designed to provide early identification of patients at risk for developing heart failure. Stage C describes patients with current or past symptoms of heart failure and underlying structural disease (majority of patients). Stage D describes patients with refractory heart failure requiring specialized treatments which may include mechanical circulatory support. This new "classification system is intended to complement but in no way replace

the New York Heart Association functional classification, which primarily gauges the severity of symptoms in patients who are in Stage C or D…although symptoms (NYHA class) might vary widely over time (in response to therapy or to progression of disease) in a patient who has already developed the clinical syndrome of HF (Stage C), the patient could never return to stage B (never had HF) …"

There are no definitions of the NYHA functional classifications included the ACC/AHA Guidelines. The authors note that this classification system "reflects a subjective assessment by a healthcare provider and can change frequently over short periods of time." "A variety of approaches have been used to quantify the degree of functional limitation imposed by HF. The most widely used scale is the NYHA functional classification, but this system is subject to considerable interobserver variability and is insensitive to important changes in exercise capacity… Maximal exercise testing, with measurement of peak oxygen uptake, has been used to identify appropriate candidates for cardiac transplantation, to determine disability, and to assist in the formulation of an exercise prescription, but its role in the general management of patients with HF has not been defined."

In the section on detailed recommendations for patients with refractory End-Stage Heart Failure (Stage D) both the 2005 guidelines and the 2009 focused update state "Consideration of an LV assist device as permanent or 'destination' therapy is reasonable in highly selected patients with refractory end-stage HF and an estimated 1-year mortality over 50% with medical therapy." This was rated class IIa, level of evidence: B, and is based upon the REMATCH trial results. The authors comment that, "Presently, destination device therapy is anticipated to benefit those patients predicted to have a 1-year survival of less than 50%. One such group could be the population of non–transplant-eligible patients requiring continuous intravenous inotropic infusions."

The authors list as a relative indication for heart transplant, "Peak VO_2 11 to 14 mL per kg per minute (or 55% predicted) and major limitation of the patient's daily activities."

6. Professional Society Position Statements

CMS did not receive professional society position statements.

7. Expert Opinion

Expert opinion was not solicited beyond the public comment process.

8. Public Comments

Initial 30-day comment period

Seven comments were received during the initial comment period, all addressing the NYHA Class IIIB heart failure population. Two commenters favored the inclusion of Class IIIB patients in national coverage while five commenters stated coverage for Class IIIB should be limited to clinical studies.

Proposed Decision Memorandum Comment Period

CMS received nine comments on the proposed decision memorandum during the 30-day comment period. The majority of commenters focused on the proposed clinical criteria for coverage.

NYHA Classification
Five commenters including the requestor (Thoratec Corp.), America's Health Insurance Plans (AHIP), the American College of Cardiology (ACC) and the Society of Thoracic Surgeons (STS) specifically addressed NYHA Classification. Thoratec and an additional commenter disagreed with excluding Class IIIB patients from coverage under this proposed decision. The ACC, STS, AHIP and an additional comment submitted by a cardiothoracic surgeon expressed support for limiting coverage of VAD destination therapy to Class IV patients.

Comment: Thoratec Corp. stated that when comparing Class IIIB study patients to Class IV, they had lower operative mortality and lower or equal adverse events and that this information and further analysis will be presented at the American Heart Association annual meeting in November. The ACC and STS state in their comment that the current trial data do not provide a basis for coverage of Class IIIB patients.

Response: We believe that the available evidence supports the exclusion of VAD coverage for Class IIIB patients and we appreciate the supportive comments from the physician societies. If additional peer-reviewed, published evidence becomes available we would be happy to receive it.

Comment: The requestor points out that specified definitions of IIIB and IV heart failure were used for the study and therefore, it considers the proposed noncoverage of this class of patients to be based on lack of consensus

rather than lack of supporting evidence. The ACC and STS state in their comment that there is an absence of a validated division between Class IIIA and IIIB and most heart failure physicians would have difficulty finding a reference or defining specifics for this population. The ACC and STS believe that Class IV characteristics are better understood in the clinical community.

Response: We agree with the ACC and STS. While definitions were developed for the study protocol we are not assured that they would translate into the field and more is needed to better define and study this population. While Class IIIB is not an indication for coverage, the Medicare policy does allow for coverage of this population and others in clinical studies and we look forward to the development of additional evidence for this population. The ACC and STS point out that the upcoming REVIVE-IT study supported by NHLBI should provide important information regarding these patients.

Peak Oxygen Consumption
Comment: Four commenters specifically addressed the requirement of peak oxygen consumption. AHIP and the requestor support the changes from 12 to 14ml/kg. Two commenters stated that the requirement of maximum peak oxygen consumption is not an appropriate measure for patients that are inotrope or balloon pump dependent as these patients may not be capable of performing the tests required to measure peak oxygen.

Response: We have revised the proposed decision and have incorporated broader language to take into account patients that are inotrope dependent or otherwise not able to physically perform such a test. The coverage requirement will read as follows:

c. have demonstrated functional limitation with a peak oxygen consumption of ≤14 ml/kg/min unless physically unable to perform the test or the test is contra-indicated.

Ejection Fraction
Comment: America's Health Insurance Plans commented that the requirement of a maximum ejection fraction should be removed to allow for flexibility in patient selection. They contend that patients with an EF of 26 and 27 would still benefit from the device.

Response: No data have been presented on the use of ventricular assist devices for destination therapy in patients with EF >25. The results of the REMATCH trial that formed the basis for the first Medicare coverage of destination therapy in 2003 required an EF <25 as did the HeartMate II trial which is the basis for the current decision. Actually, in both trials the EFs of enrolled patients were significantly lower than 25 with the average in both trials being 17. Data from other trials with higher EFs would be needed to consider a change.

Balloon Pump Dependence
Comment: Four commenters responded to the inclusion criteria of 7 day balloon pump dependence. AHIP and the requestor supported the proposed decision. A device manufacturer and a cardiothoracic surgeon provided similar comments. They pointed out that other hemodynamic support devices could be used and are supported for use

by the ACC/AHA guidelines for treating Class IV heart failure. They expressed concern that if coverage specifically addresses balloon pump dependency as an indication of coverage then physicians may inappropriately choose this type of device for their patient as opposed to other appropriate, FDA approved devices.

Response: We are not aware of any VAD destination therapy study that has enrolled patients on other hemodynamic support devices and therefore we have not reviewed evidence on this population. The HeartMate II destination study explicitly excluded patients on other ongoing mechanical circulatory support devices. Patients on other mechanical circulatory support are not excluded from Medicare coverage, rather, they would need to qualify based on other criteria.

Acute Myocardial Infarction, Shock and Recovery
Comment: Two commenters (a cardiothoracic surgeon and a device manufacturer) were concerned that the proposed policy is worded in a way that would encompass patients who would be eligible for shorter term mechanical circulatory support devices until their native heart is given the opportunity to recover function. One commenter specifically suggests that requiring Class IV heart failure for 90 days prior to implantation would make it clear that this coverage would not apply to recovery patients.

Response: We do not expect this policy to impact care and device selection for recovery patients. The policy language targets destination therapy patients and not those that are likely to recover heart function. Under this policy, coverage is limited to use of the device as an intended permanent therapy, requires chronic heart failure and further, limits coverage for destination therapy to the FDA labeled indication. The patient must also be determined ineligible for transplant which would generally require a thorough review of the patient's condition by heart failure specialists and surgeons. CMS does not have a coverage determination that explicitly applies to acute MI shock patients. The current NCD applies to postcardiotomy patients but simply states that the device used must be approved by the FDA for that purpose.

Due to the other clinical criteria for coverage which restrict the qualifying population, we will not require that patients have Class IV heart failure for 90 days prior to implementation.

Coverage of Equipment at Discharge
Comment: America's Health Insurance Plans commented that CMS should include coverage of the discharge kits associated with these devices. Included in these kits are the items necessary to use the device outside of a hospital setting.

Response: We only addressed patient selection criteria in this decision. However, we expect patients be discharged with all the necessary equipment to successfully operate the device outside the hospital.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1862(l) of the Act.) In order to be covered by Medicare, an item or service must first fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A)of the Act. This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment.

We address each of the analytic questions below.

Is the evidence adequate to conclude that VADs improve health outcomes of Medicare beneficiaries who are not candidates for transplant and who:
a. are said to have NYHA Class IIIB symptoms?

The NYHA classification system was developed in 1928 as a method of describing both the severity and prognosis for heart failure patients. It can also be used to assess response to treatment (Table 3). When last revised in 1994, none of the four classes contained a subclassification. Class III is defined as: "Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or angina pain." Class IV is defined as: "Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort in increased." While its use is long-standing and widespread, the NYHA class is not very reproducible and doesn't reliably predict the walking distance or exercise tolerance on formal testing. Class III includes a number of subjective elements, e.g., "marked limitation," and "less than ordinary activity." The definition of Class IIIb in Chavey et al. (2001), "recent history of dyspnea at rest," differs from the unpublished definition provided by Thoratec. The subclassification IIIB is not widely accepted, does not appear in professional society guidelines or position statements, and appears in few citations in the published peer-reviewed medical literature outside of the Slaughter et al. 2009 and Rogers et al. 2010 articles.

Since 1980 the American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly produced guidelines for the treatment and diagnosis of heart failure. The 2001 update of these guidelines included a new approach to classification of heart failure that emphasized both the development and progression of the disease with definition of four stages. The 2009 update to the guidelines states: "Stage D designates patients with truly refractory HF who might be eligible for specialized, advanced treatment strategies, such as mechanical circulatory support, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation…" Stage C "denotes patients with current or past symptoms of HF associated with underlying structural heart disease (the bulk of patients with HF)." Stage D appears most closely related to NYHA Class IV, but Stage C does not appear to describe patients with such advanced disease.

No definition of NYHA Class IIIB was found by CMS in reviewing both the published trial results (Slaughter, et al.

2009) and the FDA's Summary of Safety and Effectiveness

(http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040S005b.pdf). The study enrolled 31 Class III patients (4 Class IIIA and 27 Class IIIB) in the HeartMate II arm of the study and 12 Class III patients (1 Class IIIA and 11 Class IIIB) in the HeartMate XVE arm. However, neither the published report of the pivotal HeartMate II destination therapy trial nor the supplementary material accompanying it provided information about differences in outcomes between patients in NYHA class III vs. class IV.

We are aware that additional destination therapy patients outside of the pivotal group have been implanted, both as part of a continued access protocol and in several cohort studies; however detailed data by NYHA class for these patients including outcomes and complications have not been published.

While the pivotal study (Slaughter, et al. 2009) achieved overall good outcomes, Class III patients represent only about one-fourth of the enrolled patients. We have significant concern regarding the ability to replicate the study outcomes in the IIIB population outside of the controlled study. We do not believe the classification IIIB is generally accepted. Class IIIB is not a heart failure class that is included in the current ACC/AHA guidelines regarding heart failure and we are not aware that it is a classification commonly in use by heart failure specialists. Therefore, we do not believe it would be possible to identify patients accurately enough to replicate the study's selection criteria in routine clinical practice.

We propose that the evidence is not adequate to conclude that patients who have been classified by some as having Class IIIB heart failure have improved outcomes after VAD implantation. Therefore we propose to continue coverage only for Class IV heart failure patients. The current NCD as written, which we do not propose changing, allows coverage of other patient populations and indications within Investigational Device Exemption (IDE) trials and as routine costs in clinical trials defined under section 310.1 of the NCD manual. To make a consistent policy, we also propose to delete the following phrase, "and the device is used according to the FDA approved labeling instructions."

Is the evidence adequate to conclude that VADs improve health outcomes of Medicare beneficiaries who are not candidates for transplant and who:
b. have failed to respond to optimal medical management (including beta-blockers and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or patient is balloon pump dependent for 7 days or IV inotrope dependent for 14 days?

VAD implantation is typically not considered until heart failure has progressed to the point that medical management is failing to control symptoms. The current NCD requires optimal medical management for 60 of the last 90 days (67%), while the HeartMate II study (Slaughter, et al. 2009) required optimal medical management for 45 of the last 60 days (75%) for enrollment and demonstrated improved health outcomes. While over a shorter period of time, we believe this is a more intensive medical requirement when percent time is considered. Balloon pump and inpatient inotrope therapy indicate that a patient has been unresponsive to conventional medical management and required prolonged hospitalization, possibly with intensive care, for a heart failure episode. The current NCD does recognize that "continued need for intravenous inotropic therapy" may be an indication for VAD implantation, and we are proposing to combine it with the other indications based upon medication management and specify a minimum length of treatment time to qualify.

We believe that the evidence is adequate to conclude that patients that have failed to respond to optimal medical management for 45 of the last 60 days, or are balloon pump dependent for 7 days or IV inotrope dependent for 14 days have improved health outcomes after VAD implantation and propose that this should be included in the coverage criteria.

Is the evidence adequate to conclude that VADs improve health outcomes of Medicare beneficiaries who are not candidates for transplant and who:
c. have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min if not contra-indicated?

The peak oxygen consumption (VO_2max) is based upon a cardiopulmonary stress test. This test shows the maximum amount of oxygen the heart can provide to the muscles during sustained activity. VO_2max is the point at which the body cannot increase its intake of oxygen despite an increase in exercise intensity. This measure is a predictor of poor prognosis at very low levels. Commonly, a VO_2max ≤ 14 (in ml/kg/minute) is used as a criterion for heart transplant eligibility.

During the REMATCH trial, which supported the original approval for destination therapy, after 18 months of enrollment, the entry criteria were slightly modified in an effort to recruit more patients. Qualifying peak O_2 consumption was modified to ≤ 14 ml/kg/min. We noted at the time that 3 LVAD patients were enrolled under the modified criteria, but because of that small number we opted to specify the O_2 consumption level of 12 ml/kg/min that was the original requirement for trial entry as the inclusion requirement in the final coverage decision.

In a 2007 review article by Lang et al. looking at the prognostic significance of exercise induced hemodynamic variables in heart failure the authors noted that "clinical usefulness of peak VO_2 was established by a large body of data acquired over two decades and is now widely used." The American College of Cardiology/American Heart Association guidelines recommend that peak VO_2 can help determine timing for heart transplant, noting "that transplantation can be safely deferred in patients with peak exercise VO_2 levels of more than 14ml/min/kg." We believe this provides adequate evidence to propose changing the qualifying requirement for VO_2 for coverage of DT to the ≤ 14 ml/kg/min that was used as the criterion for inclusion in the HeartMate II pivotal trial.

Is the evidence adequate to conclude that VADs improve health outcomes of Medicare beneficiaries who are not candidates for transplant and who:
d. have a body surface area of < 1.5 m^2?

Body surface area (BSA) is the measured or calculated surface of a human body. For many clinical purposes BSA is a better indicator of metabolic mass than body weight because it is less affected by excess body fat. Estimation

of BSA is simpler than many measures of volume.

The device previously approved for destination therapy (Thoratec SNAP-VE LVAS) was a large pulsatile device weighing roughly five pounds, which was implanted in the abdomen. Because of the device size it could be difficult or impossible to implant in patients of small, short or very thin stature. For this reason, the device was limited to patients with body surface area (BSA) >1.5 m^2.

The study by Musci et al. (2008) demonstrates no difference in mortality outcomes after VAD implantation for patients with low BMI compared to normal BMI. Since the correlation between BMI and BSA is about r=0.9, this evidence can be generalized to persons with low body surface area.

The HeartMate II is a continuous-flow device weighing approximately one pound. The small size of the HeartMate II permits implantation in a wider variety of body types. Initial data on 10 small BSA patients was analyzed by FDA for this device used for bridge to transplant, without notable adverse events

(http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040b.pdf). In order to gather data on the impact, if any, of reduced body size on patient outcomes a cohort of small body size patients, who could not be randomized in the pivotal trial, was studied and reviewed by FDA. The FDA approval no longer specifies a minimum BSA for implantation.

While implanting physicians must determine appropriate fit of the selected device for the individual patient, we propose that the evidence is adequate to remove minimum body surface area from Medicare coverage requirements.

Summary

The HeartMate II destination therapy study succeeded in meeting the pre-specified endpoints and demonstrated that overall the study subjects that received the HeartMate II device had better health outcomes than patients that received the XVE. The as-treated analysis demonstrates a substantial survival advantage for subjects treated with HeartMate II, with survival of 58% at two years. For comparison purposes the two year results for the primary endpoint of survival in the REMATCH trial was 23% for device recipients and 8 % for medical therapy patients.

The study protocol was designed to minimize study bias and the results were obtained with adequate data quality. Improvement in device durability and lower risks associated with devices such as shown in the pivotal study are critical to potentially expanding the population of device candidates to a slightly less sick patient

population. Because of the relatively high use of inotropes and previously implanted devices most patients could be described by the 2009 ACC/AHA guidelines as Stage D. Risks related to VAD implantation remain significant and therefore should be carefully considered when determining device candidacy. As is the case with many of the clinical studies related to cardiac devices, patient enrollment is primarily comprised of Caucasian men. Minorities are generally underrepresented. As these devices are able to be used in smaller patients, we expect more women to be included in future studies. Studies should also enroll members of other underrepresented populations to better understand the potential for health disparities.

The overall results of the HeartMate II destination therapy pivotal study and additional literature support changing the peak VO_2 and body size requirements. $VO_2 \leq 14$ ml/kl/min serves as a current standard for transplant and body size requirements have and will continue to change over time as devices become smaller. Our proposal to change the medical management requirement is based on the pivotal study and that while the time on maximal medical management may be lessened by 30 days, the requirement of being treated maximally for 45 of 60 day is perhaps even more intense than the previous requirement. We are not proposing to extend coverage to Class IIIB heart failure patients. While these patients were enrolled in the pivotal study, they are a small portion of the whole group and published evidence is not available regarding their specific outcomes. However, a major consideration is the inability of heart failure specialists to replicate the entry criteria used in the pivotal study. The definition of Class IIIB was specifically for the study and is not generally accepted.

Public comment was generally in agreement with our proposed decision. We have in response to comments revised the proposed decision to address the inability of persons with certain conditions to accomplish peak oxygen consumption testing. In conclusion, we propose to change the requirements for peak VO_2, medical management and body size.

IX. Conclusion

The evidence is adequate to conclude that VAD implantation as destination therapy improves health outcomes and is reasonable and necessary when the device has received FDA approval for a destination therapy indication and only for patients with New York Heart Association (NYHA) Class IV end-stage ventricular heart failure, who are not candidates for heart transplant and who meet all of the following conditions:

a. Have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and,
b. Have a left ventricular ejection fraction (LVEF) < 25%; and,
c. Have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.

CMS is not changing any other section of 20.9 titled "Artificial Hearts and Related Devices". The final policy in its entirety is available in Appendix A with changes appearing in Section 3.

XI. References

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Appendix A

Draft NCD

20.9 - Artificial Hearts And Related Devices (Various Effective Dates Below)

A. General

A ventricular assist device (VAD) or left ventricular assist device (LVAD) is surgically attached to one or both intact ventricles and is used to assist a damaged or weakened native heart in pumping blood. Improvement in the performance of the native heart may allow the device to be removed.

An artificial heart is a biventricular replacement device which requires removal of a substantial part of the native heart, including both ventricles. Removal of this device is not compatible with life, unless the patient has a heart transplant.

B. Nationally Covered Indications

1. Postcardiotomy (effective for services performed on or after October 18, 1993)

Post-cardiotomy is the period following open-heart surgery. VADs used for support of blood circulation post-cardiotomy are covered only if they have received approval from the Food and Drug Administration (FDA) for that purpose, and the VADs are used according to the FDA-approved labeling instructions.

2. Bridge-to-Transplant

a. VADs as Bridge-to-Transplant (effective for services performed on or after January 22, 1996)

The VADs used for bridge-to-transplant are covered only if they have received approval from the FDA for that purpose, and the VADs are used according to the FDA-approved labeling instructions. All of the following criteria must be fulfilled in order for Medicare coverage to be provided for a VAD used as a bridge-to-transplant:

a. The patient is approved and listed as a candidate for heart transplantation by a Medicare-approved heart transplant center; and,

b. The implanting site, if different than the Medicare-approved transplant center, must receive written permission from the Medicare-approved heart transplant center under which the patient is listed prior to implantation of the VAD.

The Medicare-approved heart transplant center should make every reasonable effort to transplant patients on such devices as soon as medically reasonable. Ideally, the Medicare-approved heart transplant centers should determine patient-specific timetables for transplantation, and should not maintain such patients on VADs if suitable hearts become available.

b. Artificial Heart as Bridge-to-Transplant (effective for services performed on or after May 1, 2008)

An artificial heart for bridge-to-transplantation is covered when performed under coverage with evidence development (CED) when a clinical study meets all of the criteria listed below.

The clinical study must address at least one of the following questions:

• Were there unique circumstances such as expertise available in a particular facility or an unusual combination of conditions in particular patients that affected their outcomes?

• What will be the average time to device failure when the device is made available to larger numbers of patients?

• Do results adequately give a reasonable indication of the full range of outcomes (both positive and negative) that might be expected from more widespread use?

The clinical study must meet all of the following criteria:

• The study must be reviewed and approved by the FDA.

• The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.

• The research study is well supported by available scientific and medical information, or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.

• The research study does not unjustifiably duplicate existing studies.

• The research study design is appropriate to answer the research question being asked in the study.

• The research study is sponsored by an organization or individual capable of executing the proposed study successfully.

• The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated it also must be in compliance with 21 CFR Parts 50 and 56.

• All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).

• The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for coverage with study participation (CSP) or CED coverage.

• The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.

• The clinical research study is registered on the ClinicalTrials.gov Web site by the principal sponsor/investigator as demonstrated by having a National Clinical Trial control number.

• The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors

(http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

• The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

• The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability, or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act (the Act), the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The principal investigator of an artificial heart clinical study seeking Medicare payment should submit the following documentation to the Centers for Medicare & Medicaid Services (CMS) and should expect to be notified when the CMS review is complete:

- Complete study protocol (must be dated or identified with a version number);
- Protocol summary;
- Statement that the submitted protocol version has been agreed upon by the FDA;
- Statement that the above study standards are met;
- Statement that the study addresses at least one of the above questions related to artificial hearts;
- Complete contact information (phone number, email address, and mailing address); and,
- Clinicaltrials.gov registration number.

The above information should be mailed to:
Director, Coverage and Analysis Group Centers for Medicare and Medicaid Services Re: Artificial Heart Mailstop C1 -09-06 7500 Security Blvd. Baltimore, MD 21244-1850

Clinical studies that are determined by CMS to meet the above requirements will be listed on the CMS Web site at: http://www.cms.gov/MedicareApprovedFacilitie/06_artificialhearts.asp.

3. Destination Therapy
a. VADs as Destination Therapy (effective for services performed on or after October 1, 2003, patient selection criteria updated 11/09/2010 and facility criteria updated March 27, 2007)

Destination therapy is for patients that require permanent mechanical cardiac support. The VADs used for destination therapy are covered only if they have received approval from the FDA for that purpose.

Patient Selection
The VADs are covered for patients who have chronic end-stage heart failure (New York Heart Association Class IV end-stage left ventricular failure), who are not candidates for heart transplantation, and meet all of the following conditions:

a. have failed to respond to optimal medical management (including beta-blockers and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and
b. have a left ventricular ejection fraction (LVEF) <25%;
c. have demonstrated functional limitation with a peak oxygen consumption of ≤14 ml/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.

Facility Criteria
a. Facilities must have at least one member of the VAD team with experience implanting at least 10 VADs (as bridge-to-transplant or destination therapy) or artificial hearts over the course of the previous 36 months;
b. Facilities must be a member of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS); and,
c. By March 27, 2009, all facilities must meet the above facility criteria and be credentialed by the Joint Commission under the Disease Specific Certification Program for Ventricular Assist Devices (standards dated February 2007).

The Web site
http://www.cms.gov/MedicareApprovedFacilitie/VAD/list.asp#TopOfPage will be updated continuously to list all approved facilities. Facilities gaining Joint Commission certification (including prior to March 27, 2009) will be added to the Web site when certification is obtained.

Hospitals also must have in place staff and procedures that ensure that prospective VAD recipients receive all information necessary to assist them in giving appropriate informed consent for the procedure so that they and their families are fully aware of the aftercare requirements and potential limitations, as well as benefits, following VAD implantation.

b. Artificial Heart as Destination Therapy (effective for services performed on or after May 1, 2008)

An artificial heart for destination therapy is covered when performed under CED when a clinical study meets all of the criteria listed below:

The clinical study must address at least one of the following questions:

• Were there unique circumstances such as expertise available in a particular facility or an unusual combination of conditions in particular patients that affected their outcomes?

• What will be the average time to device failure when the device is made available to larger numbers of patients?

• Do results adequately give a reasonable indication of the full range of outcomes (both positive and negative) that might be expected from more wide spread use?

The clinical study must meet all of the following criteria:

• The study must be reviewed and approved by the FDA.

• The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.

• The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.

• The research study does not unjustifiably duplicate existing studies.

• The research study design is appropriate to answer the research question being asked in the study.

• The research study is sponsored by an organization or individual capable of executing the proposed study successfully.

• The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated it also must be in compliance with 21 CFR Parts 50 and 56.

• All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).

• The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CSP or CED coverage.

• The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.

• The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator as demonstrated by having a National Clinical Trial control number.

• The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors

(http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

• The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

• The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The principal investigator of an artificial heart clinical study seeking Medicare payment should submit the following documentation to CMS and should expect to be notified when the CMS review is complete:

• Complete study protocol (must be dated or identified with a version number);

• Protocol summary;

- Statement that the submitted protocol version has been agreed upon by the FDA;

- Statement that the above study standards are met;

- Statement that the study addresses at least one of the above questions related to artificial hearts;

- Complete contact information (phone number, email address and mailing address); and,

- Clinicaltrials.gov registration number.

The above information should be mailed to:
Director, Coverage and Analysis Group Centers for Medicare and Medicaid Services
Re: Artificial Heart Mailstop C1-09-06 7500 Security Blvd. Baltimore, MD 21244-1850

Clinical studies that are determined by CMS to meet the above requirements will be listed on the CMS Web site. http://www.cms.gov/MedicareApprovedFacilitie/06_artificialhearts.asp.

C. Nationally Non-Covered Indications (effective for services performed on or after May 19, 1986)
All other indications for the use of VADs or artificial hearts not otherwise listed remain non-covered, except in the context of Category B IDE clinical trials (42 CFR 405) or as a routine cost in clinical trials defined under section 310.1 of the NCD Manual.

(This NCD last reviewed April 2008.)

Appendix B

General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

* Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.

* Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.

* Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.

* Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.

* Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

* Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).

* Co-interventions or provision of care apart from the intervention under evaluation (performance bias).

* Differential assessment of outcome (detection bias).

* Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

* Randomized controlled trials

* Non-randomized controlled trials

* Prospective cohort studies

* Retrospective case control studies

* Cross-sectional studies

* Surveillance studies (e.g., using registries or surveys)

* Consecutive case series

* Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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Varicose Veins

Question: should additional treatments for varicose veins be added to the covered line with these diagnoses?

Question source: Senator Winters

Issue: Currently, only varicose veins with ulceration or infection/inflammation are on covered lines on the Prioritized List, on lines 383 CHRONIC ULCER OF SKIN and 209 SUPERFICIAL ABSCESSES AND CELLULITIS. These lines do not contain most (383) or any (209) of the minimally invasive therapies for varicose veins, which can be done in the less expensive outpatient setting. The more expensive therapies, such as vein stripping, are covered on 383, but not 209. Senator Winters expressed concern about the limited coverage of outpatient treatments for varicose veins.

Conservative therapy includes leg elevation and compression garments.

Minimally invasive treatments for varicose veins which can be done in the office setting:

sclerotherapy (CPT 36470, 36471)
endovenous ablation therapy (CPT 36475, 36476), includes laser therapy and radiofrequency ablation
stab phlebectomy (CPT 37765, 37766)
Echosclerotherapy (HCPCS S2202)

On review of the current coding on the Prioritized List for varicose veins, HERC staff identified several additional issues:

1) ICD-9 454.1 (Varicose veins of lower extremities with inflammation) is not used for varicose veins causing infection. This code is considered synonymous with stasis dermatitis, a benign skin change caused by chronic vein insufficiency in the legs. It does not belong on a covered line (209)
    a. Line 209 does not have any treatment codes for varicose veins and therefore ICD-9 454.1 has no appropriate treatment pairings currently
2) Line 1 Pregnancy has a series of varicose vein diagnosis codes, but no treatment codes for pairing
3) Some treatment codes are missing from line 649 (varicose veins without complication)

Varicose Veins

ICD-9 code	Code Description	Location	Procedures
454.0	Varicose veins of lower extremities with ulcer	**383** CHRONIC ULCER OF SKIN	Compression dressings, stab phlebectomy, ligation, division, and/or excision of varicose vein
454.1	Varicose veins of lower extremities with inflammation	**209** SUPERFICIAL ABSCESSES AND CELLULITIS	None
454.2	Varicose veins of lower extremities with ulcer and inflammation	**383**	See 454.0
454.8	Varicose veins of lower extremities with other complications	**648** VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR INFLAMMATION	All but stab phlebectomy
454.9	Asymptomatic varicose veins	**648**	See above
671.0x	Varicose veins of legs complicating pregnancy and the puerperium	**1** PREGNANCY	None
671.1x	Varicose veins of vulva and perineum complicating pregnancy and the puerperium	**1** PREGNANCY	None

ICD-10 Code	Code Description	Location	Treatments
I83.0xx	Varicose vein with ulcer	**383**	See 454.0
I83.1x	Varicose veins with inflammation	**522** PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL	None
I83.2xx	Varicose vein with both ulcer and inflammation	**383**	See 454.0
I83.81x	Varicose veins with pain	**648**	See 454.8
I83.89x	Varicose veins with other complications	**648**	See 454.8
I83.9x	Asymptomatic varicose veins	**648**	See 454.8
O22.0x	Varicose veins of lower extremity in pregnancy	**1** PREGNANCY	None

Varicose Veins

CPT code	Code Description	Location
29582-29584	Application of multi-layer compression system, lower and upper extremities	**383** **427** COMPLICATIONS OF A PROCEDURE USUALLY REQUIRING TREATMENT **525** POSTTHROMBOTIC SYNDROME **579** LYMPHEDEMA **648**
36470	Injection of sclerosing solution; single vein	**525** **553** SUBLINGUAL, SCROTAL, AND PELVIC VARICES **648**
36471	multiple veins, same leg	**525, 648**
36475-36479	Endovenous ablation therapy of incompetent vein, extremity	**525, 648**
37500	Vascular endoscopy, surgical, with ligation of perforator veins, subfascial (SEPS)	**83** PHLEBITIS AND THROMBOPHLEBITIS, DEEP
37700	Ligation and division of long saphenous vein at saphenofemoral junction, or distal interruptions	**383,525,648**
37718	Ligation, division, and stripping, short saphenous vein	**383,525,648**
37722	Ligation, division, and stripping, long (greater) saphenous veins from saphenofemoral junction to knee or below	**383,525,648**
37735	Ligation and division and complete stripping of long or short saphenous veins with radical excision of ulcer and skin graft	**83, 383,525,648**
37760	Ligation of perforator veins, subfascial, radical (Linton type), including skin graft, when performed, open, 1 leg	**83,383,525,648**
37761	Ligation of perforator vein(s), subfascial, open, including ultrasound guidance, when performed, 1 leg	**83,383,525,648**
37765	Stab phlebectomy of varicose veins, 1 extremity; 10-20 stab incisions	**383**
37766	more than 20 incisions	**383, 525**, **648**

37785	Ligation, division, and/or excision of varicose vein cluster(s), 1 leg	**83,383,525,648**
37780	Ligation and division of short saphenous vein at saphenopopliteal junction	**383, 525**, **648**
S2202	Echosclerotherapy	**Services Recommended for Non-Coverage Table**

Varicose Veins

Background:

From the December 2003 HOSC minutes:

Regarding code 37765, stab phlebotomy, Dr. Glass explained that this procedure is used only for small veins, which usually are only problematic cosmetically. Therefore, it was agreed to add this code only to the lower varicose vein line, 688.

From the September 23, 2004 HOSC minutes:

Varicose Veins

Dr. Little stated that this issue was raised by the medical directors, who expressed concern that varicose veins were covered on Line 354, Chronic ulcer of skin, unless they are asymptomatic. She recommends moving 454.8, varicose veins of lower extremities with other complications (edema, pain, swelling), and possibly 454.1, varicose veins of lower extremities with inflammation, from Line 354 to 688, Asymptomatic varicose veins. Dr. Walsh noted that the title of Line 688 would need to be changed, to eliminate the word asymptomatic. Dr. Saha stated that patients with severe venous stasis dermatitis without an ulcer should have access to medical therapy to prevent ulceration. Dr. Mangum asked if this situation would be covered as a co morbid condition, and Dr. Turek thought not. Dr. Saha suggested that these codes be moved to a medical therapy line, but not one that included vein-stripping codes. After discussion, it was agreed to move 454.1 to Line 355, Abscess and Cellulitis, and move 454.8 to line 688. Dr. Little asked the Subcommittee to reconsider the prior actions of the morning concerning post-phlebitic syndrome. For consistency, the Subcommittee agreed to move those codes with inflammation to the cellulitis line, keep those codes with ulcer on Line 354 and leave those codes with "other" complications on Line 688.

MOTION: Move ICD-9-CM codes 454.1, 459.12 and 459.32 to Cellulitis Line; move 454.8 to Line 688; delete 459.11, 459.13, 459.31 and 459.33 from Line 688; delete 459.19 and 459.39 from Line 354. Motion carries 4-0.

From the June 2009 HOSC minutes

Varicose veins

Smits reviewed a suggestion to change the treatment codes associated with varicose vein diagnoses, as well as previous deliberations on these treatments from HOSC minutes. The

HOSC did not change any treatments associated with varicose veins.

From the June 2010 HOSC minutes

Keep 459.2 on Line 655 Varicose Veins Of Lower Extremities Without Ulcer Or Inflammation.

Varicose Veins

Evidence

1) **Cochrane 2009**, sclerotherapy vs surgery for varicose veins
    a. N=9 RCTs
    b. the trend was for sclerotherapy to be evaluated as significantly better than surgery at one year; after one year (sclerotherapy resulted in worse outcomes) the benefits with sclerotherapy were less, and by three to five years surgery had better outcomes. The data on cost-effectiveness was not adequately reported.
    c. **Authors' conclusions** There was insufficient evidence to preferentially recommend the use of sclerotherapy or surgery. There needs to be more research that specifically examines both costs and outcomes for surgery and sclerotherapy
2) **Hamdan 2012,** JAMA review of treatments for varicose veins
    a. Surgical therapy was compared with compression in a randomizedcontrolled trial in patients with uncomplicated varicose veins. The REACTIV trial randomized 246 patients to lifestyle changes and compression therapy vs surgical stripping and phlebectomy. Surgery resulted in significant increase in quality of life and anatomical and symptom relief.
    b. A number of trials have looked at surgery vs endovenous therapies and have shown an early postoperative advantage with endovenous therapy, often balanced out over the course of the next several months. Local anesthesia, office-based practice, and rapid recovery without incisions account for patient preference strongly favoring endovenous techniques over surgery

Trusted sources:

1) NICE 2013

- a. Consider treatment of varicose veins if
    - i. Symptomatic (typically pain, aching, discomfort, swelling, heaviness and itching).
    - ii. Cause skin changes such as pigmentation or eczema
    - iii. Cause venous insufficiency
    - iv. Cause superficial vein thrombosis
    - v. Cause ulceration
- b. Treatments to consider
    - i. Offer endothermal ablation
    - ii. Endovenous laser treatment of the long saphenous vein
    - iii. If endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy (this is included in the procedure called endovenous ablation therapy)
    - iv. If ultrasound-guided foam sclerotherapy is unsuitable, offer surgery.
    - v. Do not offer compression hosiery to treat varicose veins unless interventional treatment is unsuitable.

Clinical Practice Guidelines:

1) **Gloviczki 2011**, Society for Vascular Surgery clinical practice guidelines for varicose veins
    a. We suggest compression therapy for patients with symptomatic varicose veins (GRADE 2C) but recommend against compression therapy as the primary treatment if the patient is a candidate for saphenous vein ablation (GRADE 1B)

b. We recommend compression therapy as the primary treatment to aid healing of venous ulceration (GRADE 1B). To decrease the recurrence of venous ulcers, we recommend ablation of the incompetent superficial veins in addition to compression therapy (GRADE 1A).
c. For treatment of the incompetent great saphenous vein (GSV), we recommend endovenous thermal ablation (radiofrequency or laser) rather than high ligation and inversion stripping of the saphenous vein to the level of the knee (GRADE 1B).
d. We recommend phlebectomy or sclerotherapy to treat varicose tributaries (GRADE 1B) and suggest foam sclerotherapy as an option for the treatment of the incompetent saphenous vein (GRADE 2C).
e. We recommend against selective treatment of perforating vein incompetence in patients with simple varicose veins (CEAP class C2; GRADE 1B), but we suggest treatment of pathologic perforating veins (outward flow duration >500 ms, vein diameter >3.5 mm) located underneath healed or active ulcers (CEAP class C5-C6; GRADE 2B).

<u>Indications for treatment of varicose veins by major insurers</u>

1) **Aetna 2015**
   a. Intractable ulceration
   b. Recurrent hemorrhage or hemorrhage requiring blood transfusion
   c. The following if symptoms persist following 3 months of prescription compression garments and analgesic therapyl:
      i. Recurrent superficial thrombophlebitis; *or*
      ii. Severe and persistent pain and swelling interfering with activities of daily living and requiring chronic analgesic medication
2) **Anthem BCBS 2015**
   a. Symptoms of venous insufficiency or recurrent thrombophlebitis (including but not limited to: aching, burning, itching, cramping, or swelling during activity or after prolonged sitting) which:
      i. are interfering with activities of daily living; **and**
      ii. persist despite appropriate non-surgical management, for no less than 6 weeks, such as leg elevation, exercise and medication; **and**
      iii. persist despite a trial of properly fitted gradient compression stockings for at least 6 weeks
      or
   b. There is ulceration secondary to stasis dermatitis;
   or
   c. There is hemorrhage from a superficial varicosity
3) **Medicare 2014**
   a. Medicare will consider interventional treatment of varicose veins (sclerotherapy, ligation with or without stripping, and endovenous radiofrequency or laser ablation) medically necessary if the patient remains symptomatic after a six-week trial of conservative therapy. The components of the conservative therapy include, but are not limited to:
      i. weight reduction,
      ii. a daily exercise plan,
      iii. periodic leg elevation, and
      iv. the use of graduated compression stockings.

b. The conservative therapy must be documented in the medical record. Inability to tolerate compressive bandages or stockings and the reason for such intolerance must be documented in the medical record.
c. The patient is considered symptomatic if any of the following signs and symptoms of significantly diseased vessels of the lower extremities are documented in the medical record:
    i. stasis ulcer of the lower leg, as above,
    ii. significant pain and significant edema that interferes with activities of daily living,
    iii. bleeding associated with the diseased vessels of the lower extremities,
    iv. recurrent episodes of superficial phlebitis,
    v. stasis dermatitis, or
    vi. refractory dependent edema.

HERC Staff Summary:
Minimally invasive therapies for varicose veins appear to be as effective as surgical vein stripping, but at lower cost due to requiring only local anesthesia and occurring in the outpatient treatment settings. Most insurers and trusted evidence sources (NICE) cover varicose veins for more indications that currently included on the Prioritized List.

Varicose Veins

HERC Staff Recommendations:

1) Move ICD-9 454.1 (Varicose veins of lower extremities with inflammation) from line 209 SUPERFICIAL ABSCESSES AND CELLULITIS to line 522 PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL
    a. No appropriate CPT codes appear on line 209
    b. This ICD-9 code does not code for infection, as was previously thought in its placement
    c. Matches placement of ICD-10 I83.1x (Varicose veins with inflammation)
2) Add CPT 29582-29584, 36470-36479, 37500, 37700-37761, 37765, 37766, 37785, 37780 to line 522 PHLEBITIS AND THROMBOPHLEBITIS, SUPERFICIAL
    a. No therapies there currently to pair with varicose vein with inflammation diagnoses
3) Do not add treatment codes to line 1 PREGNANCY
    a. Generally treated only with non-prescription support hose; usually resolves after pregnancy
4) Add CPT 37765 (Stab phlebectomy of varicose veins, 1 extremity; 10-20 stab incisions) to line 648 VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR INFLAMMATION
5) Add CPT 36470 and 36471 (Injection of sclerosing solution) and 36475-36479 (Endovenous ablation therapy of incompetent vein, extremity) to line 383 CHRONIC ULCER OF SKIN
    a. Minimally invasive therapies are as effective as the surgical treatments included on this line at lower cost
6) Change the title of line 648 to VARICOSE VEINS OF LOWER EXTREMITIES WITHOUT ULCER OR ~~INFLAMMATION~~ OTHER MAJOR COMPLICATION
7) Discuss adding prophylactic treatment for varicose veins prior to development of complications and/or adding addition indications for treatment such as hemorrhage or chronic pain

Surgery versus sclerotherapy for the treatment of varicose veins (Review)

Rigby KA, Palfreyman SSJ, Beverley C, Michaels JA

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

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[Intervention Review]

Surgery versus sclerotherapy for the treatment of varicose veins

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ABSTRACT

Background

Varicose veins are a relatively common condition and account for around 54,000 in-patient hospital episodes per year. The two most common interventions for varicose veins are surgery and sclerotherapy. However, there is little comparative data regarding their effectiveness.

Objectives

To identify whether the use of surgery or sclerotherapy should be recommended for the management of primary varicose veins.

Search strategy

Thirteen electronic bibliographic databases were searched covering biomedical, science, social science, health economic and grey literature (including current research). In addition, the reference lists of relevant articles were checked and various health services research-related resources were consulted via the internet. These included health economics and HTA organisations, guideline producing agencies, generic research and trials registers, and specialist sites.

Selection criteria

All studies that were described as randomised controlled trials comparing surgery with sclerotherapy for the treatment of primary varicose veins were identified.

Data collection and analysis

Two authors independently extracted and summarised data from the eligible studies using a data extraction sheet for consistency. All studies were cross-checked independently by the authors.

Main results

A total of 2306 references were found from our searches, 61 of which were identified as potential trials comparing surgery and sclerotherapy. However, only nine randomised trials, described in a total of 14 separate papers, fulfilled the inclusion criteria. Fifty trials were excluded and one trial is ongoing and is due for completion in 2004. The trials used a variety of outcome measures and classification systems which made direct comparison between trials difficult. However, the trend was for sclerotherapy to be evaluated as significantly better than surgery at one year; after one year (sclerotherapy resulted in worse outcomes) the benefits with sclerotherapy were less, and by three to five years surgery had better outcomes. The data on cost-effectiveness was not adequately reported.

Authors' conclusions

There was insufficient evidence to preferentially recommend the use of sclerotherapy or surgery. There needs to be more research that specifically examines both costs and outcomes for surgery and sclerotherapy.

PLAIN LANGUAGE SUMMARY

Surgery versus sclerotherapy for the treatment of varicose veins

Sclerotherapy (injection of a substance into the vein) shows greater benefits than surgery in the short term but surgery has greater benefits in the longer term. Varicose veins are a relatively common problem. Two treatments available are surgery and sclerotherapy. Both involve removal of the vein either by stripping it out (surgery) or by injecting it with a solution that causes it to collapse and be absorbed into the surrounding tissues (sclerotherapy). Neither treatment adversely affects blood flow through the limb. This review found that sclerotherapy was better than surgery in terms of treatment success, complication rate and cost at one year, but surgery was better after five years. However, the evidence was not of very good quality and more research is needed.

BACKGROUND

Varicose veins have an overall prevalence of between 20 and 60%, and approximately 25% of the adult population have at least one varicose vein (Callam 1994). Varicose veins are one of the commonest conditions requiring surgical treatment with 54,000 hospital in-patient episodes per year in England alone (OHE 2000). They also constitute a large part of the elective surgical waiting list.

People can experience a wide range of symptoms associated with their varicose veins that may not be directly attributable to the veins themselves (Bradbury 1999). The extent of the visible veins does not correlate with the severity or number of symptoms experienced (Goldman 1994; Isaacs 1995). There also appears to be a complex interaction between cosmetic dislike and perception of symptoms (Robbins 1994). The literature divides the symptoms people experience into subjective and objective physical symptoms. Subjective symptoms can include heaviness, aching, itching and cosmetic appearance. Objective physical changes can include varicose eczema, pigmentation, bleeding, and varicose ulcers. The patient can experience, to a greater or lesser degree, all of these symptoms or none at all.

Treatment of primary (simple) varicose veins is considered appropriate by the majority of vascular surgeons if the veins are symptomatic (Lees 1999). Common symptoms attributable to varicose veins include poor cosmesis (cosmetic appearance), ache and itching. Less common problems include haemorrhage (bleeding) and thrombophlebitis (inflammation of the vein wall with associated blood clot). In seeking to manage demand for varicose vein treatments the National Institute for Clinical Excellence (NICE) has produced patient referral advice (NICE 2001) as the basis for referral to a specialist.

There are currently three distinct treatment options available for varicose veins. These are conservative treatment, sclerotherapy and surgery. Conservative treatment consists of lifestyle advice and the use of compression hosiery (graduated elasticated stockings). This avoids the need for any intervention but requires good patient compliance. Sclerotherapy involves the injection of a sclerosant (e.g. sodium tetradecyl sulfate) into the varicosities followed by a period of compression treatment using bandaging or compression hosiery. Many surgical treatments are practiced; these may involve ligation of the affected stem vein (long or short saphenous veins), stripping of the affected stem veins, and avulsions (tearing away) of the varicosities. Some surgeons use a combination of surgery and injection sclerotherapy. Newer surgical treatments include subfascial ligation and PIN stripping. Subfascial ligation is a procedure that involves cutting through the skin and deep fascia (a sheet of connective tissue) and ligating (tying off) the incompetent perforating veins that link the veins in the skin to the deep veins in the muscle. PIN-stripping (Perforate Invaginate stripping) is a technique that involves stripping the vein into itself in a manner similar to turning a stocking inside out. This results in a smaller exit wound.

Despite the prevalence of varicose veins and the vast numbers of

PubMed

Abstract

Full text links

JAMA. 2012 Dec 26;308(24):2612-21. doi: 10.1001/jama.2012.111352.

Management of varicose veins and venous insufficiency.

Hamdan A[1].

Author information

Abstract

Chronic venous disease, reviewed herein, is manifested by a spectrum of signs and symptoms, including cosmetic spider veins, asymptomatic varicosities, large painful varicose veins, edema, hyperpigmentation and lipodermatosclerosis of skin, and ulceration. However, there is no definitive stepwise progression from spider veins to ulcers and, in fact, severe skin complications of varicose veins, even when extensive, are not guaranteed. Treatment options range from conservative (eg, medications, compression stockings, lifestyle changes) to minimally invasive (eg, sclerotherapy or endoluminal ablation), invasive (surgical techniques), and hybrid (combination of ≥1 therapies). Ms L, a 68-year-old woman with varicose veins, is presented. She has had vein problems over the course of her life. Her varicose veins recurred after initial treatment, and she is now seeking guidance regarding her current treatment options.

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NICE National Institute for Health and Care Excellence

Varicose veins in the legs

The diagnosis and management of varicose veins

Issued: July 2013

NICE clinical guideline 168

guidance.nice.org.uk/cg168

Contents

Introduction

Varicose veins are dilated, often palpable subcutaneous veins with reversed blood flow. They are most commonly found in the legs. Estimates of the prevalence of varicose veins vary. Visible varicose veins in the lower limbs are estimated to affect at least a third of the population. Risk factors for developing varicose veins are unclear, although prevalence rises with age and they often develop during pregnancy.

In some people varicose veins are asymptomatic or cause only mild symptoms, but in others they cause pain, aching or itching and can have a significant effect on their quality of life. Varicose veins may become more severe over time and can lead to complications such as changes in skin pigmentation, bleeding or venous ulceration. It is not known which people will develop more severe disease but it is estimated that 3–6% of people who have varicose veins in their lifetime will develop venous ulcers.

There are several options for the management of varicose veins, including:

- advice and reassurance
- interventional treatments (endothermal ablation, foam sclerotherapy and surgery)
- compression hosiery.

In 2009/10 there were 35,659 varicose veins procedures carried out in the NHS. There is no definitive system for identifying which people will benefit the most from interventional treatment and no established framework within the NHS for the diagnosis and management of varicose veins. This has resulted in wide regional variations in the management of varicose veins in the UK. This guideline was developed with the aim of giving healthcare professionals guidance on the diagnosis and management of varicose veins in the legs, in order to improve patient care and minimise disparities in care across the UK.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

Patient-centred care

This guideline offers best practice advice on the care of adults aged 18 years and over with varicose veins in the legs.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent, the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

Referral to a vascular service

- Refer people to a vascular service[1] if they have any of the following.
- Symptomatic[2] primary or symptomatic recurrent varicose veins.
- Lower-limb skin changes, such as pigmentation or eczema, thought to be caused by chronic venous insufficiency.
- Superficial vein thrombosis (characterised by the appearance of hard, painful veins) and suspected venous incompetence.
- A venous leg ulcer (a break in the skin below the knee that has not healed within 2 weeks).
- A healed venous leg ulcer.

Assessment and treatment in a vascular service

Assessment

- Use duplex ultrasound to confirm the diagnosis of varicose veins and the extent of truncal reflux, and to plan treatment for people with suspected primary or recurrent varicose veins.

Interventional treatment

- For people with confirmed varicose veins and truncal reflux:
- Offer endothermal ablation (see Radiofrequency ablation of varicose veins [NICE interventional procedure guidance 8] and Endovenous laser treatment of the long saphenous vein [NICE interventional procedure guidance 52]).
- If endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy (see Ultrasound-guided foam sclerotherapy for varicose veins [NICE interventional procedure guidance 440]).

- If ultrasound-guided foam sclerotherapy is unsuitable, offer surgery.

  If incompetent varicose tributaries are to be treated, consider treating them at the same time.

Non-interventional treatment

- Do not offer compression hosiery to treat varicose veins unless interventional treatment is unsuitable.

[1] A team of healthcare professionals who have the skills to undertake a full clinical and duplex ultrasound assessment and provide a full range of treatment.

[2] Veins found in association with troublesome lower limb symptoms (typically pain, aching, discomfort, swelling, heaviness and itching).

1 Recommendations

The following guidance is based on the best available evidence. The full guideline gives details of the methods and the evidence used to develop the guidance.

> The wording used in the recommendations in this guideline (for example words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation). See About this guideline for details.

All recommendations relate to adults aged 18 years and over.

1.1 Information for people with varicose veins

1.1.1 Give people who present with varicose veins information that includes:

- An explanation of what varicose veins are.
- Possible causes of varicose veins.
- The likelihood of progression and possible complications, including deep vein thrombosis, skin changes, leg ulcers, bleeding and thrombophlebitis. Address any misconceptions the person may have about the risks of developing complications.
- Treatment options, including symptom relief, an overview of interventional treatments and the role of compression.
- Advice on:
  - weight loss (for guidance on weight management see Obesity [NICE clinical guideline 43])
  - light to moderate physical activity
  - avoiding factors that are known to make their symptoms worse if possible
  - when and where to seek further medical help.

1.1.2 When discussing treatment for varicose veins at the vascular service[3] tell the person:

- What treatment options are available.
- The expected benefits and risks of each treatment option.
- That new varicose veins may develop after treatment.
- That they may need more than 1 session of treatment.
- That the chance of recurrence after treatment for recurrent varicose veins is higher than for primary varicose veins.

1.2 Referral to a vascular service

1.2.1 Refer people with bleeding varicose veins to a vascular service[3] immediately.

1.2.2 Refer people to a vascular service if they have any of the following.

- Symptomatic[4] primary or symptomatic recurrent varicose veins.
- Lower-limb skin changes, such as pigmentation or eczema, thought to be caused by chronic venous insufficiency.
- Superficial vein thrombosis (characterised by the appearance of hard, painful veins) and suspected venous incompetence.
- A venous leg ulcer (a break in the skin below the knee that has not healed within 2 weeks).
- A healed venous leg ulcer.

1.3 Assessment and treatment in a vascular service

Assessment

1.3.1 Use duplex ultrasound to confirm the diagnosis of varicose veins and the extent of truncal reflux, and to plan treatment for people with suspected primary or recurrent varicose veins.

Interventional treatment

1.3.2 For people with confirmed varicose veins and truncal reflux:

- Offer endothermal ablation (see Radiofrequency ablation of varicose veins [NICE interventional procedure guidance 8] and Endovenous laser treatment of the long saphenous vein [NICE interventional procedure guidance 52]).
- If endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy (see Ultrasound-guided foam sclerotherapy for varicose veins [NICE interventional procedure guidance 440]).
- If ultrasound-guided foam sclerotherapy is unsuitable, offer surgery.

  If incompetent varicose tributaries are to be treated, consider treating them at the same time.

1.3.3 If offering compression bandaging or hosiery for use after interventional treatment, do not use for more than 7 days.

Non-interventional treatment

1.3.4 Do not offer compression hosiery to treat varicose veins unless interventional treatment is unsuitable.

1.4 Management during pregnancy

1.4.1 Give pregnant women presenting with varicose veins information on the effect of pregnancy on varicose veins.

1.4.2 Do not carry out interventional treatment for varicose veins during pregnancy other than in exceptional circumstances.

1.4.3 Consider compression hosiery for symptom relief of leg swelling associated with varicose veins during pregnancy.

[3] A team of healthcare professionals who have the skills to undertake a full clinical and duplex ultrasound assessment and provide a full range of treatment

[4] Veins found in association with troublesome lower limb symptoms (typically pain, aching, discomfort, swelling, heaviness and itching).

2 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group's full set of research recommendations is detailed in appendix N of the full guideline.

2.1 Natural history of varicose veins

In people with varicose veins at CEAP (Clinical, etiological, anatomical and pathophysiological) stage C2 or C3, what are the factors that influence progression of the disease to CEAP stages C5 or C6?

Why this is important

The evidence review for the guideline showed a lack of high-quality evidence on the progression of varicose veins from CEAP stage C2 or C3 to more serious varicose veins disease. A large, observational, prospective cohort study, similar to the Framingham or Bonn veins studies, should be undertaken. The study should recruit patients with C2 and C3 disease and follow the progress of their disease for 5 years. Consideration should be given to including a genetic component in the study because genetic factors have not been studied on a large scale. The results of such a study should help to more accurately identify which patients are at risk of developing more serious disease so that interventions can be offered at an early stage to those who will benefit most.

2.2 Compression as a management option

What is the clinical and cost effectiveness of compression hosiery versus no compression for the management of symptomatic varicose veins?

Why this is important

Compression hosiery is widely used as first-line treatment for symptomatic varicose veins. In some areas of the UK a period of hosiery use is a precursor to referral to secondary care.

Discomfort and difficulty in application may cause people to stop wearing compression hosiery or wear it only occasionally. The current evidence for the benefit of compression hosiery is weak. There is little evidence of an impact on symptom relief or an improvement in quality of life. It is therefore not possible to calculate the cost effectiveness of compression hosiery.

A multicentre trial randomising compression hosiery versus no compression in patients with symptomatic varicose veins is needed. The trial should evaluate quality of life, including symptom reduction, and measure adherence with compression hosiery. In addition the trial should investigate the impact of compression on disease progression and the need for subsequent intervention.

2.3 Compression after interventional treatment

What is the clinical and cost effectiveness of compression bandaging or hosiery after interventional treatment for varicose veins compared with no compression? If there is benefit, how long should compression bandaging or hosiery be worn for?

Why this is important

The benefit of compression after interventional treatment for varicose veins is unclear. A well-conducted, multicentre, randomised controlled trial (RCT) of compression after interventional treatment would help determine whether compression is beneficial, and if so, what type is best and how long it should be worn for. The trial should include patients who have had 1 of the 3 main interventional treatments: endothermal ablation, ultrasound-guided foam sclerotherapy or surgery. The patients should be divided into 3 groups based on the type of intervention they have had. There should be 6 RCT arms, 1 arm with compression and 1 arm without, in each of the 3 patient groups. Each arm should have subgroups for compression type and duration. Adherence to compression treatment and the impact of adherence on effectiveness should also be evaluated. A cost-effectiveness analysis should be performed. If compression is beneficial, such a trial should help improve quality of life for people with varicose veins and reduce the longer-term need for retreatment.

2.4 Truncal treatment with or without concurrent tributary treatment

What is the clinical and cost effectiveness of concurrent phlebectomies or foam sclerotherapy for varicose tributaries during truncal endothermal ablation for varicose veins compared with:

- truncal endothermal ablation without concurrent phlebectomies or foam sclerotherapy?
- truncal endothermal ablation with phlebectomies or foam sclerotherapy, if needed, 6–12 weeks later?

Why this is important

Conventional truncal stripping under general anaesthetic involves synchronous phlebectomies of varicose tributaries, and in ultrasound-guided foam sclerotherapy truncal and tributary veins are treated concurrently. In contrast, endothermal ablation may be performed alone to obliterate truncal incompetence, or synchronously with phlebectomies or foam sclerotherapy and current practice varies.

Synchronous tributary treatment ensures a single treatment episode, and the removal of all symptomatic varicosities leads to a better immediate quality of life, but this takes longer and thus may be associated with increased morbidity. Deferred tributary treatment may reduce morbidity, and also mean that some patients do not need tributary treatment (or need fewer tributary treatments on smaller veins). However, it involves 2 interventions for patients who need tributary treatment. Omitting tributary treatments entirely ensures a single treatment episode, but it is unclear whether remaining varicosities will persist and impair quality of life.

At present there is limited evidence from 1 small-scale (n=50) study on the use and timing of tributary treatments after truncal endothermal ablation. There is a need for practice to be based on empirical evidence from a large and sufficiently powered RCT comparing all 3 main intervention options (no tributary treatment, concurrent tributary treatment and delayed tributary treatment).

2.5 Optimal interventional and conservative treatments at different stages of disease

What is the optimal treatment (compression, surgery, endothermal ablation or foam sclerotherapy) for varicose veins at each of the CEAP stages, that is CEAP stages 2–3, CEAP stage 4 and CEAP stages 5–6?

Why this is important

Much of the research into the optimum treatment for varicose veins has involved patients with varicose veins in CEAP stages C2 and C3, so little is known of the relative efficacies of treatment at the more severe stages of disease. Furthermore, some studies have included patients with varicose veins at a range of stages without subgrouping, which may conceal important differences in efficacy between different treatments at different stages of disease. Hence current treatment recommendations, which do not differentiate between patients with varicose veins at different stages, may not be equally effective for all patients.

A large-scale RCT that compares the 4 main treatments (compression, surgery, endothermal ablation and foam sclerotherapy) in subgroups with varicose veins at different stages is needed. The use of CEAP to categorise the disease stages is not ideal because higher CEAP stages do not necessarily indicate greater severity. However, other methods of categorisation are even more problematic. Quality-of-life measures are unlikely to reflect severity of disease because of variations in perception of symptoms. In addition, measuring the degree of venous reflux would necessitate a method of quantifying reflux in the superficial venous system in a way that adequately reflects disease severity, and such a method does not currently exist.

3 Other information

3.1 Scope and how this guideline was developed

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover.

How this guideline was developed

NICE commissioned the National Clinical Guideline Centre to develop this guideline. The Centre established a Guideline Development Group (see section 4), which reviewed the evidence and developed the recommendations.

The methods and processes for developing NICE clinical guidelines are described in The guidelines manual.

3.2 Related NICE guidance

Further information is available on the NICE website.

General

- Patient experience in adult NHS services. NICE clinical guidance 138 (2012).

Condition-specific

- Ultrasound-guided foam sclerotherapy for varicose veins. NICE interventional procedure guidance 440 (2013).
- Promoting physical activity in the workplace. NICE public health guidance 13 (2008).
- Physical activity and the environment. NICE public health guidance 8 (2008).
- Obesity. NICE clinical guideline 43 (2006).
- Four commonly used methods to increase physical activity. NICE public health guidance 2 (2006).

- Endovenous laser treatment of the long saphenous vein. NICE interventional procedure guidance 52 (2004).
- Transilluminated powered phlebectomy for varicose veins. NICE interventional procedure guidance 37 (2004).
- Radiofrequency ablation of varicose veins NICE interventional procedure guidance 8 (2003).

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About this guideline

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover.

This guideline was developed by the National Clinical Guideline Centre, which is based at the Royal College of Physicians The Centre worked with a Guideline Development Group, comprising healthcare professionals (including consultants, GPs and nurses), patients and carers, and technical staff, which reviewed the evidence and drafted the recommendations. The recommendations were finalised after public consultation.

The methods and processes for developing NICE clinical guidelines are described in The guidelines manual.

Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Development Group is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also Patient-centred care).

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Other versions of this guideline

The full guideline, Varicose veins in the legs: the diagnosis and management of varicose veins contains details of the methods and evidence used to develop the guideline. It is published by the National Clinical Guideline Centre.

The recommendations from this guideline have been incorporated into a NICE Pathway.

We have produced information for the public about this guideline.

Implementation

Implementation tools and resources to help you put the guideline into practice are also available.

Changes after publication

July 2013: minor maintenance.

Your responsibility

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. 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, and informed by the summaries of product characteristics of any drugs.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to 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.

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The care of patients with varicose veins and associated chronic venous diseases: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum

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The Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) have developed clinical practice guidelines for the care of patients with varicose veins of the lower limbs and pelvis. The document also includes recommendations on the management of superficial and perforating vein incompetence in patients with associated, more advanced chronic venous diseases (CVDs), including edema, skin changes, or venous ulcers. Recommendations of the Venous Guideline Committee are based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system as strong (GRADE 1) if the benefits clearly outweigh the risks, burden, and costs. The suggestions are weak (GRADE 2) if the benefits are closely balanced with risks and burden. The level of available evidence to support the evaluation or treatment can be of high (A), medium (B), or low or very low (C) quality. The key recommendations of these guidelines are: We recommend that in patients with varicose veins or more severe CVD, a complete history and detailed physical examination are complemented by duplex ultrasound scanning of the deep and superficial veins (GRADE 1A). We recommend that the CEAP classification is used for patients with CVD (GRADE 1A) and that the revised Venous Clinical Severity Score is used to assess treatment outcome (GRADE 1B). We suggest compression therapy for patients with symptomatic varicose veins (GRADE 2C) but recommend against compression therapy as the primary treatment if the patient is a candidate for saphenous vein ablation (GRADE 1B). We recommend compression therapy as the primary treatment to aid healing of venous ulceration (GRADE 1B). To decrease the recurrence of venous ulcers, we recommend ablation of the incompetent superficial veins in addition to compression therapy (GRADE 1A). For treatment of the incompetent great saphenous vein (GSV), we recommend endovenous thermal ablation (radiofrequency or laser) rather than high ligation and inversion stripping of the saphenous vein to the level of the knee (GRADE 1B). We recommend phlebectomy or sclerotherapy to treat varicose tributaries (GRADE 1B) and suggest foam sclerotherapy as an option for the treatment of the incompetent saphenous vein (GRADE 2C). We recommend against selective treatment of perforating vein incompetence in patients with simple varicose veins (CEAP class C_2; GRADE 1B), but we suggest treatment of pathologic perforating veins (outward flow duration ≥500 ms, vein diameter ≥3.5 mm) located underneath healed or active ulcers (CEAP class C_5-C_6; GRADE 2B). We suggest treatment of pelvic congestion syndrome and pelvic varices with coil embolization, plugs, or transcatheter sclerotherapy, used alone or together (GRADE 2B). (J Vasc Surg 2011;53:2S-48S.)

Abbreviations ACCP, American College of Chest Physicians; ASVAL, ablation sélective des varices sous anesthésie locale (ie, ambulatory selective varicose vein ablation under local anesthesia); AVF, American Venous Forum; AVVQ, Aberdeen Varicose Vein Questionnaire; CHIVA, cure conservatrice et hémodynamique de l'insuffisance veineuse en ambulatiore (ie, ambulatory conservative hemodynamic treatment of varicose veins); CI, confidence interval; CT, computed tomography; CVI, chronic venous insufficiency; CVD, chronic venous disease; DVT, deep venous thrombosis; EVLA, endovenous laser ablation; EVLT, endovenous laser therapy; FDA, U.S. Food and Drug Administration; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; GSV, great saphenous vein; HL/S,

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high ligation and stripping; ICP, intermittent compression pump; IVC, inferior vena cava; IVUS, intravascular ultrasonography; MPFF, micronized purified flavonoid fraction; MR, magnetic resonance; OR, odds ratio; PAPS, percutaneous ablation of perforators; PE, pulmonary embolism; PIN, perforate invaginate (stripping); PRO, patient-reported outcome; PTFE, polytetrafluoroethylene; QALY, quality-adjusted life-year; QOL, quality of life; RCT, randomized controlled trial; REVAS, recurrent varicose veins after surgery; RF, radiofrequency; RFA, radiofrequency ablation; RR, relative risk; SEPS, subfascial endoscopic perforator surgery; SF-36, Short-Form 36-Item Health Survey; SFJ, saphenofemoral junction; SSV, small saphenous vein; STS, sodium tetradecyl sulfate; SVS, Society for Vascular Surgery; TIPP, transilluminated powered phlebectomy; VCSS, Venous Clinical Severity Score; VTE, venous thromboembolism

SUMMARY OF GUIDELINES FOR MANAGEMENT OF PATIENTS WITH VARICOSE VEINS AND ASSOCIATED CHRONIC VENOUS DISEASES

Guideline No.	*Guideline title*	*GRADE of recommendation*	*Level of evidence*
		1. Strong 2. Weak	A. High quality B Moderate quality C. Low or very low quality
	1. Clinical examination		
1.1	For clinical examination of the lower limbs for chronic venous disease, we recommend inspection (telangiectasia, varicosity, edema, skin discoloration, corona phlebectatica, lipodermatosclerosis, ulcer), palpation (cord, varicosity, tenderness, induration, reflux, pulses, thrill, groin or abdominal masses), auscultation (bruit), and examination of ankle mobility. Patients should be asked for symptoms of chronic venous disease, which may include tingling, aching, burning, pain, muscle cramps, swelling, sensations of throbbing or heaviness, itching skin, restless legs, leg tiredness, and fatigue.	1	A
	2. **Duplex scanning**		
2.1	We recommend that in patients with chronic venous disease, a complete history and detailed physical examination are complemented by duplex scanning of the deep and superficial veins. The test is safe, noninvasive, cost-effective, and reliable.	1	A
2.2	We recommend that the four components of a complete duplex scanning examination for chronic venous disease should be visualization, compressibility, venous flow, including measurement of duration of reflux, and augmentation.	1	A
2.3	We recommend that reflux to confirm valvular incompetence in the upright position of the patients be elicited in one of two ways: either with increased intra-abdominal pressure using a Valsalva maneuver to assess the common femoral vein and the saphenofemoral junction, or for the more distal veins, use of manual or cuff compression and release of the limb distal to the point of examination.	1	A
2.4	We recommend a cutoff value of 1 second for abnormally reversed flow (reflux) in the femoral and popliteal veins and of 500 ms for the great saphenous vein, the small saphenous vein, the tibial, deep femoral, and the perforating veins.	1	B
2.5	We recommend that in patients with chronic venous insufficiency, duplex scanning of the perforating veins is performed selectively. We recommend that the definition of "pathologic" perforating veins includes those with an outward flow of duration of ≥500 ms, with a diameter of ≥3.5 mm and a location beneath healed or open venous ulcers (CEAP class C_5-C_6).	1	B
	3. Plethysmography		
3.1	We suggest that venous plethysmography be used selectively for the noninvasive evaluation of the venous system in patients with simple varicose veins (CEAP class C_2).	2	C
3.2	We recommend that venous plethysmography be used for the noninvasive evaluation of the venous system in patients with advanced chronic venous disease if duplex scanning does not provide definitive information on pathophysiology (CEAP class C_3-C_6).	1	B
	4. Imaging studies		

Continued.

Guideline No.	*Guideline title*	*GRADE of recommendation*	*Level of evidence*
4.1	We recommend that in patients with varicose veins and more advanced chronic venous disease, computed tomography venography, magnetic resonance venography, ascending and descending contrast venography, and intravascular ultrasonography are used selectively, including but not limited to post-thrombotic syndrome, thrombotic or nonthrombotic iliac vein obstruction (May-Thurner syndrome), pelvic congestion syndrome, nutcracker syndrome, vascular malformations, venous trauma, tumors, and planned open or endovascular venous interventions.	1	B
	5. Laboratory evaluation		
5.1	We recommend that in patients with varicose veins, evaluation for thrombophilia is needed selectively for those with recurrent deep venous thrombosis, thrombosis at a young age, or thrombosis in an unusual site. Laboratory examinations are needed in patients with long-standing venous stasis ulcers and in selected patients who undergo general anesthesia for the treatment of chronic venous disease.	1	B
	6. Classification		
6.1	We recommend that the CEAP classification be used for patients with chronic venous disease. The basic CEAP classification is used for clinical practice, and the full CEAP classification system is used for clinical research.	1	A
6.2	We recommend that primary venous disorders, including simple varicose veins, be differentiated from secondary venous insufficiency and from congenital venous disorders because the three conditions differ in pathophysiology and management.	1	B
	7. Outcome assessment		
7.1	We recommend that the revised Venous Clinical Severity Score is used for assessment of clinical outcome after therapy for varicose veins and more advanced chronic venous disease.	1	B
7.2	We recommend that a quality-of-life assessment is performed with a disease-specific instrument to evaluate patient-reported outcome and the severity of chronic venous disease.	1	B
7.3	We recommend duplex scanning for follow-up of patients after venous procedures who have symptoms or recurrence of varicose veins.	1	B
7.4	We recommend reporting procedure-related minor and major complications after therapy.	1	B
	8. Medical therapy		
8.1	We suggest venoactive drugs (diosmin, hesperidin, rutosides, sulodexide, micronized purified flavonoid fraction, or horse chestnut seed extract [aescin]) in addition to compression for patients with pain and swelling due to chronic venous disease, in countries where these drugs are available.	2	B
8.2	We suggest using pentoxifylline or micronized purified flavonoid fraction, if available, in combination with compression, to accelerate healing of venous ulcers.	2	B
	9. Compression therapy		
9.1	We suggest compression therapy using moderate pressure (20 to 30 mm Hg) for patients with symptomatic varicose veins.	2	C
9.2	We recommend against compression therapy as the primary treatment of symptomatic varicose veins in patients who are candidates for saphenous vein ablation.	1	B
9.3	We recommend compression as the primary therapeutic modality for healing venous ulcers.	1	B
9.4	We recommend compression as an adjuvant treatment to superficial vein ablation for the prevention of ulcer recurrence.	1	A
	10. Open venous surgery		
10.1	For treatment of the incompetent great saphenous vein, we suggest high ligation and inversion stripping of the saphenous vein to the level of the knee.	2	B
10.2	To reduce hematoma formation, pain, and swelling, we recommend postoperative compression. The recommended period of compression in C_2 patients is 1 week.	1	B

Continued.

Guideline No.	*Guideline title*	*GRADE of recommendation*	*Level of evidence*
10.3	For treatment of small saphenous vein incompetence, we recommend high ligation of the vein at the knee crease, about 3 to 5 cm distal to the saphenopopliteal junction, with selective invagination stripping of the incompetent portion of the vein.	1	B
10.4	To decrease recurrence of venous ulcers, we recommend ablation of the incompetent superficial veins in addition to compression therapy.	1	A
10.5	We suggest preservation of the saphenous vein using the ambulatory conservative hemodynamic treatment of varicose veins (CHIVA) technique only selectively in patients with varicose veins, when performed by trained venous interventionists.	2	B
10.6	We suggest preservation of the saphenous vein using the ambulatory selective varicose vein ablation under local anesthesia (ASVAL) procedure only selectively in patients with varicose veins.	2	C
10.7	We recommend ambulatory phlebectomy for treatment of varicose veins, performed with saphenous vein ablation, either during the same procedure or at a later stage. If general anesthesia is required for phlebectomy, we suggest concomitant saphenous ablation.	1	B
10.8	We suggest transilluminated powered phlebectomy using lower oscillation speeds and extended tumescence as an alternative to traditional phlebectomy for extensive varicose veins.	2	C
10.9	For treatment of recurrent varicose veins, we suggest ligation of the saphenous stump, ambulatory phlebectomy, sclerotherapy, or endovenous thermal ablation, depending on the etiology, source, location, and extent of varicosity.	2	C
	11. Endovenous thermal ablation		
11.1	Endovenous thermal ablations (laser and radiofrequency ablations) are safe and effective, and we recommend them for treatment of saphenous incompetence.	1	B
11.2	Because of reduced convalescence and less pain and morbidity, we recommend endovenous thermal ablation of the incompetent saphenous vein over open surgery.	1	B
	12. Sclerotherapy of varicose veins		
12.1	We recommend liquid or foam sclerotherapy for telangiectasia, reticular veins, and varicose veins.	1	B
12.2	For treatment of the incompetent saphenous vein, we recommend endovenous thermal ablation over chemical ablation with foam.	1	B
	13. Treatment of perforating veins		
13.1	We recommend against selective treatment of incompetent perforating veins in patients with simple varicose veins (CEAP class C_2).	1	B
13.2	We suggest treatment of "pathologic" perforating veins that includes those with an outward flow duration of ≥500 ms, with a diameter of ≥3.5 mm, located beneath a healed or open venous ulcer (CEAP class C_5-C_6).	2	B
13.3	For treatment of "pathologic" perforating veins, we suggest subfascial endoscopic perforating vein surgery, ultrasonographically guided sclerotherapy, or thermal ablations.	2	C
	14. Treatment of pelvic varicose veins		
14.1	We recommend noninvasive imaging with transabdominal and/or transvaginal ultrasonography, computed tomography, or magnetic resonance venography in selected patients with symptoms of pelvic congestion syndrome or symptomatic varices in the distribution of the pubis, labia, perineum, or buttocks.	1	C
14.2	We recommend retrograde ovarian and internal iliac venography in patients with pelvic venous disease, confirmed or suspected by noninvasive imaging studies, in whom an intervention is planned.	1	C
14.3	We suggest treatment of pelvic congestion syndrome and pelvic varices with coil embolization, plugs, or transcatheter sclerotherapy, used alone or together.	2	B
14.4	If less invasive treatment is not available or has failed, we suggest surgical ligation and excision of ovarian veins to treat reflux.	2	B

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Clinical Policy Bulletin:
Varicose Veins
Number: 0050

Policy

1. Aetna considers the following procedures medically necessary for treatment of varicose veins when the following criteria are met: great saphenous vein, accessory saphenous vein, or small saphenous vein ligation / division / stripping, radiofrequency endovenous occlusion (VNUS procedure), and endovenous laser ablation of the saphenous vein (ELAS) (also known as endovenous laser treatment (EVLT)).

    1. Incompetence at the saphenofemoral junction or saphenopopliteal junction is documented by Doppler or duplex ultrasound scanning, and all of the following criteria are met:

        1. Documented reflux duration of 500 milliseconds (ms) or greater in the vein to be treated; *and*
        2. Vein size is 4.5 mm or greater in diameter (not valve diameter at junction); *and*
        3. Saphenous varicosities result in *any* of the following:

            1. Intractable ulceration secondary to venous stasis; *or*
            2. More than 1 episode of minor hemorrhage from a ruptured superficial varicosity; or a single significant hemorrhage from a ruptured superficial varicosity, especially if transfusion of blood is required; *or*
            3. Saphenous varicosities result in *either* of the following, and symptoms persist despite a 3-month trial of conservative management* (e.g., analgesics and prescription gradient support compression stockings):

                1. Recurrent superficial thrombophlebitis; *or*
                2. Severe and persistent pain and swelling interfering with activities of daily living and requiring chronic analgesic medication.

                *Note: A trial of conservative management is not required for persons with persistent or recurrent varicosities who

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- Review History
- Definitions

Additional Information
- Clinical Policy Bulletin Notes

have undergone prior endovenous catheter ablation procedures or stripping/division/ligation in the same leg because conservative management is unlikely to be successful in this situation.

2. Endovenous ablation procedures are considered medically necessary for the treatment of incompetent perforating veins with vein diameter of 3.5 mm or greater with outward flow duration of 500 milliseconds duration or more, located underneath an active or healed venous stasis ulcer.

3. Endovenous ablation procedures are considered medically necessary adjunctive treatment of symptomatic accessory saphenous veins for persons who meet medical necessity criteria for endovenous ablation above and who are being treated or have previously been treated by one of the procedures listed above for incompetence (i.e., reflux) at the saphenofemoral junction or saphenopopliteal junction.

Note: Initially, endovenous ablation therapy of the first vein and of the second and subsequent veins in each affected extremity is considered medically necessary when criteria are met. (Note: Thus one primary code and one secondary code are considered medically necessary for initial endovenous ablation treatment.) Additional endovenous ablation therapy is considered medically necessary for persons with persistent or recurrent junctional reflux of the greater saphenous vein, lesser saphenous vein following initial endovenous ablation therapy. Additional endovenous ablation therapy may also be necessary for treatment of accessory saphenous veins as noted above. These procedures are considered experimental and investigational for treatment of varicose tributaries and accessory veins other than the accessory saphenous vein. These procedures are considered cosmetic for all other indications.

Note: Doppler or duplex ultrasound studies are considered necessary prior to varicose vein treatment to assess the anatomy and to determine whether there is significant reflux at the saphenofemoral or saphenopopliteal junction requiring surgical repair, and after completion of the treatment to determine the success of the procedure and detect thrombosis. Ultrasound guidance is inclusive of the VNUS or ELAS procedures.

Note: The term endovenous catheter ablation (EVCA) is a non-specific term that refers to the several catheter based minimally invasive alternatives to surgical stripping such as radiofrequency endovenous occlusion (VNUS procedure) and endovenous laser ablation of the saphenous vein (ELAS). In assessing the medical necessity of EVCA, reference should be made to the specific technique that is being employed.

2. Aetna considers liquid or foam sclerotherapy (endovenous chemical ablation) medically necessary adjunctive treatment of symptomatic saphenous veins, varicose tributaries, accessory, and perforator veins 2.5 mm or greater in diameter for persons who meet medical necessity criteria for varicose vein treatment in section I above and who are being treated or have previously been treated by one or more of the procedures noted in section I above for incompetence (i.e., reflux) at the saphenofemoral junction or saphenopopliteal junction.

Sclerotherapy is considered experimental and investigational for treatment of reflux

of the saphenofemoral junction or saphenopopliteal junction the because sclerotherapy has not been proven to be effective for treatment of junctional reflux. Sclerotherapy alone has not been shown to be effective for persons with reflux at the saphenofemoral or saphenopopliteal junctions; under established guidelines, individuals with reflux should also be treated with endovenous ablation, ligation or division of the junction to reduce the risk of varicose vein recurrence. Sclerotherapy is considered cosmetic for treatment of veins less than 2.5 mm in diameter and for all other indications.

Note: Since ultrasound-monitored or duplex-guided techniques for sclerotherapy have not been shown to definitively increase the effectiveness or safety of this procedure, these tests are only considered medically necessary when initially performed to determine the extent and configuration of varicose veins. Ultrasound- or radiologically guided or monitoring techniques are of no proven value when performed solely to guide the needle or introduce the sclerosant into the varicose veins.

Note: The number of medically necessary sclerotherapy injection sessions varies with the number of anatomical areas that have to be injected, as well as the response to each injection. Usually 1 to 3 injections are necessary to obliterate any vessel, and 10 to 40 vessels, or a set of up to 20 injections in each leg, may be treated during one treatment session. Initially, up to two sets of injections of sclerosing solution in multiple veins in each affected leg (i.e., a total of four sets of injections if both legs are affected) are considered medically necessary when criteria are met. (Note: A set of injections is defined as multiple sclerotherapy injections during a treatment session.) Additional sets of injections of sclerosing solution are considered medically necessary for persons with persistent or recurrent symptoms.

3. Aetna considers ambulatory phlebectomy or transilluminated powered phlebectomy (TriVex System) medically necessary adjunctive treatment of symptomatic saphenous veins, varicose tributaries, accessory, and perforator veins 2.5 mm or greater in diameter for persons who meet the medical necessity criteria for varicose vein treatment in section I above and who are being treated or have previously been treated by one or more of the procedures noted in section I above for incompetence (i.e., reflux) at the saphenofemoral junction or saphenopopliteal junction. Ambulatory phlebectomy or transilluminated powered phlebectomy is considered experimental and investigational for treatment of junctional reflux as these procedures have not been proven to be effective for these indications. Ambulatory phlebectomy and the TriVex system is considered cosmetic for veins less than 2.5 mm in diameter and all other indications. Note: Transilluminated powered phlebectomy has not been proven to be superior to other methods of varicose vein removal. Therefore, the TriVex procedure should be billed as any other varicose vein removal procedure.

   Note: Initially, up to two multiple stab phlebectomy incisions in each affected extremity (i.e., a total of four multiple stab incisions if both legs are affected) are considered medically necessary when criteria are met. Additional multiple stab phlebectomy incisions are considered medically necessary for persons with persistent or recurrent symptoms. (Note: A set of stab phlebectomy incisions is defined as multiple stab phlebectomy incisions during a treatment session.)

4. Aetna considers photothermal sclerosis (also referred to as an intense pulsed light source, e.g., the PhotoDerm VascuLight, VeinLase), which is used to treat small

veins such as small varicose veins and spider veins, cosmetic because such small veins are cosmetic problems and do not cause pain, bleeding, ulceration, or other medical problems.

5. Aetna considers transdermal laser treatment experimental and investigational for the treatment of large varicose veins because it has not been proven in direct comparative studies to be as effective as sclerotherapy and/or ligation and vein stripping in the treatment of the larger varicose veins associated with significant symptoms (pain, ulceration, inflammation). Note: Although transdermal Nd:YAG laser has been shown to be effective for the treatment of telangiectasias and reticular veins, treatment of these small veins is considered cosmetic.

6. Aetna considers mechanicochemical ablation (MOCA) (ClariVein) experimental and investigational for varicose veins because it has not been proven to be as effective as established alternatives.

7. Aetna considers polidocanol injection (Asclera) as cosmetic; although Asclera has been approved by the Food and Drug Administration (FDA) for the treatment of telangiectasias and reticular veins less than 3 mm in diameter, treatment of these small veins is considered cosmetic.

8. Aetna considers subfascial endoscopic perforator vein surgery (SEPS) medically necessary for the treatment of members with advanced chronic venous insufficiency secondary to primary valvular incompetence of superficial and perforating veins, with or without deep venous incompetence, when conservative management has failed. Aetna considers SEPS experimental and investigational for the treatment of members with post-thrombotic syndrome, varicose veins, and other indications because its effectiveness for these indications has not been established.

9. Aetna considers valvular reconstruction medically necessary for chronic venous insufficiency.

Background

Varicose veins are a common condition. In adult western populations visible varicose veins are present in 20 to 25 % of women and 10 to 15 % of men. In most persons, varicose veins do not cause symptoms other than poor cosmesis. Varicose vein surgery is one of the most commonly performed cosmetic procedures in the United States.

Most varicose veins do not require medical treatment (Tapley et al, 2003). In some cases, however, the circulation may be hindered enough to cause swelling of the foot and ankle, discomfort, a tingling sensation, or a feeling of heaviness. For most people with varicose veins, wearing specially fitted elastic stockings is all that is needed. The stockings should be carefully fitted to the individual, providing the most pressure in the lowest part of the leg. The stockings should be put on when first arising in the morning, preferably before getting out of bed. Exercise such as walking or cycling also helps promote better circulation from the lower part of the body. Resting with the legs elevated will help promote circulation; in contrast, sitting with the legs crossed can aggravate the condition. Authorities have recommended 6 or more months as a reasonable duration for a trial conservative management (NHS, 2005).

A substantial proportion of varicose vein symptoms respond to conservative management. A randomized controlled clinical trial compared surgery (n = 124) to conservative

management (n = 122) of varicose veins (Michaels et al, 2006). Conservative management consisted of lifestyle advice relating to exercise, leg elevation, management of weight and diet, and the use of compression hosiery. In the surgical arm of the trial patients received the same lifestyle advice but also underwent surgical treatment, consisting of flush ligation of sites of reflux, stripping of the long saphenous vein and multiple phlebectomies, as appropriate. Although a greater proportion of patients assigned to surgery plus lifestyle advice at relieving symptoms at 1 year, approximately one-third of subjects assigned to conservative management reported some relief from conservative management with compression hosiery. At 2 years, there was no significant difference in symptom improvement between groups assigned to conservative management versus surgery. The authors posited that the lack of significant difference in symptomatology between groups at 2 years may have been due to cross-overs, with 7 patients in the conservative management group opting for surgery in year 1 and 37 patients opting for surgery in year 2. The study also found that persons assigned to surgery plus lifestyle advice had a greater improvement in cosmesis and quality of life than persons assigned to lifestyle advice alone, although it is not known whether improvements in quality of life were primarily related to improvements in cosmesis versus reductions in symptomatology. Weaknesses of the study included a substantial loss to follow-up in all groups. Fifteen of the 124 patients assigned to surgery either refused surgery in favor of conservative management or declined surgery due to fitness. Of the remaining 109 patients who underwent surgery, 43 were lost to follow up by the first year. Of subjects assigned to conservative treatment, 21 were lost to follow-up by the first year. The authors observed that, although surgery was more effective at improving symptomatology at 1 year, a substantial proportion of patients assigned to conservative treatment reported resolution or improvements in aching (26 %), heaviness (46 %), itching (56 %), and swelling (68 %). In addition, a substantial proportion of persons assigned to conservative management reported improvements in cosmesis. "Indeed, 22 % of the latter reported that they no longer had cosmetic concerns. These observations suggest a substantial benefit from surgery but perhaps support the case for careful evaluation of patients' symptoms and problems when considering surgical treatment."

An editorialist noted that the short follow-up of subjects assigned to surgery may result in an underestimate of the costs and an exaggeration of the benefits of surgery (van Rij, 2006). By the third year, only 40 % of subjects in the study by Michaels et al assigned to surgery were assessed. The editorialist noted, however, that most recurrences are diagnosed later than 3 years. Focusing on the short-term may lead to an under-estimate of cost and an over-estimate of benefit. The editorialist stated that prospective comparisons of durability up to 5 years and longer are infrequent and yet by this time the recurrence rate may be as high as 50 %.

In patients with varicose veins, leg pain may be associated with superficial thrombophlebitis or venous leg ulcers. In evaluating the role of varicose vein surgery in treatment of these conditions, the effectiveness of varicose vein surgery must be compared to conservative management.

If the patient is suffering from superficial thrombophlebitis, conservative management is indicated. According to available guidelines, uncomplicated superficial thrombophlebitis is usually treated symptomatically with heat, simple analgesia, non-steroidal anti-inflammatory drugs (NSAIDs), and compression stockings (SCHIN, 2002). Treatment should continue until symptoms have completely subsided (usually 2 to 6 weeks to subside but the thrombosed vein may be palpable and tender for months). More severe thrombophlebitis, as indicated by the degree of pain and redness and the extent of abnormality, should be treated by bed rest with elevation of the extremity and application

of hot, wet compresses.

Leg ulcers arising from venous problems are called venous (varicose or stasis) ulcers. The main conservative treatment has been to apply a firm compression garment (bandage or stocking) to the lower leg in order to help the blood return back up the leg. Cullum et al (2002) conducted a meta-analysis of the literature on the effectiveness of compression bandaging and stockings in the treatment of varicose leg ulcers. The authors concluded that compression increases ulcer-healing rates compared with no compression. The authors also found that multi-layered systems are more effective than single-layered systems. High compression is more effective than low compression but there are no clear differences in the effectiveness of different types of high compression. In a meta-analysis, Nelson et al (2002) found circumstantial evidence of the benefit of compression in reducing recurrence of varicose ulcers. The authors also noted that recurrence rates may be lower in high compression hosiery than in medium compression hosiery and therefore patients should be offered the strongest compression with which they can comply.

According to a systematic review of the evidence, pentoxifilline has also been shown to be effective for treatment of venous leg ulcers (Nelson et al, 2002). According to the systematic evidence review, compression has been shown to prevent venous leg ulcers. The effectiveness of vein surgery for prevention or treatment of venous ulcers is "unknown" (Nelson et al, 2002).

Beyond conservative therapy, the treatment of varicose veins in the lower legs includes injection/compression sclerotherapy and surgical stripping or ligation or a combination of these approaches depending upon the severity of the condition. Despite many years of experience, there is still a disappointingly high recurrence rate of varices because many patients are inadequately investigated before treatment. As it has been shown that physical examination alone is unreliable, pre-treatment Doppler or Duplex ultrasound examination must be performed for localization of the sites of incompetence to allow the individualization of the treatment strategy for each patient. Photographs or office diagrams may be helpful in assessing the size and extent of the varices.

Under established guidelines, the basic tenet of successful treatment is to eliminate the primary and secondary sources of the reflux. These sources are usually a nearby perforator, or most often a major junction that causes redirected venous return through veins with intact valves.

Sclerotherapy has been found to be more effective in patients with dilated superficial or residual varicose veins, recurrent varicosities or incompetent perforating veins of small to moderate size (less than 6 mm) without vein reflux. Large varicosities do not respond as well as small varicosities to sclerotherapy (Rosenberg, 2006; MSAC, 2011; MAS, 2011). Inadvertent intra-arterial injection has been an untoward sequela of sclerotherapy. Almost all cases of painful varicosities are associated with junctional reflux. When reflux at the saphenofemoral and/or saphenopopliteal junctions is present, accepted guidelines provide that sclerotherapy should not be performed until surgical ligation and division of the junction has been done. The junctions themselves can not be adequately treated by sclerotherapy as junctional reflux must be addressed by endovenous ablation methods or surgical ligation or stripping (Jakobsen, 1979; MSAC, 2008; MSAC, 2011). Although varicosities can occasionally be present in the absence or reflux, there is a lack of evidence from reliable clinical studies of the effectiveness of sclerotherapy in relieving symptomatic varicosities not associated with junctional reflux. The sole randomized controlled clinical trial (n = 25) to address the efficacy of sclerotherapy in varicosities not associated with junctional reflux (Kalhe and Leng, 2004) evaluated sclerotherapy

efficacy in obliterating varicosities, but did not address its effectiveness at relieving pain. Although sclerotherapy can be used to treat visible subcuticular veins (i.e., spider angiomas, and telangiectasias) less than 2.5 mm in size, these small veins do not cause symptoms and their treatment is purely cosmetic (MSAC, 2011).

Doppler ultrasound is often used in conjunction with other non-invasive physiologic testing to characterize the anatomy and physiology of the varicose vein network prior to injection or surgical intervention. However, duplex scans are also sometimes utilized during the sclerotherapy procedure itself. Their purported usefulness in this regard includes the localization of deep or inaccessible injection sites, such as when there are extensive networks of large deep varicosities, areas of significant reflux between superficial and deep systems, or risks to arterial structures. Ultrasound has also been used to monitor the effectiveness of compressive sclerotherapy in obliterating the lumen of the target vein and reducing reflux/retrograde flow. However, these indications have not been scientifically validated. There is little evidence, in the form of randomized prospective clinical trials, to support that ultrasound makes a significant difference in optimizing outcome or decreasing complications, from sclerotherapy for varicose veins, when compared to non-ultrasound-guided techniques. A structured evidence review conducted by the Alberta Heritage Foundation for Medical Research (AHFMR) (2003) concluded that “the reviewed evidence does not adequately address the questions; which sclerosant is superior and which technique with or without ultrasound guidance is most efficacious.”

The size of the vein has been correlated with the presence of significant saphenous reflux. The compliant greater saphenous vein (GSV) adjusts its luminal size to the level of transmural pressure, and measurement of its diameter has been shown to reflect the severity of hemodynamic compromise in limbs with GSV reflux. In a cohort study, Navarro, et al. (2002) evaluated the relationship of GSV diameter determined in the thigh and calf to clinical severity of reflux in 112 legs in 85 consecutive patients with saphenofemoral junction and truncal GSV incompetence. The authors stated that they found that the GSV diameter proved to be a relatively accurate measure of hemodynamic impairment and clinical severity in a model of saphenofemoral junction and GSV incompete ce, predicting not only the absence of abnormal reflux, but also the presence of critical venous incompetence. A GSV diameter of 5.5 mm or less predicted the absence of abnormal reflux, with a sensitivity of 78 %, a specificity of 87 %, positive and negative predictive values of 78 %, and an accuracy of 82 %.

Ligation and division of the saphenofemoral and/or saphenopopliteal junction is indicated in patients with symptomatic varicose veins who have failed conservative management, when reflux of greater than 0.5 seconds is demonstrated by Doppler examination or Duplex scanning. The literature states that operative excision of varicose veins in the leg(s) should be reserved for those that are very large (greater than 6 mm), extensive in distribution, or occur in large clusters. Ligation alone usually results in a high recurrence rate of the varicose vein, which may then require sclerotherapy treatment (MSAC, 2008). Stripping of the greater and/or lesser saphenous vein, performed in conjunction with ligation and division of their respective junctions, is indicated when the saphenous veins themselves show varicose changes (usually greater than 1 cm in diameter). Varicose vein surgery and/or sclerotherapy during pregnancy is not appropriate because dilatation of veins in the legs is physiologic and will revert to normal after delivery, at which time a more accurate appraisal can be made. Visible subcuticular veins (i.e., spider angiomas, and telangiectasias) less than 2.5 mm in size do not cause symptoms and their treatment is purely cosmetic.

Ambulatory phlebectomy (AP) (also known as microphlebectomy) is a minimally invasive

procedure performed under local anesthesia, and is an accepted outpatient therapy for the removal of varicose veins. This treatment allows excision of almost all of the large varicose veins except the proximal long saphenous vein, which is better-managed by stripping. Non-refluxing varicose veins on the surface of the leg, not including the saphenous veins, may be treated as an outpatient procedure under local anaesthetic using ambulatory phlebectomy (MSAC, 2011). However, recurrence rates can be high if the source of the reflux is not treated (MSAC, 2011). The junctions themselves can not be treated with simple phlebectomy as junctional reflux must be addressed by endovenous ablation methods or rarely by surgical ligation and stripping (MSAC, 2011; Weiss, 2007). Patients can ambulate immediately after AP. Complications associated with AP include blister formation, localized thrombophlebitis, skin necrosis, hemorrhage, and persistent edema. The use of broad compression pads following AP reduces hemorrhage and enhances resorption.

The TriVex System (transilluminated powered phlebectomy) is an alternative method of providing ambulatory phlebectomy. This entails endoscopic resection and ablation of the superficial veins using an illuminator and a "powered vein rejector", a small powered surgical device. In this procedure, veins are marked with a magic marker. In order to enhance visualization of the veins, a bright light is introduced into the leg through a tiny incision. The powered vein rejector, which has a powered oscillating end, is then introduced to cut and dislodge the veins. The pieces of vein are then gently retrieved by suction down a tube. Transilluminated powered phlebectomy is usually performed in the hospital on an outpatient basis and under general anesthesia or using local anesthesia with sedation.

The manufacturer of the TriVex System states that the unique illumination feature allows the surgeon to quickly and accurately target and remove the vein and then visually confirm its complete extraction. The manufacturer claims that this new process makes varicose vein removal more effective, complete and less traumatic for patients, by reducing the number of incisions required to perform the procedure and the duration of surgery. The manufacturer also claims that this method not only reduces the pain associated with varicose vein removal but also reduces the potential for post-operative infection. There is inadequate evidence, however, in the published peer-reviewed medical literature substantiating these claims. The potential advantages of the TriVex System over standard ambulatory phlebectomy have not been proven. Therefore, the TriVex procedure should be billed as any other varicose vein removal procedure.

The term endovenous catheter ablation (EVCA) has been used to refer to the several new catheter based minimally invasive alternatives to surgical stripping, including laser ablation and radiofrequency ablation. Endovenous catheter ablation and surgical ligation/stripping are indicated for treatment of the same general population: patients in whom the great and/or small saphenous veins have reflux or incompetence of 0.5 seconds or longer demonstrated on duplex scanning, and varicose vein symptoms significantly impinge on quality of life (MSAC, 2011). These patients have exhausted conservative treatment measures, and sclerotherapy is considered unlikely to provide successful results. Endovenous laser ablation and radiofrequency ablation are essentially identical except for the use of different specialized equipment and catheters, with thermal energy delivered through either a radiofrequency catheter or laser fiber (MSAC, 2011). The objectives of the two treatments are the same, being the destruction or ablation of a refluxing vein or segment of vein via application of thermal energy. The procedure to place the catheter within the vein is the same for radiofrequency ablation and endovenous laser ablation, also both procedures are conducted under duplex ultrasonography guidance (MSAC, 2011). The physiological mechanism of vein ablation is also the same, with thermal energy producing endothelial and vein wall damage, denaturing and occluding the

vein to close the vein, abolishing venous reflux and visible varicosities (MSAC, 2011).

Endovenous laser ablation of saphenous vein (ELAS) is a treatment alternative to surgical ligation and stripping of the greater saphenous vein. Endovenous laser therapy for varicose veins is indicated for patients with clinically documented primary venous reflux, confirmed by duplex ultrasound, of the great or small saphenous veins (MSAC, 2008). Endovenous laser ablation is only suitable for patients with large, saphenous varicose veins, as the catheter requires saphenous veins with a minimum 4.5mm in diameter.These patients have exhausted other conservative treatment measures and sclerotherapy is considered unlikely to be successful (MSAC, 2008). After ultrasound examination to confirm the site and extent of saphenous reflux, a catheter is introduced into the damaged vein along a guide wire via percutaneous puncture at the distal extent of the diseased saphenous vein (MSAC, 2008). Perivascular infiltration of dilute local anesthetic along the length of the vein is then performed under ultrasound guidance to collapse the lumen and compress the vein onto the catheter, to dissipate heat generated during the procedure so as to prevent tissue damage, and to anesthetise the vein (MSAC). The guide wire is replaced with a laser probe introduced through the catheter to just below the saphenofemoral or saphenopopliteal junction, with positioning confirmed by ultrasound. Laser energy is then applied as the fiber and catheter are slowly withdrawn so as to close the vein and abolish venous reflux. Pulses of laser light are emitted inside the vein, and the vein collapses, and seals shut. This procedure may be performed in the office under local anesthesia. A bandage or compression hose is placed on the treated leg following the treatment. The procedure is performed on an outpatient basis.

Endovenous laser treatment can only be used for large veins, as a catheter must be inserted into the lumen of the vein to be treated (MSAC, 2008).. Endovenous laser treatment is not viable on saphenous veins smaller than 4.5 mm in diameter, and cannot be used for the treatment of small veins or telangiectases. Smaller veins may be treated with sclerotherapy or ambulatory phlebectomy.

A range of laser wavelengths can be used to achieve occlusion; there is no strong evidence to indicate that any particular wavelength is superior to any other (MSAC, 2008). One systematic evidence review reported that the short term (within 6 months) reported occlusion rates of the GSV and SSV found in studies of endovenous laser therapy were all greater than 90%.

Absolute contraindications to ELAS treatment include occlusive deep venous thrombosis and pregnancy. Relative contraindications include occlusive arterial disease, hypercoabulability, tortuous veins, and inability to ambulate (MSAC, 2008).

Endoluminal radiofrequency thermal heating (VNUS Closure Procedure) has been used with or without ligation and division for treatment of incompetence of the saphenofemoral and saphenopopliteal junction. To perform the radiofrequency ablation (RFA) procedure, the affected leg is prepared and draped, and a superficial local anaesthetic agent is used to anesthetize the site of cannulation. A radiofrequency catheter is inserted into the lumen of the greater saphenous vein, starting at its junction with the femoral vein. Under some protocols, the placement of the catheter is guided by duplex ultrasonography. The radiofrequency catheter heats the inner lumen of the vein to 85°C, with subsequent scarring and closure of the treated vein. The procedure is performed in an office setting without general anesthesia; treatment time averages 20 mins. Adverse sequelae include purpura, erythema and pain, which generally resolve days or weeks after treatment, and indurated fibrous cords that may remain for several months.

Upon completion of the RFA procedure, the site of venous puncture is dressed, and

compression stockings and/or bandages are applied as appropriate to reduce the risk of venous thromboembolism and to reduce postoperative bruising and tenderness (MSAC, 2011). Non-steroidal anti-inflammatory drugs are commonly used for post-procedural pain relief. For most patients additional procedures such as sclerotherapy or phlebectomy are required for the treatment of superficial veins below the knee, any tributary varicose veins, and telangiectases. These procedures may be performed during the RFA or endovenous laser treatment procedure, or over one or two follow-up visits.

Radiofrequency ablation is designed as a single-use therapeutic intervention, delivered as a single course of treatment per affected leg to obliterate the great or small saphenous veins through the application of thermal energy (MSAC, 2011). While generally indicated for primary varicose veins, re-treatment of varicose veins with RFA may be possible in some patients where neovascularisation or revascularisation has occurred. However, revascularization in the short term following treatment is uncommon. Studies reporting on radiofrequency ablation with the more efficient second generation catheters report ablation rates close to 100% at 6-month follow-up with no major adverse events (MAS, 2011).

Prospective case series extending to 24 months have shown success rates with RFA similar to those reported for vein ligation and stripping. Weiss and Weiss (2002) reported complete disappearance of the treated saphenous vein in 90 % of 21 patients followed for 24 months. Endothermal radiofrequency thermal heating may be performed with or without high ligation of the greater saphenous vein. Chandler et al (2000) found no statistically significant difference in 1-year success rates from endovenous radiofrequency catheter ablation in 120 limbs treated without saphenofemoral ligation and 60 limbs treated with saphenofemoral ligation. The authors concluded that "these early results suggest that extended sapheno-femoral junction (SFJ) ligation may add little to effective GSV [greater saphenous vein] obliteration, but our findings are not sufficiently robust to warrant abandonment of SFJ ligation as currently practiced in the management of primary varicose veins associated with GSV reflux."

Pivotal studies of endovenous catheter ablation (endovenous laser ablation and endovenous radiofrequency ablation) procedures have focused on junctional incompetence. There is a lack of evidence of the effectiveness of endovenous catheter ablation procedures for treatment of varicose tributaries and perforator veins. In addition, there are no studies comparing endovenous catheter ablation procedures to standard methods of treating varicose tributaries and perforator veins with sclerotherapy and ambulatory phlebectomy.

The Society for Interventional Radiologists (2003) has a position statement on VNUS that states that “(d)uplex ultrasound is necessary to map the anatomy of the venous system prior to the procedure, and imperative during the procedure for correct catheter placement and for proper tumescent anesthetic administration to minimize potential complications. Duplex ultrasound also is necessary for follow-up after endovenous ablation.”

Sadick (2000) has noted that the new less-invasive technologies for treatment of varicose veins must be evaluated with caution. "Long-term studies with other technologies must be compared with surgical ligation of the incompetent SFJ (saphenofemoral junction). Six-month and 5-year follow-ups are two different end points. The latter is a more accurate time interval of therapeutic efficacy."

Subfascial endoscopic perforator vein surgery (SEPS) is a minimally invasive endoscopic procedure that eliminates the need for a large incision in the leg. It has been explored as an alternative to the traditional open surgical treatment of chronic venous insufficiency.

The aim of the procedure is to interrupt incompetent medial calf perforating veins to reduce venous reflux and decrease ambulatory venous hypertension in critical areas above the ankle where venous ulcers most frequently develop. Kalra and Gloviczki (2002) stated that available evidence confirmed the superiority of SEPS over open perforator ligation, but do not address its role in the surgical treatment of advanced chronic venous insufficiency (CVI) and venous ulceration. Ablation of superficial reflux by high ligation and stripping of the greater saphenous vein with avulsion of branch varicosities is concomitantly performed in the majority of patients undergoing SEPS. The clinical and hemodynamic improvements attributable to SEPS thus are difficult to ascertain. As with open perforator ligation, clinical and hemodynamic results are better in patients with primary valvular incompetence (PVI) than in those with the post-thrombotic (PT) syndrome. Until prospective, randomized, multicenter clinical studies are performed to address lingering questions regarding the effectiveness of SEPS, the procedure is recommended in patients with advanced CVI secondary to PVI of superficial and perforating veins, with or without deep venous incompetence. The performance of SEPS in patients with PT syndrome remains controversial.

Contraindications for SEPS include associated arterial occlusive disease, infected ulcer, a non-ambulatory patient, and a medically high-risk patient. Diabetes, renal failure, liver failure, morbid obesity, ulcers in patients with rheumatoid arthritis, or scleroderma, and presence of deep vein obstruction at the level of the popliteal vein or higher on pre-operative imaging are relative contraindications. Patients with extensive skin changes, circumferential large ulcers, recent deep vein thrombosis, severe lymphedema, or large legs may not be suitable candidates (Kalra and Gloviczki, 2002).

McDonagh et al (2002, 2003) has reported on the effectiveness of ultrasound-guided foam sclerotherapy (comprehensive objective mapping, precise image-guided injection, anti-reflux positioning and sequential sclerotherapy (COMPASS) technique) in the treatment persons with varicosities of the greater saphenous vein with saphenous vein reflux. Published studies of the COMPASS technique involve relatively short-term follow up. Study subjects were followed for 3 years, and for only 2 years after completion of a series of repeat sclerotherapy injections that were administered over 1 year. In addition, these studies do not include a comparable group of subjects treated with surgery, which has been the primary method of treating incompetent long saphenous veins. Thus, it is not possible to reach definitive conclusions about the durability of results of the COMPASS technique or its effectiveness compared with surgery for treatment of greater saphenous vein varicosities and saphenofemoral incompetence. In addition, published studies of the COMPASS technique come from a single group of investigators. In reviewing the study by McDonagh (2002), Allegra (2003) commented: “Surgical treatment has a long history with 5-20 year follow-ups being routine. The 3 year follow-up in the present study is certainly not comparable …. This study does not answer questions raised against ultrasound guided sclerotherapy. It would be important to have the relevant aspects of this study duplicated, reproduced, and verified.”

Published long-term randomized controlled clinical studies have demonstrated that surgery plus sclerotherapy is more effective than surgery alone for treatment of varicosities associated with incompetence of the saphenofemoral junction. Belcaro et al (2003) reported on the results from the Venous Disease International Control (VEDICO) trial, the first long-term randomized controlled clinical trial of foam sclerotherapy. The VEDICO trial involved 749 patients with varicose veins and saphenous vein incompetence who were randomly treated by six different approaches: standard sclerotherapy, high-dose sclerotherapy, surgical ligation, stab avulsion, foam sclerotherapy, and combined surgery (ligation or stab avulsion) and high dose sclerotherapy. At 10 years, the occurrence of new veins was 56 % for standard sclerotherapy, 51 % for foam sclerotherapy, 49 % for

high-dose sclerotherapy, 41 % for stab avulsion, 38 % for ligation, and 27 % for combined surgery and sclerotherapy.

Belcaro et al (2000) reported on the results of a randomized controlled clinical study comparing ultrasound-guided sclerotherapy with surgery alone or surgery combined with sclerotherapy in 96 patients with varicose veins and superficial venous incompetence. Although all approaches were reported to be effective in controlling the progression of venous incompetence, surgery appeared to be the most effective method on a long-term basis, and that surgery combined with sclerotherapy may be more effective than surgery alone. After 10 years follow-up, no incompetence of the saphenofemoral junction was observed in both groups assigned to surgery, compared to 18.8 % of limbs of subjects assigned to ultrasound-guided sclerotherapy. Of limbs treated with ultrasound-guided sclerotherapy, 43.8 % of the distal venous systems were incompetent, compared to 36 % of limbs of subjects treated with surgery alone, and 16.1 % of limbs of subjects treated with surgery plus sclerotherapy.

The L'Agence Nationale d' Accreditation et d'Evaluation en Sante (l'ANAES) (Grange et al, 1998) conducted a systematic review of the literature on the indications of surgery for varicose veins of the legs. Given the lack of good scientific evidence on the various treatments for primary varicose veins, the working group made recommendations based on professional agreement. They concluded that surgery is the treatment of choice for saphenous veins with reflux. An evidence review of surgical treatments for deep venous incompetence by the Alberta Heritage Foundation for Medical Research (Scott and Corabain, 2003) stated that "(s)clerotherapy is particularly effective in superficial venous incompetence when there is a large vein located in close proximity to the ulcer. However, surgery is indicated when there is substantial proximal incompetence in a saphenous vein."

A comprehensive evidence review of sclerotherapy for varicose veins conducted by the Alberta Heritage Foundation for Medical Research (2003) concluded that "the reviewed evidence does not adequately address the questions; which sclerosant is superior and which technique with or without ultrasound guidance is most efficacious … In recent years, new methods such as ES (endovascular sclerotherapy) and foam sclerotherapy (using ultrasound guidance) have been developed and proposed to improve the safety and efficacy of sclerotherapy for various types of varicose veins. Evidence about these new techniques for treating patients with incompetence of the long saphenous vein is limited." The assessment concluded that although "(s)clerotherapy appears to be the treatment of choice for reticular varicosities, telangiectasia and other small, unsightly blood vessels … (t)he place of sclerotherapy as the first treatment for larger varicose veins (saphenous or non-saphenous) remains controversial."

There is a lack of reliable evidence that one type of sclerosant is significantly better than any other (Tisi 2007; Jia et al, 2006). Jia and colleagues (2007) evaluated the safety and effectiveness of foam sclerotherapy for varicose veins. The authors concluded that serious adverse events associated with foam sclerotherapy are rare. However, there is insufficient evidence to allow a meaningful comparison of the effectiveness of this treatment with that of other minimally invasive therapies or surgery.

Kendler and associates (2007) noted that "(r)ecently the use of foam sclerotherapy had a renaissance. Several studies have documented the efficacy of foam sclerotherapy in selected patients. The possibility of treating patients in an outpatient setting, with low costs and rapidly, makes foam sclerotherapy very attractive compared to invasive and minimally invasive methods. However long-term follow-ups in properly controlled randomized trials are needed before foam sclerotherapy can be recommended as a routine

procedure".

The FDA has approved Asclera (polidocanol) injection (BioForm Medical Inc., Franksville, WI) to close spider veins (tiny varicose veins less than 1 millimeter in diameter) and reticular veins (those that are 1 to 3 millimeters in diameter). As these small veins have not been demonstrated to cause symptoms, treatment of these small veins is considered cosmetic.

There is emerging evidence for the Ambulatory Conservative Hemodynamic Management of Varicose Veins (CHIVA) method. In an open-label, randomized controlled trial, Pares and colleagues (2010) compared the effectiveness of the Ambulatory Conservative Hemodynamic Management of Varicose Veins (CHIVA) method for the treatment of varicose veins with respect to the standard treatment of stripping. According to the authors, CHIVA consists of minimally invasive surgical procedures under local anesthesia that are based on hemodynamic analysis of the legs with pulsed Doppler ultrasound. A total of 501 adult patients with primary varicose veins were treated in a single center. They were assigned to an experimental group, the CHIVA method (n = 167) and 2 control groups: stripping with clinic marking (n = 167) and stripping with Duplex marking (n = 167). The outcome measure was clinical recurrence within 5 years, assessed clinically by previously trained independent observers. Duplex ultrasonography was also used to assess recurrences and causes. In an intention-to-treat analysis, clinical outcomes in the CHIVA group were better (44.3 % cure, 24.6 % improvement, 31.1 % failure) than in both the stripping with clinic marking (21.0 % cure, 26.3 % improvement, 52.7 % failure) and stripping with Duplex marking (29.3 % cure, 22.8 % improvement, 47.9 % failure) groups. The ordinal odds ratio between the stripping with clinic marking and CHIVA groups, of recurrence at 5- year follow-up, was 2.64, (95 % confidence interval (CI): 1.76 to 3.97, $p < 0.001$). The ordinal odds ratio of recurrence at 5-year follow-up, between the stripping with Duplex marking and CHIVA group, was 2.01 (95 % CI: 1.34 to 3.00, $p < 0.001$). The authors concluded that these findings indicated that the CHIVA method is more effective than stripping with clinical marking or stripping with Duplex marking to treat varicose veins. Furthermore, when carrying out a stripping intervention, Duplex marking does not improve the clinical results of this ablative technique.

In a randomized study, Rasmussen et al (2011) compared 4 treatments for varicose GSVs. A total of 500 consecutive patients (580 legs) with GSV reflux were randomized to endovenous laser ablation (EVLT, 980 and 1,470 nm, bare fiber), radiofrequency ablation (RFA), ultrasound-guided foam sclerotherapy (USGFS) or surgical stripping using tumescent local anesthesia with light sedation. Mini-phlebectomies were also performed. Patients were examined with duplex imaging before surgery, and after 3 days, 1 month and 1 year. At 1 year, 7 (5.8 %), 6 (4.8 %), 20 (16.3 %) and 4 (4.8 %) of the GSVs were patent and refluxing in the laser, radiofrequency, foam and stripping groups respectively ($p < 0.001$). One patient developed a pulmonary embolus after foam sclerotherapy and 1 a deep vein thrombosis after surgical stripping. No other major complications were recorded. The mean (S.D.) post-intervention pain scores (scale 0 to 10) were 2.58 (2.41), 1.21 (1.72), 1.60 (2.04) and 2.25 (2.23), respectively ($p < 0.001$). The median (range) time to return to normal function was 2 (0 to 25), 1 (0 to 30), 1 (0 to 30) and 4 (0 to 30) days, respectively ($p < 0.001$). The time off work, corrected for weekends, was 3.6 (0 to 46), 2.9 (0 to 14), 2.9 (0 to 33) and 4.3 (0 to 42) days, respectively ($p < 0.001$). Disease-specific quality-of-life and Short Form 36 (SF-36) scores had improved in all groups by 1-year follow-up. In the SF-36 domains bodily pain and physical functioning, the radiofrequency and foam groups performed better in the short-term than the others. The authors concluded that all treatments were efficacious. The technical failure rate was highest after foam sclerotherapy, but both RFA and foam were associated with a faster recovery and less post-operative pain than EVLT and stripping.

In a Cochrane review, Nesbitt et al (2011) reviewed available randomized controlled trial (RCT) data comparing USGFS, RFA and EVLT to conventional surgery (high ligation and stripping (HL/S)) for the treatment of great saphenous varicose veins. The Cochrane Peripheral Vascular Diseases (PVD) Group searched their Specialised Register (July 2010) and CENTRAL (The Cochrane Library 2010, Issue 3). In addition the authors performed a search of EMBASE (July 2010). Manufacturers of EVLT, RFA and sclerosant equipment were contacted for trial data. All RCTs of EVLT, RFA, USGFS and HL/S were considered for inclusion. Primary outcomes were recurrent varicosities, re-canalization, neovascularization, technical procedure failure or need for re-intervention, patient quality of life (QoL) scores and associated complications. Secondary outcomes were type of anesthetic, procedure duration, hospital stay and cost. A total of 13 reports from 5 studies with a combined total of 450 patients were included. Rates of re-canalization were higher following EVLT compared with HL/S, both early (within four months) (5/149 versus 0/100; odds ratio (OR) 3.83, 95 % CI: 0.45 to 32.64) and late re-canalization (after 4 months) (9/118 versus 1/80; OR 2.97 95 % CI: 0.52 to 16.98), although these results were not statistically significant. Technical failure rates favored EVLT over HL/S (1/149 versus 6/100; OR 0.12, 95 % CI: 0.02 to 0.75). Recurrence following RFA showed no difference when compared with surgery. Re-canalization within 4 months was observed more frequently following RFA compared with HL/S although not statistically significant (4/105 versus 0/88; OR 7.86, 95 % CI: 0.41 to 151.28); after 4 months no difference was observed. Neovascularization was observed more frequently following HL/S compared with RFA, but again this was not statistically significant (3/42 versus 8/51; OR 0.39, 95 % CI: 0.09 to 1.63). Technical failure was observed less frequently following RFA compared with HL/S although this was not statistically significant (2/106 versus 7/96; OR 0.48, 95 % CI: 0.01 to 34.25). No RCTs comparing HL/S versus USGFS met the study inclusion criteria. QoL scores and operative complications were not amenable to meta-analysis. The authors concluded that currently available clinical trial evidence suggests RFA and EVLT are at least as effective as surgery in the treatment of great saphenous varicose veins. There are insufficient data to comment on USGFS. They stated that further randomized trials are needed; and they should aim to report and analyze results in a congruent manner to facilitate future meta-analysis.

Mueller and Raines (2013) stated that the ClariVein system is the first venous ablation technique to employ a hybrid (dual-injury) technique built into 1 catheter-based delivery system. Endo-mechanical abrasion is produced by the tip of the catheter's rotating wire (mechanical component); and EVCA is via simultaneous injection of sclerosant over the rotating wire (chemical component). The author was an early adopter of this technique and via experience has developed a detailed step-by-step protocol. To date, there have been 2 pivotal clinical studies published using the ClariVein system. These data were compared with the results using other methods of endovenous ablation. The authors concluded that the ClariVein system has the potential to become a first-line treatment.

Lawson et al (2013) noted that less invasive endovenous techniques have been shown to be as effective as open surgery in the treatment of varicose veins. Furthermore, they cause less post-operative bruising and pain and enable early return to normal activities and work. Tumescent anesthesia is safe and obviates complications of general or spinal anesthesia. Drawbacks are a steep learning curve and painful administration during treatment. Tumescentless techniques like ClariVein or VenaSeal Sapheon Closure System are recently under investigation. Short-term results of VenaSeal are comparable with thermal ablation. The procedure is safe without serious adverse events. Peri-operative pain and patient discomfort with this tumescentless approach is minimal but post-operative recovery is temporarily hindered by thrombophlebitis in 14 to 15 % of

patients. One-year results in a small feasibility study has demonstrated durable closure at this end-point. No longer-term results are available. A randomized control trial between VenaSeal and Covidien ClosureFast is in a preparatory phase.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

36470	Injection of sclerosing solution; single vein
36471	multiple veins, same leg
36475	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated
+ 36476	second and subsequent veins treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
36478	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated
+ 36479	second and subsequent veins treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
37500	Vascular endoscopy, surgical, with ligation of perforator veins, subfascial (SEPS)
37700	Ligation and division of long saphenous vein at saphenofemoral junction, or distal interruptions
37718	Ligation, division, and stripping, short saphenous vein
37722	Ligation, division, and stripping, long (greater) saphenous veins from saphenofemoral junction to knee or below
37735	Ligation and division and complete stripping of long or short saphenous veins with radical excision of ulcer and skin graft and/or interruption of communicating veins of lower leg, with excision of deep fascia
37760	Ligation of perforator veins, subfascial, radical (Linton type), including skin graft, when performed, open, 1 leg
37761	Ligation of perforator vein(s), subfascial, open, including ultrasound guidance, when performed, 1 leg
37765	Stab phlebectomy of varicose veins, one extremity; 10-20 stab incisions [ambulatory]
37766	more than 20 incisions [ambulatory]
37780	Ligation and division of short saphenous vein at saphenopopliteal junction (separate procedure)
37785	Ligation, division, and/or excision of varicose vein cluster(s), one leg

CPT codes not covered for indications listed in the CPB:

36011	Selective catheter placement, venous system; first order branch (e.g., renal vein, jugular vein)
36468	Single or multiple injections of sclerosing solutions, spider veins (telangiectasia); limb or trunk
37241	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; venous, other than hemorrhage (eg, congenital or acquired venous malformations, venous and capillary hemangiomas, varices, varicoceles)
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
76942	Ultrasonic guidance for needle placement (eg, biopsy, aspiration, injection, localization device), imaging supervision and interpretation [not covered when performed solely to guide the needle or introduce the sclerosant into the varicose veins]
76998	Ultrasonic guidance, intraoperative [not covered when performed solely to guide the needle or introduce the sclerosant into the varicose veins]

Other CPT codes related to the CPB:

+ 37250	Intravascular ultrasound (non-coronary vessel) during diagnostic evaluation and/or therapeutic intervention; initial vessel (List separately in addition to code for primary procedure)
+ 37251	each additional vessel (List separately in addition to code for primary procedure)
75820, 75822	Venography, extremity, unilateral or bilateral, radiological supervision and interpretation
93922	Limited bilateral non-invasive physiologic studies of upper or lower extremity arteries, (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus bidirectional, Doppler waveform recording and analysis at 1-2 levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus volume plethysmography at 1-2 levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries with transcutaneous oxygen tension measurements at 1-2 levels)
93923	Complete bilateral non-invasive physiologic studies of upper or lower extremity arteries, 3 or more levels (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental blood pressure measurements with bidirectional Doppler waveform recording and analysis at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental volume plethysmography at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental transcutaneous oxygen tension measurements at 3 or more level(s), or single level study with provocative functional maneuvers (eg, measurements with postural

	provocative tests or measurements with reactive hyperemial)
93924	Non-invasive physiologic studies of lower extremity arteries, at rest and following treadmill stress testing, (ie, bidirectional Doppler waveform or volume plethysmography recording and analysis at rest with ankle/brachial indices immediately after and at timed intervals following performance of a standardized protocol on a motorized treadmill plus recording of time of onset of claudication or other symptoms, maximal walking time, and time to recovery) complete bilateral study
93970	Duplex scan of extremity veins including responses to compression and other maneuvers; complete bilateral study
93971	unilateral or limited study

HCPCS codes covered if selection criteria are met:

S2202	Echosclerotherapy

Other HCPCS codes related to the CPB:

A6530 - A6549	Compression stockings

ICD-9 codes covered if selection criteria are met:

451.0 - 451.2	Phlebitis and thrombophlebitis of superficial and deep vessels of lower extremities
453.40 - 453.42	Acute venous embolism and thrombosis of deep vessels of lower extremity
453.50 - 453.52	Chronic venous embolism and thrombosis of deep vessels of lower extremity
453.6	Venous embolism and thrombosis of superficial vessels of lower extremity
454.0	Varicose veins of lower extremities with ulcer
454.1	Varicose veins of lower extremities with inflammation
454.2	Varicose veins of lower extremities with ulcer and inflammation
454.8	Varicose veins of lower extremities with other complications
459.1	Postphlebitic syndrome
459.81	Venous (peripheral) insufficiency, unspecified [not covered for saphenopopliteal reflux]

ICD-9 codes not covered for indications listed in the CPB:

454.9	Asymptomatic varicose veins
671.00 - 671.04	Varicose veins of legs in pregnancy and the puerperium, unspecified as to episode of care or not applicable, delivered, with or without mention of antepartum condition, delivered, with mention of postpartum complication, antepartum condition or complication, or postpartum condition or complication
671.20 - 671.24	Superficial thrombophlebitis in pregnancy and the puerperium, unspecified as to episode of care or not applicable, delivered, with or without mention of antepartum condition, delivered, with mention of postpartum complication, antepartum condition or complication, or

	postpartum condition or complication
671.90 - 671.94	Unspecified venous complication in pregnancy and the puerperium, unspecified as to episode of care or not applicable, delivered, with or without mention of antepartum condition, delivered, with mention of postpartum complication, antepartum condition or complication, or postpartum condition or complication

Other ICD-9 codes related to the CPB:

440.23	Atherosclerosis of the extremities with ulceration
440.24	Atherosclerosis of the extremities with gangrene
448.0	Hereditary hemorrhagic telangiectasia
448.1	Nevus, non-neoplastic
448.9	Other and unspecified capillary diseases
707.10 - 707.19	Ulcer of lower limbs, except pressure ulcer
729.5	Pain in limb
729.81	Swelling of limb
782.3	Edema
785.4	Gangrene
V12.51	Personal history of venous thrombosis and embolism
V12.52	Personal history of thrombophlebitis

Mechanicochemical ablation (MOCA) (ClariVein):

No specific code

CPT codes covered if selection criteria are met:

36475	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated
+36476	second and subsequent veins treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
36478	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated
+36479	second and subsequent veins treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)

CPT codes not covered for indications listed in the CPB:

37204	Transcatheter occlusion or embolization (eg, for tumor destruction, to achieve hemostasis, to occlude a vascular malformation), percutaneous, any method, non-central nervous system, non-head or neck

The above policy is based on the following references:

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Medical Policy

Subject:	Treatment of Varicose Veins (Lower Extremities)		
Policy #:	SURG.00037	**Current Effective Date:**	01/13/2015
Status:	Revised	**Last Review Date:**	11/13/2014

Description/Scope

This document addresses various modalities (listed below) for the treatment of valvular incompetence (i.e., reflux) of the greater or lesser saphenous veins and associated varicose tributaries as well as telangiectatic dermal veins.

- Endoluminal radiofrequency ablation (also known as VNUS Closure™ System or Venefit™ Procedure);
- Endoluminal laser ablation (also known as EVLT™ or ELAS);
- Endovenous thermal ablation (EVTA) which includes radiofrequency and laser ablation;
- Endoluminal cryoablation;
- Sclerotherapy;
- Echosclerotherapy (also known as ultrasound-guided sclerotherapy);
- Mechanochemical ablation (for example: ClariVein®).

Cosmetic: In this document, procedures are considered cosmetic when intended to change a physical appearance that would be considered within normal human anatomic variation. Cosmetic services are often described as those that are primarily intended to preserve or improve appearance.

Position Statement

Medically Necessary:

Endoluminal radiofrequency ablation or endoluminal laser ablation, of the greater saphenous vein (GSV) **or** lesser saphenous veins (LSV) is **medically necessary** when the following criteria are met:

1. Junctional (saphenofemoral for GSV; saphenopopliteal for LSV) incompetence (that is, reflux with retrograde flow greater than 0.5 second duration) based on vein anatomy is demonstrated by Doppler or duplex ultrasound scanning; **and**
2. One or more of the following criteria (a, b, or c) are met:
    a. Symptoms of venous insufficiency or recurrent thrombophlebitis (including but not limited to: aching, burning, itching, cramping, or swelling during activity or after prolonged sitting) which:
        - are interfering with activities of daily living; **and**
        - persist despite appropriate non-surgical management, for no less than 6 weeks, such as leg elevation, exercise and medication; **and**
        - persist despite a trial of properly fitted gradient compression stockings for at least 6 weeks

        or
    b. There is ulceration secondary to stasis dermatitis;
    or
    c. There is hemorrhage from a superficial varicosity.

Sclerotherapy or echosclerotherapy, including ultrasound guided foam sclerotherapy (UGFS), of varicose tributary or extension (for example, anterolateral thigh vein, anterior accessory saphenous vein, or Giacomini vein[s]) or perforator veins greater than 3.0 mm in diameter with demonstrated reflux is **medically necessary** when the following criteria are met:

A. When performed at the same time as an endoluminal radiofrequency ablation procedure or endoluminal laser ablation procedure which meets the criteria above; or
B. When performed for the treatment of residual or recurrent symptoms which meet the following criteria:
    1. Surgical ligation and stripping, endoluminal radiofrequency ablation, or endoluminal laser ablation of the greater or lesser saphenous veins was previously performed; **and**
    2. One or more of the following criteria (a, b, or c) are met:
        a. Symptoms of venous insufficiency or recurrent thrombophlebitis (including but not limited to: aching, burning, itching, cramping, or swelling during activity or after prolonged sitting) which:
            - are interfering with activities of daily living; **and**
            - persist despite appropriate non-surgical management for 6 weeks, excluding similar management prior to the required treatment of the greater or lesser saphenous vein; and
            - persist despite a trial of properly fitted gradient compression stockings for at least 6 weeks, excluding similar management prior to the required treatment of the greater or lesser saphenous vein;

            or
        b. There is ulceration secondary to stasis dermatitis;

        or
        c. There is hemorrhage from a superficial varicosity.

Not Medically Necessary:

Endoluminal radiofrequency ablation, endoluminal laser ablation, sclerotherapy and echosclerotherapy (including UGFS) are each considered **not medically necessary** when the above criteria are not met.

Investigational and Not Medically Necessary:

Endoluminal radiofrequency ablation and endoluminal laser ablation, are each considered **investigational and not medically** necessary for all other uses in the lower extremities including, but not limited to:

a. As an alternative to perforator vein ligation; **or**
b. As treatment of saphenous vein tributaries or extensions (for example, anterolateral thigh, anterior accessory saphenous and Giacomini veins); **or**
c. As an alternative to adjunctive sclerotherapy or echosclerotherapy of symptomatic varicose tributaries.

Endoluminal cryoablation is considered **investigational and not medically necessary.**

Mechanochemical ablation of any vein is considered **investigational and not medically necessary.**

Sclerotherapy or echosclerotherapy (including UGFS) is considered **investigational and not medically necessary:**

a. As the sole***** treatment of symptomatic varicose tributary or extension or perforator veins in the presence of valvular incompetence of the greater or lesser saphenous veins (by Doppler or duplex ultrasound scanning); **or**
b. As the sole treatment of symptomatic varicose tributary or perforator veins in the absence of saphenous vein reflux or major saphenous vein tributary reflux; **or**
c. For the treatment of secondary varicose veins resulting from deep-vein thrombosis or arteriovenous fistulae when used to treat valvular incompetence (that is, reflux) of the greater or lesser saphenous veins with or without associated ligation of the saphenofemoral junction; **or**
d. When performed as part of other protocols for sclerotherapy, including, but not limited to the COMPASS protocol, for the treatment of valvular incompetence (that is, reflux) of the greater or lesser saphenous veins

Note: COMPASS is an acronym for Comprehensive Objective Mapping, Precise Image-guided

Injection, Antireflux Positioning and Sequential Sclerotherapy.

***** Sole refers to sclerotherapy without concomitant or prior ligation (with or without vein stripping), or endoluminal radiofrequency ablation, or endoluminal laser ablation for valvular incompetence of the greater or lesser saphenous veins

Cosmetic and Not Medically Necessary:

Treatment using sclerotherapy or various laser treatments (including tunable dye or pulsed dye laser, for example, PhotoDerm®, VeinLase™, Vasculite™) of the telangiectatic dermal veins (for example, reticular, capillary, venule), which may be described as "spider veins" or "broken blood vessels" is considered **cosmetic and not medically necessary.**

Rationale

In 2011, Gloviczki and colleagues released clinical practice guidelines for the Society for Vascular Surgery and the American Venous Forum. The authors summarized available venous research related to the care of individuals with varicose veins and associated chronic venous diseases. The available evidence was graded by quality and relevance of data. Recommendations were based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system as strong (GRADE 1) if the benefits clearly outweighed the risks, burden, and costs and (GRADE 2) if the benefits closely balanced with risks and burden. The level of available evidence to support the evaluation or treatment was stated to be of high (A), medium (B), or low or very low (C) quality. Key recommendations included:

- All patients with varicose veins or more severe chronic venous disease (CVD) being considered for treatment must have a duplex ultrasound scanning of the deep and superficial veins. The GSV, small saphenous vein (SSV) (also known as the lesser saphenous vein [LSV]), anterior accessory of the great saphenous vein (AAGSV) and posterior accessory of the great saphenous vein (PAGSV) incompetence must have a reflux time greater than 500 msec. "Pathologic" perforating veins includes those with outward flow of 500 ms or more, with a diameter of at least 3.5 mm, located beneath a healed or open venous ulcer (GRADE 1B).
- The clinical, etiology, anatomy, pathological (CEAP)classification is to be used for patients with CVD (GRADE 1A) and the revised Venous Clinical Severity Score is to be used to assess treatment outcome (GRADE 1B).
- Compression therapy is to be used for patients with symptomatic varicose veins (GRADE 2C) but compression therapy is not recommended as the primary treatment if the patient is a candidate for saphenous vein ablation (GRADE 1B).
- Compression therapy is to be used as the primary treatment to aid healing of venous ulceration (GRADE 1B).
- To decrease the recurrence of venous ulcers, ablation of the incompetent superficial veins in addition to compression therapy is recommended (GRADE 1A).
- For treatment of the incompetent great saphenous vein (GSV), we recommend endovenous thermal ablation (radiofrequency or laser) rather than high ligation and inversion stripping of the saphenous vein to the level of the knee (GRADE 1B).
- Phlebectomy or sclerotherapy to treat varicose tributaries (GRADE 1B) and suggest foam sclerotherapy as an option for the treatment of the incompetent saphenous vein (GRADE 2C).
- Selective treatment of perforating vein incompetence in patients with simple varicose veins (CEAP class C2; GRADE 1B) is not recommended, but suggest treatment of pathologic perforating veins (outward flow duration >500 ms, vein diameter >3.5 mm) located underneath healed or active ulcers (CEAP class C5-C6; GRADE 2B).
- Suggest treatment of pelvic congestion syndrome and pelvic varices with coil embolization, plugs, or transcatheter sclerotherapy, used alone or together (GRADE 2B).

These guidelines do not address treating symptomatic tributaries or perforators when GSV/LSV is not diseased. Also of note, treatment of perforators is only supported if associated with an ulcer.

The location of junctional incompetence will vary based on the individual's vein anatomy. The

termination of the GSV is the saphenofemoral junction (SFJ). GSV disease develops when there is pathologic reflux at this junction. Lesser saphenous vein anatomy is more variable. Approximately 2/3 of the time, the lesser saphenous vein terminates in the popliteal vein, and LSV disease then develops when there is pathologic reflux of the saphenopopliteal junction (SPJ). However, the LSV can terminate in the GSV or in accessory veins. Accordingly, the location of pathologic reflux may vary.

Endovenous Thermal Ablation (EVTA):
Gloviczki and colleagues (2011) addressed endovenous thermal ablation (laser and radiofrequency) as a safe and effective procedure for the treatment of saphenous incompetence. These ablative procedures are associated with less pain and morbidity than open surgery. Sclerotherapy is recommended for treatment for telangiectasia, reticular veins and varicose veins. Endovenous thermal ablation is recommended over sclerotherapy for treatment of an incompetent saphenous vein.

Khilnani and colleagues (2010) address the use of EVTA for perforator and surface varicose veins in guidelines from a multi-society consensus:

> The use of EVTA to close incompetent perforating veins has been described. At this point, the indications and contraindications for use as well as the success rates and safety of this approach have only recently begun to be evaluated. The use of EVTA to close surface varicose veins is not encouraged. These veins are usually too tortuous for current generation devices to pass through. Also, these veins are very superficial; EVTA of such veins carries a high risk of thermal skin injury.

In a joint statement, the American Venous Forum (AVM) and the Society of Interventional Radiology (SIR) addressed the research of endovenous ablation (EVA) as an alternative to GSV stripping for reflux disease (Kundu, 2007):

> This document provides recommended reporting standards for physicians performing clinical research studies evaluating EVA in the treatment of lower extremity venous reflux and is thereby expected to facilitate comparison between the results of different studies and to improve the overall quality of clinical research on venous disease.

Endoluminal radiofrequency (RF) ablation (thermal heating):
The VNUS ClosureSystem (VNUS Medical Technologies, Inc., San Jose, CA) received U.S Food and Drug Administration (FDA) 510k clearance in 1999. VNUS has been evaluated as an alternative to vein ligation and stripping or stripping alone for the treatment of saphenofemoral or saphenopopliteal junction incompetence and saphenous vein reflux. Endoluminal RF ablation of the saphenous vein is based on the principle of treating reflux disease by control of the point of reflux and isolation of the refluxing saphenous vein from circulation. The current evidence suggests that this procedure has success rates similar to those reported for surgical ligation and stripping with less postoperative pain and faster postoperative recovery. The use of this procedure outside the criteria specified in the position statement has not been adequately evaluated to allow conclusions regarding efficacy (Lurie, 2005; Rautio, 2002). The VNUS Closure System is now known as the Venefit Procedure (Covidien, Mansfield, MA).

Endovenous/Endoluminal laser ablation:
Venacure EVLT (Angiodynamics, Inc., Latham, NY) received FDA 510k clearance in 2002. EVLT of the greater saphenous vein has been studied in two large-scale case series studies and several smaller case series. These studies demonstrate lower relapse rates when compared with ligation and stripping, as well as comparable symptom relief and complication rates similar to endoluminal radiofrequency ablation. With respect to long-term outcomes and head-to-head comparison with other therapies, including ligation and stripping or RF ablation, the data is not adequate to make sufficient comparisons. The use of this procedure outside the criteria specified in the position statement has not been adequately evaluated to allow conclusions regarding efficacy (Darwood, 2008; Min, 2003; Rasmussen, 2007).

In a meta-analysis, van den Bos and colleagues (2009) reported that the literature supported minimally invasive interventions in the treatment of lower extremity varicosities despite the lack of large controlled studies. Comparing the outcomes of RF and laser ablation of the GSV and LSV in

the literature showed that laser ablation was more effective than RF ablation. They also stated that larger controlled studies are necessary to validate the clinical efficacy of RF and laser procedures.

RF or laser ablation for veins other than the saphenous veins (e.g. anterolateral thigh, anterior accessory saphenous and Giacomini veins) has been proposed. Peden and colleagues (2007) and Elias and colleagues (2007) addressed the feasibility of endoluminal RF and endovenous laser ablation for refluxing perforator veins. They concluded that additional clinical studies are needed to validate these treatment techniques. Van den Bos and colleagues (2009) reported on RF ablation of 14 incompetent perforator veins (IPV) in 12 individuals. At 3 months of follow-up, 9 (64%) of the 14 perforators treated were obliterated on ultrasound examination and the other 5 showed remaining reflux. The authors found that while RF ablation of perforator veins may be a promising procedure, further standardization of the procedure is required, as well as comparative clinical trials between RF ablation and standard therapies. In a small study, Bush and colleagues (2007) reported laser and sclerotherapy ablation of the Giacomini vein in 14 individuals. The ablations were successful and without complications. No recanalization occurred during a 2 to 4 year follow-up. In a small comparative clinical trial (n=69), Park and colleagues evaluated the safety and efficacy of endovenous laser ablation for either IPVs or great saphenous veins GSVs without evidence of saphenofemoral reflux over a period of 12 months. Endovenous ablation resulted in similar closure rates between the 2 groups (100% at 3, 6, and 12 months for both vein types). However, technical failure of the procedure was higher in subjects with IPVs compared with GSVs, and study authors determined that endovenous ablation might not be suitable as a primary treatment method for IPVs.

Endovenous laser ablation has been considered for treatment of refluxing saphenous tributaries. This was addressed in 1 small study of 18 participants (Bush, 2007) and a case report of 2 individuals (Theivacumar, 2007)

Theivacumar and colleagues (2009) proposed treating sapheno-femoral reflux and preserving the GSV by laser ablation of the anterior accessory great saphenous vein (AAGSV) in those with isolated sapheno-femoral junction (SFJ)/AAGSV reflux. They studied 66 individuals with SFJ reflux treated with EVLT, which included GSV ablation with 33 matched individuals with (SFJ)/AAGSV reflux treated with EVLT of the AAGSV. This feasibility study showed successful laser ablation of the AAGSV when the vein was relatively straight, at least 10 cm long, greater than or equal to 3 mm in diameter, and free of varicosities within the treatment length. Both groups had similar outcomes (e.g., sclerotherapy for residual varicosities). Doppler ultrasound (DUS) was performed at 6, 12, and 52 weeks to assess SFJ and tributary competence and ablation of the axial vein. Absence of flow in a noncompressible vein or a non-visible axial (GSV or AAGSV) vein on ultrasound represented successful ablation. The AAGSV was not visible in those treated for SFJ/AAGSV reflux. The authors reported that isolated SFJ/AAGSV reflux occurs in only 10% of those with reflux. In conventional surgery, many surgeons strip a competent GSV because of the risk that neovascularization after SFJ ligation may result in GSV reflux and recurrence. The authors stated that selective ablation of incompetent axial veins preserves a healthy GSV for other coronary or vascular procedures, if needed. In summary, they concluded that this procedure requires randomized controlled studies (RCTs) and long-term follow-up to properly assess health outcomes.

Nesbitt and colleagues (2011) published a Cochrane review of RCT to assess advantages or disadvantages of endovenous ablation (RF and laser) with foam sclerotherapy compared with conventional surgical, saphenofemoral junction ligation and stripping of GSV varices. Primary outcomes included:

- Recurrence, recanalization, or neovascularization;
- Procedure failure re-operation, or post-operative complications;
- Treatment satisfaction at pre- and post-procedure.

The authors reviewed 13 reports from 5 studies that met the inclusion criteria with a combined total of 450 subjects. Their findings indicated that early recurrence and recanalisation of GSV varices appears to be similar whether treated by conventional surgery or endovenous ablation, and the risk of recanalisation in the ablation group appears to increase with time post-ablation. Further, they found that neovascularisation could occur with both ablation and surgical procedures; although the

risk was reduced following endovenous ablation compared with conventional surgery, the trend was not statistically significant. There appears to be no differences in satisfaction and quality of life (QOL) measures between endovenous and conventional treatments; however, the return to normal activities and work may be sooner following RFA compared with conventional surgery. These findings were based upon the 3-year follow up data.

Rasmussen and colleagues (2011) reported a RCT of 500 subjects comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for GSV. The primary outcome was the failure rate at 1 year. Significantly more GSVs were open and refluxing at 1 year in the ultrasound guided foam sclerotherapy (UGFS) group than in the other groups ($P<0.001$). There was no statistically significant differences among patent GSVs in the 3 other groups ($P=0.543$).

Endoluminal Cryoablation:

In 2009, Klem and colleagues conducted a RCT and reported that endoluminal cryoablation (n=249) was inferior to conventional stripping (n=245) for treating individuals with symptomatic varicose veins. A total of 44% of individuals in the endoluminal cryoablation group and 15% in the conventional stripping group had persistent GSVs. The Aberdeen Varicose Vein Questionnaire (AVVQ) also showed better results for conventional stripping (score of 11.7) in comparison with cryoablation (score of 8.0). There were no differences between the groups in SF-36 subscores, and neural damage was the same (12%) in both groups.

Mechanochemical Ablation

Elias and colleagues (2012) described an industry-sponsored safety and efficacy study of the ClariVeinsystem. Thirty greater saphenous veins in 29 subjects were treated with this device. GSVs with diameters greater than 12 mm were excluded. A total of 77% of veins were CEAP Class 2; 7% in Class 3 (varicose veins and edema) and 16% in class 4a (varicose veins with skin changes). At 6 months of follow-up, 1 vein had recanalized, for a primary closure rate of 96.7%. No pain during the procedure or adverse events were reported.

Sclerotherapy:

There is sufficient evidence in the peer-reviewed medical literature to support the use of sclerotherapy when used *adjunctively* for the treatment of symptomatic varicose tributaries when performed either at the same time as surgical ligation and stripping, endoluminal radiofrequency ablation, or endoluminal laser ablation of the saphenous vein, **or** for the treatment of residual or recurrent symptomatic varicose tributaries following the above procedures (Tisi, 2006).

Sclerotherapy as the *sole* treatment of symptomatic varicose tributaries of the GSV is not indicated in the presence of saphenofemoral or saphenopopliteal junctional reflux. The published studies indicate that such treatment, without definitive treatment of valvular incompetence (i.e., reflux) of the saphenous veins with stripping and ligation or other surgical treatments (e.g., endoluminal RF ablation, or endoluminal laser ablation), provides minimal long-term benefit and leads to high recurrence rates. Individuals who undergo definitive treatment, as well as adjunctive sclerotherapy of the varicose tributaries, have shown better long-term results, lower rates of recurrence, and better QOL scores.

The overwhelming majority of varicosities of the saphenous tributaries are related to co-existing valvular incompetence (i.e. reflux) of the greater or lesser saphenous veins. However, a small subset of individuals (up to 14%) may be symptomatic in the absence of underlying reflux. Sclerotherapy as a sole therapy has been proposed for these individuals; however, the evidence base is small to support the use of sclerotherapy as a sole therapy. In 1 randomized study of 25 individuals, those receiving sclerosant reported a higher obliteration rate compared with those receiving normal saline at 12-weeks follow-up. The study does not address the key issue of long-term symptom resolution (Kahle, 2004).

Sclerotherapy directed at the underlying refluxing saphenous veins (as opposed to the visible varicosities of the tributary veins) requires ultrasound guidance. This procedure may be referred to as echosclerotherapy or ultrasound-guided sclerotherapy. The goal of ultrasound-guided foam sclerotherapy (UGFS) when treating varicose veins is to damage the endothelial surface of the vein to cause scarring and blockage of the treated vein. Under local anesthesia, the sclerosant foam is

injected into the affected veins using ultrasound guidance. The foam sclerosant causes an inflammatory reaction in the vein wall, causing vein blockage. Compression bandages are applied after the procedure for a period of time.

Controlled studies have shown that sclerotherapy/echosclerotherapy of the underlying refluxing greater or lesser saphenous veins is associated with a higher rate of recurrence compared to ligation and stripping (Belcaro, 2003). Van den Bos and colleagues (2009) conducted a well-designed meta-analysis of 64 studies (12,320 limbs) evaluating treatment of lower extremity varicosities, including GSVs and SSVs. Study authors reported that UGFS was comparable to conventional surgical stripping, but not as effective as EVLA. Comparable results were observed between UGFS and RFA. In a recent Cochrane systematic review, Nesbitt and colleagues (2014) conducted a recent systematic review including RCTs evaluating UGFS, EVLT, or RFA for minimally invasive treatment of GSVs compared with standard surgical treatment. The study authors concluded that UGFS, EVLT, and RFA are at least as effective as surgery for the treatment of GSVs. In a primary RCT conducted by Biemans (2013), UGFS was not as effective as EVLA in the short term, but comparable to high ligation and stripping. According to the study authors, 5-year follow-up results are still pending.

The Comprehensive Objective Mapping, Precise Image-guided Injection (i.e., echosclerotherapy), Antireflux Positioning and Sequential Sclerotherapy (COMPASS) procedure represents a distinct sclerotherapy protocol for the treatment of valvular incompetence (i.e. reflux) of the greater or lesser saphenous veins. The evidence regarding this techniques, in particular the study published by Belcaro and colleagues (2003), suffers from flaws in study design, including a failure to address specific information in regard to participant selection criteria, no description of the randomization process, and a failure to include appropriate comparator groups, including standard surgical treatment consisting of vein stripping and ligation. In addition, one of the surgical reference arms was not a part of the randomization process, but was a retrospective historical control group. Additionally, the re-treatment that occurred because of ongoing ultrasound monitoring was generally defined as a continuation of the initial therapy in the COMPASS protocol, rather than true recurrences or treatment failures. This aspect of the COMPASS protocol may be responsible for the low "recurrence rate" reported in the published studies. With the COMPASS protocol, individuals are viewed as being in the latter "phases" of therapy for prolonged periods of time. Some reports indicate that individuals have received therapy in excess of 1year. This is in contrast to alternative treatment methods, including standard surgical techniques, laser ablation or radiofrequency ablation procedures, that are completed within 7 to 10 days.

PhotoDerm, VeinLase, and Vasculite are laser devices primarily used in treating telangiectatic and reticular veins and other skin related applications. There is no compelling evidence that these conditions have any significantly negative health impact and fail to meet the criteria for medical necessity. However, there is adequate evidence that these treatment methods do significantly decrease the appearance of these superficial veins. Therefore, these techniques are considered primarily cosmetic in nature.

Conservative treatment

Compression therapy is the basic and most frequently used treatment of varicose veins of the lower extremities. Compression is recommended to decrease ambulatory venous hypertension to those with CVD in addition to lifestyle modifications that include weight loss, exercise, and elevation of the legs during the day whenever possible (Gloviczki, 2011). However, there is uncertainty regarding the need for conservative treatment before any intervention for simple varicose veins. Michaels and colleagues (2006) reported results of a randomized trial performed at two large UK hospitals that compared surgery with conservative treatment for uncomplicated varicose veins (n=246). Conservative treatment consisted of lifestyle changes (i.e., exercise, management of weight and diet, leg elevation), and the use of compression hosiery. In the surgical arm of the study, subjects received the same lifestyle advice but also underwent surgical treatment. The primary outcome of the study was clinical effectiveness at 1 year, as measured by a QOL questionnaire. There were significant losses to follow-up due to individuals failing to attend or withdrawing from the trial (21 of 122 following conservative treatment and 43 of 124 after surgery). The authors reported a QOL benefit from surgery at 2 years post treatment and benefits were also reported in symptomatic and anatomical measures. Limitations of this study included a high dropout rate due to many subjects opting to undergo surgical treatment to cosmetically

improve their varicose veins. This was the first randomized trial comparing surgery with conservative treatment for varicose veins. Additional well-designed studies are warranted.

Duplicate greater saphenous vein (GSV)
True duplicate GSV systems have been reported, however this is an uncommon occurrence. The duplicate GSV system will lie in the same plane, parallel to the skin, and run along the aponeurotic deep fascia. These two GSVs will also have the same diameter draining a common cutaneous territory. An anterior accessory vein (AASV) is often mistaken for a duplication of the GSV, but the AASV is usually smaller and does not drain the same cutaneous territory as the GSV. A true duplicate GSV is not an accessory vein and should be treated as any other GSV.

Background/Overview

Veins carry deoxygenated and nutrient depleted blood back to the heart and lungs. The veins located in the legs must work against gravity to move the blood upward toward the heart and lungs. The vascular system in the legs consists of the superficial and deep veins. The superficial veins lie on top of the muscles of the leg and include the GSV and the lesser saphenous vein (LSV) and their associated tributaries. The deep veins lie deep within the muscle compartments and generally parallel their associated arteries. The deep veins include the tibial, popliteal and femoral veins. The superficial and deep veins run vertically within the leg and are connected by perforator veins in a ladder like pattern. One-way valves are present in all the leg veins. These valves act against gravity to prevent the blood from flowing backwards (refluxing) to the legs instead of flowing towards the heart and lungs . Reflux of blood back into the vein causes dilation of the vessel, restriction of adequate blood flow to portions of the leg, and in some cases, discomfort or pain. Varicose veins are found most often on the back of the calf or on the inside of the leg between the groin and ankle. The most common valvular failures occur at the saphenofemoral junction (groin) between the GSV and the common femoral vein or at the saphenopopliteal junction (knee) between the LSV and the popliteal vein. Venous anatomy can vary significantly between individuals by the absence or presence of accessory and tributary veins. The following are some examples and locations (GSV or LSV) of these veins:

- anterior accessory (GSV): indicates any venous segment ascending parallel to the GSV and located anteriorly, both in the leg and in the thigh;
- posterior accessory (GSV): indicates any venous segment ascending parallel to the GSV and located posteriorly, both in the leg and in the thigh;
- superficial accessory (GSV): indicates any venous segment ascending parallel to the GSV and located more superficially above the saphenous fascia, both in the leg and in the thigh;
- cranial extension (LSV): courses between the biceps femoris and semimembranosus muscles A cranial extension of the LSV that communicates with the GSV via the posterior thigh circumflex vein is often termed the vein of Giacomini;
- superficial accessory (LSV): ascends parallel to the LSV and is located more superficially, above the saphenous fascia;
- anterior thigh circumflex vein: is a tributary vein of the GSV (or of the anterior accessory GSV) ascending obliquely in the anterior thigh;
- posterior thigh circumflex vein: is a tributary vein of the GSV (or of the posterior accessory GSV), which ascends obliquely in the posterior thigh.

An imaging technique called ultrasound or duplex scanning can be used to identify whether venous reflux is in the superficial, deep or perforating veins. It also can help determine whether reflux is confined to veins above or below the knee. This information is important in diagnosing the cause of this condition and in the planning of treatment.

The venous severity score is used for the assessment of clinical outcomes after therapy for varicose veins and more advanced chronic venous disease. Nine clinical characteristics of chronic venous disease are graded from 0 to 3 (absent, mild, moderate, severe) with specific criteria to avoid overlap or arbitrary scoring.

Some form of venous disorder affects approximately 80 million Americans and varicose veins are present in about 30% of women and 10% to 20% of men. Often, varicose veins present as a cosmetic concern but they may cause symptoms such as cramping, throbbing, burning, swelling,

feeling of heaviness or fatigue, and may interfere with activities of daily living. There is frequent confusion between varicose veins and "spider veins," which are small blue or red veins at the surface of the skin. Spider veins, also known as telangiectatic dermal veins, spider nevi, or broken blood vessels, while potentially unattractive, are not associated with any physical symptoms and are a benign condition.

Treatment for symptomatic varicose veins includes conservative measures such as frequent elevation of affected leg(s), walking, weight reduction and avoidance of prolonged sitting, analgesics and the use of compression stockings. The key to treatment of varicose veins is prevention of reflux in the short and long saphenous veins that connect to the major veins in the hip and pelvic area (femoral veins), a condition referred to as saphenofemoral reflux. When this non-invasive approach fails to relieve symptoms, several invasive options exist, as described below.

Standard procedures

Surgical ligation and stripping

The traditional therapy for venous reflux in the saphenous vein is surgical ligation and stripping. This begins with an incision in the groin region to expose the saphenous vein. The surgeon then ligates (ties off) the saphenous vein and small veins in the area. A second incision is made either just below the knee or at the ankle for the same purpose. Once both ends of the vein are free, a wire-like instrument is threaded through the vein, from the groin to the second incision, and secured to the vein. The vein is then pulled out (or "stripped") and removed from the leg.

Microphlebectomy

Also known as ambulatory phlebectomy or stab avulsion, microphlebectomy is a technique to remove varicose veins. In this procedure, several tiny incisions are made in the skin through which the varicose vein is removed. This technique is best suited for tortuous varicosities where passage of a probe or catheter cannot be accomplished.

Hook phlebectomy

Hook phlebectomy, also known as avulsion phlebectomy or small incision avulsion, is a surgical procedure performed alone or together with vein stripping. During avulsion phlebectomy, the surgeon makes a series of tiny incisions in the leg to remove varicose veins with a hook. Historically, hook phlebectomy has been performed as a blind procedure involving multiple incisions.

Subfascial endoscopic perforating vein surgery (SEPS)

SEPS is a minimally invasive surgical technique used to treat chronic venous ulcers caused by incompetent perforating veins due to chronic venous insufficiency. Prior to SEPS, the perforator veins were treated via an open surgical technique however, the open surgical approach had significant complication rates, including poor healing of incisions in ulcerated skin. Once the affected perforators are identified by imaging, the target veins are accessed percutaneously by instruments used to separate the connective tissue (fascia) from the incompetent perforator, and ligation is then accomplished by clip or cautery.

Trans-Illuminated Powered Phlebectomy (TIPP):

The TIPP technique uses the TRIVEX™ System. Through a small incision, a fiber optic illuminator is positioned nearby the varicose vein. A resector with a rotating blade is then guided through the skin next to the vein. Suction draws the vein into the tip of the vein resector, and the vein fragments are removed by suction.

Alternative procedures

Endoluminal radiofrequency ablation (VNUS Closure, now known as the VenefitProcedure) System:

Also known as radiofrequency endovenous occlusion, endoluminal RF ablation is typically performed by using a thin catheter inserted into the saphenous vein through a small opening in the skin. Radiofrequency energy is then delivered through the end of the catheter to heat the saphenous vein wall, causing it to collapse, scar and close. However, there is a lack of clinical evidence to

sufficiently demonstrate the clinical efficacy for vessels other than the saphenous vein.

Endovenous Laser Treatment (EVLT):
Endovenous laser ablation of the saphenous vein utilizes a small laser fiber that is inserted through a small incision in the skin into the vein. Pulses of laser light are emitted inside the vein, heating the vein wall causing it to collapse, scar and seal shut. A bandage or compression hose is placed on the treated leg following the treatment.

Sclerotherapy:
Sclerotherapy of varicose tributaries may be used adjunctively with stripping and ligation, RF ablation or endovenous laser ablation of the GSV. During this procedure, a chemical known as a sclerosing agent, typically a 0.5%-3% solution of sodium tetradecyl sulfate (STS), is injected into the vein to collapse its walls and eliminate blood flow. Following the procedure, pressure is applied to the vein through padding and compression stockings that are typically worn for 7 to 10 days. This continuous pressure allows a scar to form between the two walls of the vein preventing the further development of varicosities. Individual response to each injection can vary and it may require more than one injection to obliterate a vessel.

Echosclerotherapy is a term used to describe ultrasound-guided sclerotherapy where the veins are injected under direct ultrasound visualization.

Comprehensive Objective Mapping, Precise Image-guided Injection, Antireflux Positioning and Sequential Sclerotherapy (COMPASS) is a variation of ultrasound-guided sclerotherapy, and has been proposed as a treatment for varicose veins. This therapy uses ultrasound-guided sclerotherapy, followed by multiple diagnostic ultrasound imaging procedures, and sclerotherapy treatments for the treatment of subsequent varicose veins. This therapy may involve several weeks or months of treatment.

Mechanochemical Ablation:
Endovenous mechanochemical ablation utilizes both sclerotherapy and mechanical damage to the lumen. Following ultrasound imaging, a disposable catheter with a motor drive is inserted into the distal end of the target vein and advanced until it reaches the saphenofemoral junction. As the catheter is pulled back, a wire rotates within the lumen of the vein. At the same time, a liquid sclerosant (sodium tetradecyl sulfate) is infused near the rotating wire. It is hypothesized that mechanical ablation allows for better efficacy of the sclerosant, without the need for the tumescent anesthesia used in RF ablation or EVLT.

Note: The term "varicose veins" does not apply to telangiectatic (spider) veins or reticular veins. Similar to varicose veins, these veins are created when the valves that control the blood flow in the veins weaken. This causes the formerly small veins located just below the skin to become engorged with blood. As a result, these veins widen, becoming visible beneath the skin, but are generally not associated with pain, bleeding, ulceration, or other medical problems, and therefore their treatment is considered purely cosmetic.

Definitions

Activities of daily living (ADL): a term used in healthcare that refers to everyday routines involving personal care, such as bathing, dressing, toileting and meal preparation. An inability to perform these tasks indicates a functional mobility deficit.

Anti-embolism hose (also called elastic stockings or compression stockings)**:** A type of stocking worn to prevent the formation of blood clots in the legs (thromboses); assisting in the return flow of the blood to the heart, and prevention of pooling in the veins; there are three support grades of prescription hose; mild to severe support (15-20, 20-30, 30-40 mmHg) which are generally used to assist with a medical condition and light support (8-15 mmHg) that may be used as a preventive measure.

Arteriovenous fistulae: A condition where a vein and artery are directly connected without the usual intervening small vessels.

Catheter ablation: A technique involving the application of either radiofrequency or laser energy

through an endovenous catheter for the purpose of ablating varicose vein tissue of the GSV or LSV; this does not include the "closure" or ablation of a vein using the injection of a sclerosing agent through a hollow catheter.

CEAP (clinical, etiology, anatomy, pathological) classification: A descriptive classification for chronic venous disorders. Used for the classification of varicose veins.

CEAP Description

1. Clinical classification

C0 No visible or palpable signs of venous disease
C1 Telangiectases or reticular veins
C2 Varicose veins
C3 Edema
C4a Pigmentation and/or eczema
C4b Lipodermatosclerosis and/or atrophie blanche
C5 Healed venous ulcer
C6 Active venous ulcer
CS Symptoms, including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction
CA Asymptomatic

2. Etiologic classification

Ec Congenital
Ep Primary
Es Secondary (postthrombotic)
En No venous etiology identified

3. Anatomic classification

As Superficial veins
Ap Perforator veins
Ad Deep veins
An No venous location identified

4. Pathophysiologic classification

Pr Reflux
Po Obstruction
Pr,o Reflux and obstruction
Pn No venous pathophysiology identifiable

Adapted from Eklöf, 2004.

Perforator veins: Connect the superficial veins to the deep veins.

PhotoDerm: A pulsed laser light treatment to aesthetically treat a specific area of leg telangiectasis.

Reticular vein: Dilated bluish subdermal vein, generally 1 mm to less than 3 mm in diameter and usually tortuous.

Synonyms include blue veins, subdermal varices and telangiectasia.

Saphenofemoral reflux: A backflow of blood in the veins causing varicose vein symptoms and bulging.

Saphenous vein:A vein that serves as the principal blood vessel returning blood from the surface of the leg back to the trunk.

Sclerotherapy: A treatment for varicose veins in which a chemical is injected into the vein causing the vein to shrink and close.

Stasis dermatitis: A condition caused by too little circulation in the legs; it begins with swelling of the ankles and progresses to tan-colored skin, patchy reddening, tiny, round, purplish-red spots,

and hardening of the skin.

Subfascial: Below the fascia; fascia is a strong connective tissue that performs a number of functions, including surrounding and providing structural support within the body.

Telangiectasia**:** Dilated superficial blood vessels, especially of the upper reticular dermal plexus.

Thrombophlebitis:Inflammation of a vein, along with the formation of a clot; this occurs most commonly as the result of injury to the vessel wall, abnormal increased clotting capacity of the blood (hypercoagulability), infection, or a chemical irritation.

Tributary vein:A superficial vein branch that flows into larger veins.

Varicose vein or varicosity: Veins that are abnormally swollen or enlarged due to weakening in the vein's wall. Measured in an upright position they are 3 mm in diameter or greater.

Venous insufficiency:An abnormal circulatory condition marked by decreased return of venous blood from the legs to the trunk of the body.

Venous Severity Score: A score used for the assessment of clinical outcomes after therapy for varicose veins and more advanced chronic venous disease.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

36470	Injection of sclerosing solution; single vein
36471	Injection of sclerosing solution; multiple veins, same leg
36475	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated
36476	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; second and subsequent veins treated in a single extremity, each through separate access sites
36478	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated
36479	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; second and subsequent veins treated in a single extremity, each through separate access sites

HCPCS

S2202	Echosclerotherapy

ICD-9 Procedure	***[For dates of service prior to 10/01/2015]***
39.92	Injection of sclerosing agent into vein

ICD-9 Diagnosis	***[For dates of service prior to 10/01/2015]***
448.0	Hereditary hemorrhagic telangiectasia
451.0-451.2	Phlebitis and thrombophlebitis of vessels of lower extremities
453.6	Venous embolism and thrombosis of superficial vessels of lower extremity
454.0-454.8	Varicose veins of lower extremities [with complications]
459.11-459.19	Postphlebitic syndrome [with complications]
459.81	Venous (peripheral) insufficiency, unspecified
459.89	Other specified disorders of circulatory system (phlebosclerosis)
707.10-707.19	Ulcer of lower limbs, except decubitus

729.5	Pain in limb
729.81	Swelling of limb
747.64	Other anomalies of peripheral vascular system, lower limb vessel anomaly
782.3	Edema
785.4	Gangrene
V12.51	Personal history of venous thrombosis and embolism
V12.52	Personal history of thrombophlebitis

ICD-10 Procedure	***[For dates of service on or after 10/01/2015]***
065P3ZZ-065Q4ZZ	Destruction of greater saphenous vein [right or left, by percutaneous or percutaneous endoscopic approach; includes codes 065P3ZZ, 065P4ZZ, 065Q3ZZ, 065Q4ZZ]
065R3ZZ-065S4ZZ	Destruction of lesser saphenous vein [right or left, by percutaneous or percutaneous endoscopic approach; includes codes 065R3ZZ, 065R4ZZ, 065S3ZZ, 065S4ZZ]
06LP0ZZ-06LQ4ZZ	Occlusion of greater saphenous vein [right or left, by approach; includes codes 06LP0ZZ, 06LP3ZZ, 06LP4ZZ, 06LQ0ZZ, 06LQ3ZZ, 06LQ4ZZ]
06LR0ZZ-06LS4ZZ	Occlusion of lesser saphenous vein [right or left, by approach; includes codes 06LR0ZZ, 06LR3ZZ, 06RP4ZZ, 06LS0ZZ, 06LS3ZZ, 06LS4ZZ]
3E030TZ	Introduction of destructive agent into peripheral vein, open approach
3E033TZ	Introduction of destructive agent into peripheral vein, percutaneous approach

ICD-10 Diagnosis	***[For dates of service on or after 10/01/2015]***
I78.0	Hereditary hemorrhagic telangiectasia
I80.00-I80.9	Phlebitis and thrombophlebitis
I82.501-I82.599	Chronic embolism and thrombosis of deep veins of lower extremity
I82.5Y1-I82.5Y9	Chronic embolism and thrombosis of unspecified deep veins of proximal lower extremity
I82.5Z1-I82.5Z9	Chronic embolism and thrombosis of unspecified deep veins of distal lower extremity
I82.811-I82.819	Embolism and thrombosis of superficial veins of lower extremities
I83.001-I83.899	Varicose veins of lower extremities [with complications]
I87.011-I87.099	Postthrombotic syndrome [with complications]
I87.2	Venous insufficiency (chronic) (peripheral)
I87.8	Other specified disorders of veins (phlebosclerosis)
I96	Gangrene, not elsewhere classified
L97.101-L97.929	Non-pressure chronic ulcer of lower limb, not elsewhere classified
M79.604-M79.606	Pain in leg
M79.661-M79.669	Pain in lower leg
Q27.32	Arteriovenous malformation of vessel of lower limb
Q27.8	Other specified congenital malformations of peripheral vascular system
R22.40-R22.43	Localized swelling, mass and lump, lower limb
R60.0	Localized edema
Z86.71	Personal history of venous thrombosis and embolism
Z86.72	Personal history of thrombophlebitis

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above, when criteria are not met, and for the following diagnosis

ICD-9 Diagnosis	***[For dates of service prior to 10/01/2015]***
454.9	Asymptomatic varicose veins

ICD-10 Diagnosis	***[For dates of service on or after 10/01/2015]***
I83.90-I83.93	Asymptomatic varicose veins of lower extremities

When services are Cosmetic and Not Medically Necessary:
For the procedure codes listed above, for the following diagnosis, or when the code describes a procedure indicated in the Position Statement section as cosmetic and not medically necessary.

ICD-9 Diagnosis	***[For dates of service prior to 10/01/2015]***
448.1	Nevus non-neoplastic (spider veins)

ICD-10 Diagnosis	***[For dates of service on or after 10/01/2015]***

I78.1	Nevus non-neoplastic (spider veins)

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above, for all other diagnoses, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

When services are also Investigational and Not Medically Necessary:

CPT

37799	Unlisted procedure, vascular surgery [when specified as COMPASS protocol, endoluminal cryoablation or mechanochemical ablation of varicose veins]

ICD-9 Diagnosis ***[For dates of service prior to 10/01/2015]***
All diagnoses

ICD-10 Diagnosis ***[For dates of service on or after 10/01/2015]***
All diagnoses

When services are Cosmetic and Not Medically Necessary:

CPT

36468	Single or multiple injections of sclerosing solutions, spider veins (telangiectasia); limb or trunk
96999	Unlisted special dermatological service or procedure [when specified as tunable dye or pulsed dye laser treatment]

ICD-9 Diagnosis ***[For dates of service prior to 10/01/2015]***
All diagnoses

ICD-10 Diagnosis ***[For dates of service on or after 10/01/2015]***
All diagnoses

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	11/13/2014	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Description, Rationale and Reference sections.
Revised	11/14/2013	MPTAC review. Clarified medically necessary statement for junctional (saphenofemoral or saphenopopliteal as appropriate based on vein anatomy) incompetence. Rationale, Background and Reference sections updated.
Revised	08/08/2013	MPTAC review. Mechanochemical ablation of any vein added as an investigational and not medically necessary statement. Rationale, Coding, Reference and Index sections updated.
Revised	02/14/2013	MPTAC review. Position statement reformatted. Description, Rationale, Reference, and Index sections updated.
Revised	05/10/2012	MPTAC review. Medically Necessary criteria reorganized. Rationale and References updated.
Revised	05/19/2011	MPTAC review. Addition of reticular vein to position statement. Description, Rationale and References updated.
Revised	05/13/2010	MPTAC review. Medically necessary and investigational and not medically necessary criteria revised to address saphenofemoral and saphenopopliteal junction incompetence and endoluminal cyoablation. Rationale, Background, Coding and References updated.
	10/01/2009	Updated Coding section with 10/01/2009 ICD-9 changes; removed ICD-9 diagnosis code 453.8 (no longer applicable).
Revised	05/21/2009	MPTAC review. Vein anatomy clarified in position statement. Background updated to address standard therapies. References updated.
Revised	11/20/2008	MPTAC review. Criteria updated to address saphenous vein tributaries and extensions. Rationale, Background, Coding and References updated.
Revised	11/29/2007	MPTAC review. Criteria for perforator ligation clarified. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary" and the phrase "cosmetic/not medically necessary" was clarified to read "cosmetic and not medically necessary." References updated.

Revised	12/07/2006	MPTAC review. Minimal pressure criteria (30mmHg) for compression stockings deleted. Coding updated; removed HCPCS S2130, S2131 deleted 12/31/2004.
Revised	03/23/2006	MPTAC review.
	11/21/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.	10/28/2004	SURG.00037	Treatment of Varicose Veins (lower extremities)
WellPoint Health Networks, Inc.	03/11/2004	3.01.23	Endosaphenous Radiofrequency or Laser Ablation for Treatment of Primary Venous Insufficiency
	09/23/2004	Clinical Guideline	Sclerotherapy-Varicose Veins
	12/02/2004	Clinical Guideline	Treatment of Refluxing Saphenous Vein in Patients with Varicose Veins

Local Coverage Determination (LCD): Varicose Veins of the Lower Extremity, Treatment of (L25519)

Contractor Information

Contractor Name	Contract Number	Contract Type	Jurisdiction
National Government Services, Inc. opens in new window	13101	A and B and HHH MAC	J - K

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LCD Information

Document Information

LCD ID
L25519

LCD Title
Varicose Veins of the Lower Extremity, Treatment of

Jurisdiction
Connecticut

Original Effective Date
For services performed on or after 12/01/2007

Revision Effective Date
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Revision Ending Date
N/A

Retirement Date
N/A

Notice Period Start Date
01/01/2011

Notice Period End Date
N/A

CMS National Coverage Policy Language quoted from Centers for Medicare and Medicaid Services (CMS), National Coverage Determinations (NCDs) and coverage provisions in interpretive manuals is italicized throughout the policy. NCDs and coverage provisions in interpretive manuals are not subject to the LCD Review Process (42 CFR 405.860[b] and 42 CFR 426 [Subpart D]). In addition, an administrative law judge may not review an NCD. See §1869(f)(1)(A)(i) of the Social Security Act.

Unless otherwise specified, *italicized* text represents quotation from one or more of the following CMS sources:

Title XVIII of the Social Security Act (SSA):

Section 1862(a)(1)(A) excludes expenses incurred for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Section 1833(e) prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

Coverage Guidance
Coverage Indications, Limitations, and/or Medical Necessity

Abstract:

Varicose veins are caused by venous insufficiency as a result of valve reflux (incompetence). The venous insufficiency results in dilated, tortuous, superficial vessels that protrude from the skin of the lower extremities. Spider veins (telangiectases) are dilated capillary veins that are most often treated for cosmetic purposes. Treatment of telangiectases (CPT code 36468) is not covered by Medicare.

Ligation and stripping of varicose veins is a treatment option that aims to eliminate reflux at the saphenofemoral junction. The treatment of choice for moderate to large symptomatic varicose veins, ligation and stripping of the saphenous vein, has the lowest failure rate.

Sclerotherapy, injecting sclerosing solutions directly into the abnormal veins, is an alternative occasionally selected for the treatment of varicose veins without significant saphenofemoral or saphenopopliteal incompetence. However, it is not considered to be as reliable and effective as surgical ligation and stripping.

Sclerotherapy for cosmetic purposes is considered not medically necessary. Sclerotherapy is considered medically necessary for the treatment of small to medium sized vessels (less than 4 mm in diameter.) Sclerotherapy is not considered medically necessary for vessels larger than 4 mm in diameter.

Foam sclerotherapy of the saphenous vein at its junction with the deep venous system has been proposed as an alternative to ligation or saphenectomy, but its efficacy lacks sufficient scientific evidence to support its widespread use. The current consensus is that most recommendations for conventional sclerotherapy also apply to foam sclerotherapy.

Sclerotherapy of the saphenous vein at its junction with the deep system is not a covered procedure.

Non-compressive sclerotherapy involves injection of a sclerosant into a vein without the application of a compressive dressing. Because it is not effective in producing long-term obliteration of the incompetent veins, noncompressive sclerotherapy is not covered by Medicare.

Compressive sclerotherapy is the injection of the sclerosant into an empty vein (elevated limb) followed by application of a compressive bandage or dressing. This is the most commonly performed sclerotherapy procedure for varicose veins of the lower extremity. Compressive sclerotherapy is indicated for local small to medium symptomatic varices, isolated incompetent perforators, or recurrence of symptomatic varices after adequate surgical removal of varices. It is not considered an appropriate option for large, extensive or truncal varicosities.

High ligation and compression sclerotherapy refers to ligation of a truncal junction (saphenofemoral or saphenopopliteal) followed by compressive sclerotherapy of one or more veins.

Endovenous radiofrequency ablation (EFRA) and laser ablation are minimally invasive alternatives to vein ligation and stripping. Endovenous radiofrequency ablation is FDA-approved for treatment of the greater saphenous vein, perforators and tributary veins. Endovenous laser ablation is FDA-approved for the treatment of varicose veins and varicosities associated with superficial reflux of the greater saphenous vein.

Indications:

Medicare will consider interventional treatment of varicose veins (sclerotherapy, ligation with or without stripping, and endovenous radiofrequency or laser ablation) medically necessary if the patient remains symptomatic after a six-week trial of conservative therapy. The components of the conservative therapy include, but are not limited to:

- weight reduction,
- a daily exercise plan,
- periodic leg elevation, and
- the use of graduated compression stockings.

The conservative therapy must be documented in the medical record. Inability to tolerate compressive bandages or stockings and the reason for such intolerance must be documented in the medical record.

The patient is considered symptomatic if any of the following signs and symptoms of significantly diseased vessels of the lower extremities are documented in the medical record:

- stasis ulcer of the lower leg, as above,
- significant pain and significant edema that interferes with activities of daily living,
- bleeding associated with the diseased vessels of the lower extremities,
- recurrent episodes of superficial phlebitis,
- stasis dermatitis, or
- refractory dependent edema.

Additional indications and limitations are discussed according to type of treatment. Surgery, EFRA and laser ablation, or sclerotherapy are typically not performed for varicose veins that develop or worsen during pregnancy because most will spontaneously resolve or improve after delivery.

In addition to the requirement for failure of a six-week trial of conservative treatment and the symptoms described above, coverage of endovenous ablation therapy is limited to patients with:

- a maximum vein diameter of 20 mm for laser ablation;
- absence of thrombosis or vein tortuosity, which would impair catheter advancement; and
- absence of significant peripheral artery disease.

Radiofrequency/laser ablation is covered only for treatment of the lesser or greater saphenous veins to improve symptoms attributable to saphenofemoral or saphenopopliteal reflux. Coverage is only for FDA devices specifically approved for these procedures.

Non-cosmetic sclerotherapy will also be covered if performed in conjunction with surgical ligation or stripping procedures in appropriately selected patients.

Limitations:

Duplex ultrasound is often used in conjunction with other non-invasive physiologic testing to define the anatomy and physiology of the varicose vein network prior to injection or surgical intervention. There is adequate evidence that the pre-procedural ultrasound is helpful, and Medicare will cover a pre-procedure Duplex scan (CPT code 93970 or 93971) used in conjunction with other non-invasive physiologic testing (CPT code 93965) to determine the extent and configuration of the varicosities. NGS expects that these studies will be performed by the provider planning to provide the therapy. NGS will allow this study once per provider or provider group. Clinical experience supports the use of ultrasound during the sclerotherapy procedure, and evidence shows that the outcomes may be improved and complication rates may be minimized when ultrasound guidance is used.

Medicare will cover intraoperative ultrasonic guidance in situations when it is medically necessary.

Medicare includes payment for the ultrasound in the payment for the ERFA and laser ablation procedures.

Cosmetic surgery is statutorily excluded from coverage by Medicare. The following interventional treatments are considered to be cosmetic and will be denied as such:

- Interventional treatment of asymptomatic varicosities.
- Treatment of telangiectases (36468).
- Sclerotherapy for cosmetic purposes.

Medicare cannot cover services which are not reasonable and necessary for the *treatment of illness or injury or to improve the functioning of a malformed body member.* The following interventional treatments are not considered medically reasonable or necessary and are denied as such:

- Interventional treatment of symptomatic varicosities without documentation of a failed six week trial of conservative therapy.
- Sclerotherapy for vessels larger than 4 mm in diameter.
- Reinjection following recanalization or failure of vein closure without recurrent signs or symptoms.
- Sclerotherapy of the saphenous vein at its junction with the deep system.
- Noncompressive sclerotherapy.
- Compressive sclerotherapy for large, extensive or truncal varicosities.
- Sclerotherapy, ligation and/or stripping of varicose veins, or endovenous ablation therapy are not covered for patients with severe distal arterial occlusive disease; obliteration of deep venous system; an allergy to the sclerosant; or a hypercoaguable state.
- Any interventional treatment that uses equipment or sclerosants not approved for such purposes by the FDA.
- Laser ablation of veins with a diameter greater than 20 mm.
- Endovenous ablation therapy in the presence of thrombosis or venous tortuosity which would impair catheter advancement.

CPT codes 37760 and 37761 should not be reported in conjunction with CPT codes 76937, 76942, 76998 or 93971.

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Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

011x Hospital Inpatient (Including Medicare Part A)
012x Hospital Inpatient (Medicare Part B only)
013x Hospital Outpatient
071x Clinic - Rural Health
073x Clinic - Freestanding
077x Clinic - Federally Qualified Health Center (FQHC)
085x Critical Access Hospital

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory; unless specified in the policy services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

Revenue codes only apply to providers who bill these services to the Part A MAC. Revenue codes do not apply to physicians, other professionals and suppliers who bill these services to the Part B MAC.

Please note that not all revenue codes apply to every type of bill code. Providers are encouraged to refer to the FISS revenue code file for allowable bill types. Similarly, not all revenue codes apply to each CPT/HCPCS code. Providers are encouraged to refer to the FISS HCPCS file for allowable revenue codes.
0330 Radiology - Therapeutic and/or Chemotherapy Administration - General Classification
0360 Operating Room Services - General Classification
0490 Ambulatory Surgical Care - General Classification
0510 Clinic - General Classification
0520 Free-Standing Clinic - General Classification

CPT/HCPCS Codes
Group 1 Paragraph: CPT Code 37799 should be used to report "Trivex Procedure"

Group 1 Codes:

36468	SINGLE OR MULTIPLE INJECTIONS OF SCLEROSING SOLUTIONS, SPIDER VEINS (TELANGIECTASIA); LIMB OR TRUNK
36470	INJECTION OF SCLEROSING SOLUTION; SINGLE VEIN
36471	INJECTION OF SCLEROSING SOLUTION; MULTIPLE VEINS, SAME LEG
36475	ENDOVENOUS ABLATION THERAPY OF INCOMPETENT VEIN, EXTREMITY, INCLUSIVE OF ALL IMAGING GUIDANCE AND MONITORING, PERCUTANEOUS, RADIOFREQUENCY; FIRST VEIN TREATED
36476	ENDOVENOUS ABLATION THERAPY OF INCOMPETENT VEIN, EXTREMITY, INCLUSIVE OF ALL IMAGING GUIDANCE AND MONITORING, PERCUTANEOUS, RADIOFREQUENCY; SECOND AND SUBSEQUENT VEINS TREATED IN A SINGLE EXTREMITY, EACH THROUGH SEPARATE ACCESS SITES (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
36478	ENDOVENOUS ABLATION THERAPY OF INCOMPETENT VEIN, EXTREMITY, INCLUSIVE OF ALL IMAGING GUIDANCE AND MONITORING, PERCUTANEOUS, LASER; FIRST VEIN TREATED
36479	ENDOVENOUS ABLATION THERAPY OF INCOMPETENT VEIN, EXTREMITY, INCLUSIVE OF ALL IMAGING GUIDANCE AND MONITORING, PERCUTANEOUS, LASER; SECOND AND SUBSEQUENT VEINS TREATED IN A SINGLE EXTREMITY, EACH THROUGH SEPARATE ACCESS SITES (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
37700	LIGATION AND DIVISION OF LONG SAPHENOUS VEIN AT SAPHENOFEMORAL JUNCTION, OR DISTAL INTERRUPTIONS
37718	LIGATION, DIVISION, AND STRIPPING, SHORT SAPHENOUS VEIN
37722	LIGATION, DIVISION, AND STRIPPING, LONG (GREATER) SAPHENOUS VEINS FROM SAPHENOFEMORAL JUNCTION TO KNEE OR BELOW
37735	LIGATION AND DIVISION AND COMPLETE STRIPPING OF LONG OR SHORT SAPHENOUS VEINS WITH RADICAL EXCISION OF ULCER AND SKIN GRAFT AND/OR INTERRUPTION OF COMMUNICATING VEINS OF LOWER LEG, WITH EXCISION OF DEEP FASCIA
37760	LIGATION OF PERFORATOR VEINS, SUBFASCIAL, RADICAL (LINTON TYPE), INCLUDING SKIN GRAFT, WHEN PERFORMED, OPEN,1 LEG
37761	LIGATION OF PERFORATOR VEIN(S), SUBFASCIAL, OPEN, INCLUDING ULTRASOUND GUIDANCE, WHEN PERFORMED, 1 LEG
37765	STAB PHLEBECTOMY OF VARICOSE VEINS, 1 EXTREMITY; 10-20 STAB INCISIONS
37766	STAB PHLEBECTOMY OF VARICOSE VEINS, 1 EXTREMITY; MORE THAN 20 INCISIONS
37780	LIGATION AND DIVISION OF SHORT SAPHENOUS VEIN AT SAPHENOPOPLITEAL JUNCTION (SEPARATE PROCEDURE)
37799	UNLISTED PROCEDURE, VASCULAR SURGERY
76942	ULTRASONIC GUIDANCE FOR NEEDLE PLACEMENT (EG, BIOPSY, ASPIRATION, INJECTION, LOCALIZATION DEVICE), IMAGING SUPERVISION AND INTERPRETATION
93965	NONINVASIVE PHYSIOLOGIC STUDIES OF EXTREMITY VEINS, COMPLETE BILATERAL STUDY (EG, DOPPLER WAVEFORM ANALYSIS WITH RESPONSES TO COMPRESSION AND OTHER MANEUVERS, PHLEBORHEOGRAPHY, IMPEDANCE PLETHYSMOGRAPHY)
93970	DUPLEX SCAN OF EXTREMITY VEINS INCLUDING RESPONSES TO COMPRESSION AND OTHER MANEUVERS; COMPLETE BILATERAL STUDY
93971	DUPLEX SCAN OF EXTREMITY VEINS INCLUDING RESPONSES TO COMPRESSION AND OTHER MANEUVERS; UNILATERAL OR LIMITED STUDY

ICD-9 Codes that Support Medical Necessity

Group 1 Paragraph: It is the responsibility of the provider to code to the highest level specified in the ICD-9-CM (e.g., to the fourth or fifth digit). The correct use of an ICD-9-CM code listed below does not assure coverage of a service. The service must be reasonable and necessary in the specific case and must meet the criteria specified in this determination.

Coverage of CPT codes 76942, 93965, 93970 and 93971 is not limited to the ICD-9-CM codes listed below.

CPT Codes 36470, 36471, 36475, 36476, 36478, 36479, 37700, 37718, 37722, 37735, 37760, 37761, 37765, 37766, 37780 and 37799

Group 1 Codes:

451.0	PHLEBITIS AND THROMBOPHLEBITIS OF SUPERFICIAL VESSELS OF LOWER EXTREMITIES
451.2	PHLEBITIS AND THROMBOPHLEBITIS OF LOWER EXTREMITIES UNSPECIFIED
454.0	VARICOSE VEINS OF LOWER EXTREMITIES WITH ULCER
454.1	VARICOSE VEINS OF LOWER EXTREMITIES WITH INFLAMMATION
454.2	VARICOSE VEINS OF LOWER EXTREMITIES WITH ULCER AND INFLAMMATION
454.8	VARICOSE VEINS OF LOWER EXTREMITIES WITH OTHER COMPLICATIONS

459.31 CHRONIC VENOUS HYPERTENSION WITH ULCER
459.32 CHRONIC VENOUS HYPERTENSION WITH INFLAMMATION
459.33 CHRONIC VENOUS HYPERTENSION WITH ULCER AND INFLAMMATION

ICD-9 Codes that DO NOT Support Medical Necessity
Paragraph: Use of any ICD-9-CM code not listed in the "ICD-9-CM Codes that Support Medical Necessity" section of this LCD will be denied. In addition, the following ICD-9 CM codes are specifically listed as not supporting medical necessity for emphasis, and to avoid any provider errors.

Claims listing the following ICD-9-CM code will be considered as cosmetic and denied for lack of medical necessity:
448.1 Spider nevus

CPT codes 36470, 36471, 36475, 36476, 36478, 36479, 37700, 37718, 37722, 37735, 37760, 37761, 37765, 37766, 37780 and 37799 (when used to report "Trivex Procedure"), submitted for any of the following ICD-9-CM codes will be denied as not medically necessary:

Codes:
448.0 HEREDITARY HEMORRHAGIC TELANGIECTASIA
448.1 NEVUS NON-NEOPLASTIC
448.9 OTHER AND UNSPECIFIED CAPILLARY DISEASES
459.10 POSTPHLEBETIC SYNDROME WITHOUT COMPLICATIONS
459.11 POSTPHLEBETIC SYNDROME WITH ULCER
459.12 POSTPHLEBETIC SYNDROME WITH INFLAMMATION
459.13 POSTPHLEBETIC SYNDROME WITH ULCER AND INFLAMMATION
459.19 POSTPHLEBETIC SYNDROME WITH OTHER COMPLICATION

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General Information

Associated Information
Documentation Requirements:

The patient's medical record must contain documentation that fully supports the medical necessity for services included within this LCD. (Please see "Indications and Limitations of Coverage.") This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures.

The patient's medical record must document the following:

- history and physical findings supporting a diagnosis of symptomatic varicose veins;
- failure of an adequate trial of conservative treatment as described in the "Indications" section of this LCD;
- exclusion of other causes of edema, ulceration and pain in the limbs;
- performance of appropriate tests to confirm the presence and location of incompetent perforating veins;
- location and number of varicosities, level of incompetence of the vein and the veins involved; and
- necessity of utilizing ultrasound guidance, if used.

The medical record must also include pre-treatment photographs of the varicose veins for which claims for sclerotherapy are submitted to Medicare. These photographs must be made available to the Medicare Administrative Contractor (MAC) upon request for review.

Appendices:

Not applicable

Utilization Guidelines:

Coverage for podiatrists is limited by scope of practice specific to the state in which the service is provided.

Medicare recognizes that multiple injections are needed to perform sclerotherapy and that responses differ due to the anatomical site being treated. Medicare would not expect to see the following when performing sclerotherapy:

- More than three sclerotherapy sessions for each leg.
- Only one sclerotherapy service per treatment session should be reported for either leg, regardless of how many veins are treated per session.

Patients are not expected to require ablation of the saphenous vein by radiofrequency or laser more than once for either leg.

A duplex ultrasound examination will be allowed when performed within 1 week (preferably within 72 hours) of EFRA to check for any evidence of thrombus extension from the saphenofemoral junction into the deep system.

Sources of Information and Basis for Decision
This bibliography presents those sources that were obtained during the development of this policy. National Government Services is not responsible for the continuing viability of Web site addresses listed below.

American Academy of Dermatology. Guidelines of care for sclerotherapy treatment of varicose and telangiectatic leg veins. http://www.aadassociation.org/Guidelines/sclero.html. Accessed on May 3, 2005.

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Sadick N. Advances in the treatment of varicose veins: ambulatory phlebectomy, foam sclerotherapy, endovascular laser and radiofrequency closure. *Dermatologic Clinics*. 23(3). W.B. Saunders Company.

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Teruya T, Ballard J. New approaches for the treatment of varicose veins. *Surgical Clinics of North America*. 85(5). W.B. Saunders Company.

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Thibault P. Sclerotherapy and ultrasound-guided sclerotherapy: *The Vein Book*. London U. Elsevier Academic Press; 2007:189-199.

Trelles M. The 800-nm diode laser in the treatment of leg veins: Assessment at 6 months. *Journal of American Academy of Dermatology*. 54(2).

Other Medicare contractor policies consulted in development of the draft:

First Coast Service Options Local Coverage Determination (LCD) [L23082]

Sources added based on a reconsideration request:

Manfrini S, Vincenzo G, Danielsson G, et al. Endovenous management of saphenous vein reflux. Endovenous Reflux Management Study Group. *J Vasc Surg*. 2000;32:330-342.

Van Rij AM, Andre M, Jones GT, Hill G and Jiang P. Neovascularization and recurrent varicose veins: more histologic and ultrasound evidence. Department of Surgery, Dunadin School of Medicine, University of Otago, New Zealand. *J Vasc Surg*. 2004;40:298-302.

Van Rij AM, Jiang P, Solomon O, Ross CA, Hill G. Recurrence after varicose vein surgery: A prospective long-term clinical study with duplex ultrasound scanning and air plethysmography. Department of Surgery, Dunadin School of Medicine, University of Otago, New Zealand. *J Vasc Surg*. 2003;38:935-943.

Varicose Veins, Essentials of Diagnosis. *McGraw-Hill's Access Medicine*. Chapter 36, Veins & Lyphatics, The Veins, Disease of the Venous Sytem. http://www.acessmedicine.com. Accessed on April 8, 2009.

References reviewed for a reconsideration request received March 2014:

Bánhidy F, Ács N, Puhó EH, Czeizel AE. Varicose veins of lower extremities in pregnant women and birth outcomes. *Cent Eur J Public Health.* 2010;18(3):161–168.

Delaney CL, Russell DA, Iannos J, Spark JI. Is endovenous laser ablation possible while taking warfarin? *Phebology.* 2012;27(5):231-234.

Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg.* 2011;53:2S-48S.

Riesenman PJ, de Fritas DJ, Konigsberg SG, Kasirajan K. Noninterruption of warfarin therapy is safe and does not compromise outcome in patients undergoing endovenous laser therapy (EVLT). *Vasc Endovascular Surgery.* 2011;45(6):524-526.

Theivacumar NS, Gough MJ. Influence of warfarin on the success of endovenous laser ablation (EVLA) of the great saphenous vein (GSV). *Eur J Vasc Endovasc Surg.* 2009;38(4):506-510.

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Biemans AA, Kockaert M, Akkersdijk GP, et al. Comparing endovenous laser ablation, foam sclerotherapy, and conventional surgery for great saphenous varicose veins. *J Vasc Surg.* 2013;58(3):727-734.

Todd KL III, Wright DI, Gibson K, et al. The VANISH-2 study: a randomized, blinded, multicenter study to evaluate the efficacy and safety of polidocanol endovenous microfoam 0.5% and 1.0% compared with placebo for the treatment of saphenofemoral junction incompetence. *Phlebology.* 2014;29(9):608-618.

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Revision History Information

Please note: Most Revision History entries effective on or before 01/24/2013 display with a Revision History Number of "R1" at the bottom of this table. However, there may be LCDs where these entries will display as a separate and distinct row.

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
12/01/2014	R10	Revised verbiage in the "Abstract" section for foam sclerotherapy of the saphenous vein at its junction with the deep venous system to state that it lacks "sufficient" rather than "significant" evidence to support its widespread use. Added two (2) references to the "Sources of Information and Basis for Decision" section.	• Other
09/01/2014	R9	No comment and notice periods required and none given. This revision updates the NGS MAC numerical jurisdictional designation to the new MAC Lettered jurisdiction designation(s). No other changes were made to this LCD.	• Change to Lettered Jurisdiction Designation
07/01/2014	R8	Based on a reconsideration request, the following statements were added to the "Indications" section: Inability to tolerate compressive bandages or stockings and the reason for such intolerance must be documented in the medical record.	• Reconsideration Request

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
		Surgery, EFRA and laser ablation, or sclerotherapy are typically not performed for varicose veins that develop or worsen during pregnancy because most will spontaneously resolve or improve after delivery. The non-coverage for sclerotherapy, ligation and/or stripping of varicose veins, or endovenous ablation therapy for pregnant women and patients on anti-coagulant therapy was removed from the "Limitations" section. The non-coverage for "patients with the inability to tolerate compressive bandages or stockings" was also removed from this section. Five (5) references were added to the "Sources of Information and Basis for Decision" section. Minor template changes were made to reflect current template language. No comment and notice periods required and none given.	
10/25/2013	R7	10/25/2013: This LCD was revised to add the Jurisdiction K Maine, Massachusetts, New Hampshire, Rhode Island and Vermont Part B Contract Numbers 14112, 14212, 14312, 14412 and 14512. The CMS Statement of Work for the Jurisdiction K Medicare Administrative Contractor (MAC) requires that the contractor consolidate LCDs and retain the most clinically appropriate LCD within the jurisdiction. Coverage of each LCD begins when the state/contract number combination officially is integrated into the Jurisdiction. On the CMS Medicare Coverage Database, this date is known as either the Original Effective Date or the Revision Effective Date.	• Change in Assigned States or Affiliated Contract Numbers
10/18/2013	R6	10/18/2013: This LCD was revised to add the Jurisdiction K Maine, Massachusetts, New Hampshire, Rhode Island and Vermont Part A Contract Numbers 14111, 14211, 14311, 14411 and 14511. The CMS Statement of Work for the Jurisdiction K Medicare Administrative Contractor (MAC) requires that the contractor consolidate LCDs and retain the most clinically appropriate LCD within the jurisdiction. Coverage of each LCD begins when the state/contract number combination officially is integrated into the Jurisdiction. On the CMS Medicare Coverage Database, this date is known as either the Original Effective Date or the Revision Effective Date.	N/A
09/07/2013	R5	09/07/2013 - This LCD was revised to add the Jurisdiction 6 Illinois Part B Contract Number 06102, Minnesota Part B Contract Number 06202 and Wisconsin Part B Contract Number 06302. The CMS Statement of Work for the Jurisdiction 6 Medicare Administrative Contractor (MAC) requires that the contractor consolidate LCDs and retain the most clinically appropriate LCD within the jurisdiction. Coverage of each LCD begins when the state/contract number combination officially is integrated into the Jurisdiction. On the CMS Medicare Coverage Database, this date is known as either the Original Effective Date or the Revision Effective Date.	N/A
08/10/2013	R4	08/10/2013 - This LCD was revised to add the Jurisdiction 6 Minnesota Part A Contract Number 06201. The CMS Statement of Work for the Jurisdiction 6 Medicare Administrative Contractor (MAC) requires that the contractor consolidate LCDs and retain the most clinically appropriate LCD within the jurisdiction. Coverage of each LCD begins when the state/contract number combination officially is integrated into the Jurisdiction. On the CMS Medicare Coverage Database, this date is known as either the **Original Effective Date or the Revision Effective Date.**	N/A
07/13/2013	R3		N/A

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
		07/13/2013 - This LCD was revised to add the Jurisdiction 6 Illinois Part A Contract Number 06101 and Wisconsin MAC Part A Contract Number 06301. The CMS Statement of Work for the Jurisdiction 6 Medicare Administrative Contractor (MAC) requires that the contractor consolidate LCDs and retain the most clinically appropriate LCD within the jurisdiction. Coverage of each LCD begins when the state/contract number combination officially is integrated into the Jurisdiction. On the CMS Medicare Coverage Database, this date is known as either the Original Effective Date or the Revision Effective Date.	
04/01/2013	R2	R9 (effective 04/01/2013): CPT code 76937 was removed from the "CPT/HCPCS Codes" section and in the explanatory note in the "ICD-9 -CM Codes that Support Medical Necessity" section and replaced with CPT code 76942. This coding change is retroactive to November 1, 2012. Minor template changes were made to reflect current template language. No comment and notice periods required and none given.	N/A
		R8 (effective 11/01/2012): CPT code 76942 was removed from the "CPT/HCPCS Codes" section and in the explanatory note in the "ICD-9 -CM Codes that Support Medical Necessity" section and replaced with CPT code 76937. Annual LCD review per CMS *Program Integrity Manual,* Chapter 13, Section 13.4[C]. The entire LCD was reviewed. Minor template changes were made to reflect current template language. No comment and notice periods required and none given.	
		08/20/2012 - In accordance with Section 911 of the Medicare Modernization Act of 2003, carrier number 00630 is removed from this LCD. Effective on this date, claims processing for Indiana Part B is performed by Wisconsin Physician Services, the Part A/Part B MAC contractor for this state.	
		07/23/2012 - In accordance with Section 911 of the Medicare Modernization Act of 2003, fiscal intermediary numbers 00130 and 00452 are removed from this LCD. Effective on this date, claims processing for Indiana and Michigan is performed by Wisconsin Physician Services, the Part A/Part B MAC contractor for these states.	
11/01/2012	R1	R7 (effective 01/01/2012): Annual LCD review per CMS *Program Integrity Manual*, Chapter 13, Section 13.4[C]. The entire LCD was reviewed. Minor template changes were made to reflect current template language. No comment and notice periods required and none given.	N/A
		10/17/2011 - In accordance with Section 911 of the Medicare Modernization Act of 2003, fiscal intermediary numbers 00160 and 00332 are removed from this LCD. Effective on this date, claims processing for Kentucky –Part A and Ohio – Part A is performed by CGS Administrators, LLC, the Part A/Part B MAC contractor for these states.	
		05/16/2011 - In accordance with Section 911 of the Medicare Modernization Act of 2003, fiscal intermediary number 00453 is removed from this LCD. Effective on this date, claims processing for Virginia and West Virginia is performed by Palmetto Government Benefits Administration, the Part A/Part B MAC contractor for these states.	
		04/30/2011 - In accordance with Section 911 of the Medicare Modernization Act of 2003, carrier number 00660 is removed from this LCD. Effective on this date, claims processing for Kentucky is performed by Cigna Government Services, the Part A/Part B MAC contractor for this state.	

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change

R6 (effective 01/01/2011): Annual LCD review per CMS *Program Integrity Manual,* Chapter 13, Section 13.4[C]. The entire LCD was reviewed. Minor template changes were made to reflect current template language. No comment and notice periods required and none given

R5 (effective 01/01/2010): LCD revised for annual HCPCS update for 2010. Based on the 2010 CPT Book, the following statement was added to the "Limitations" section:

CPT codes 37760 and 37761 should not be reported in conjunction with CPT codes 76937, 76942, 76998 or 93971.

CPT code 37761 was added to the "CPT/HCPCS Codes" section. The terminology for CPT code 37760 was revised for dates of service on or after 01/01/2010.

CPT code 37761 was added to the explanatory notes in the "ICD-9-CM Codes that Support Medical Necessity" and "ICD-9-CM Codes that DO NOT Support Medical Necessity" sections.

The following explanatory note was added to the "ICD-9-CM Codes that Support Medical Necessity" section:

Coverage of CPT codes 76942, 93965, 93970 and 93971 is not limited to the diagnoses listed below.

Minor template changes were made to reflect current template language. No comment and notice periods required and none given.

R4 (effective 05/01/2009): Source of revision – Internal. The LCD was revised as follows:

As a result of conflicting information, the limitation listed below was revised:

Cosmetic surgery is statutorily excluded from coverage by Medicare. The following interventional treatments are considered to be cosmetic and will be denied as such:

CPT Codes 36470, 36471, 36475, 36476, 36478, 36479, 37700, 37718, 37722, 37735, 37760, 37765, 37766, 37780 and 37799 were added as an explanatory note to the "ICD-9-CM Codes that Support Medical Necessity" section.

ICD-9-CM codes 459.10, 459.11, 459.12, 459.13 and 459.19 were inadvertently included in the "ICD-9-CM Codes that Support Medical Necessity" section and were removed.

CPT code 36468 was removed from the explanatory note in the "ICD-9-CM Codes that DO NOT Support Medical Necessity" section.

Corrected several sources in the "Sources of Information and Basis for Decision" section to reflect the guidelines in the *AMA Manual of Style*.

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change

The changes listed in this revision do NOT apply to the states of Maine (contract 00180), Massachusetts (contract 00181), or Vermont and New Hampshire (contract 00270); however, all other instructions, coverage provisions, and requirements in the LCD remain in effect for these states.

No comment and notice periods required and none given.

R3 (effective 03/01/2009): Source of revision – Internal. Minor template changes were made to reflect current template language.

R2 This revised LCD is effective for all National Government Services jurisdictions on July 18, 2008 with these exceptions: for Connecticut – Part B the LCD is effective on August 1, 2008; for Upstate New York – Part B, the LCD is effective on September 1, 2008; and for New York and Connecticut – Part A, the LCD is effective on November 14, 2008. For New York – Part A (contract 00308), the content of this SIA is currently in effect but the SIA will be transferred to the J-13 contract number 13201 on November 14, 2008.

This LCD was revised to add the Jurisdiction 13 (J-13) MAC contractor numbers.

The CMS Statement of Work for the J13 Medicare Administrative Contract (MAC) requires that the contractor retain the most clinically appropriate LCD within the jurisdiction. This NGS policy is being promulgated to the J13 MAC as the most clinically appropriate LCD within that jurisdiction.

The NGS roster of LCDs has been developed under the combined experience of seven Medicare contractor medical directors. The criteria for inclusion in this roster includes areas of identified CERT errors, especially repetitive errors; high volume/high dollar/pervasive problems; patient safety issues; potential for automation; beneficiary access to new technology; implementation of NCD; narrative medical necessity parameters for medical review and provider education; and CMS/law enforcement mandates.

NGS LCDs have undergone an advice and comment process from the providers in 23 states. This advice and comment process, the most comprehensive among all Medicare contractors, has ensured that NGS policies have benefited from the most in-depth and scientifically rigorous scrutiny. The NGS policy development process has resulted in the most clinically appropriate LCDs for providers and Medicare beneficiaries.

Added the following reference which was provided with a reconsideration request to the "Sources of Information and Basis for Decision" section:

Thibault P. Sclerotherapy and ultrasound-guided sclerotherapy: *The Vein Book*. London U. Elsevier Academic Press; 2007:189-199.

R1 (effective 02/01/2008): Sources of revision - Reconsideration request. Sources of information were added. In the Limitation section, the paragraph outlining cosmetic surgery exclusion has been clarified. The paragraph for the ICD-9-CM codes that do not support medical necessity has been clarified. No comment and notice periods required and none given.

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change

08/18/2008 - In accordance with Section 911 of the Medicare Modernization Act of 2003, fiscal intermediary number 00454 was removed from this LCD as the claims processing for American Samoa, California, Guam, Hawaii, Nevada and Northern Mariana Islands was transitioned to Palmetto GBA, the Part A/Part B MAC contractor in these states.

11/14/2008 - In accordance with Section 911 of the Medicare Modernization Act of 2003, fiscal intermediary number 00308 is removed from this LCD. Effective on this date, claims processing for Delaware is performed by Highmark Medicare Services, the Part A/Part B MAC contractor for this state, and the claims processing for New York and Connecticut is performed by National Government Services under the J-13 MAC contract; carrier number 00805 is removed, and claims processing for New Jersey is performed by Highmark Medicare Services, the Part A/Part B MAC contractor for this state.

05/15/2009 - In accordance with Section 911 of the Medicare Modernization Act of 2003, fiscal intermediary numbers 00180 and 00181 were removed from this LCD as the claims processing for Maine and Massachusetts was transitioned to NHIC, the Part A/Part B MAC contractor in these states.

06/05/2009 - In accordance with Section 911 of the Medicare Modernization Act of 2003, fiscal intermediary number 00270 was removed from this LCD as the claims processing for New Hampshire and Vermont was transitioned to NHIC, the Part A/Part B MAC contractor in these states.

****

The following are administrative notes entered by the Medicare Coverage Database Contractor:

11/09/2008 - The description for CPT/HCPCS code 37765 was changed in group 1
11/09/2008 - The description for CPT/HCPCS code 37766 was changed in group 1

11/15/2009 - The description for CPT/HCPCS code 37760 was changed in group 1
11/15/2009 - The description for CPT/HCPCS code 37765 was changed in group 1
11/15/2009 - The description for CPT/HCPCS code 37766 was changed in group 1

3/7/2010 - The description for Bill Type Code 73 was changed
3/7/2010 - The description for Bill Type Code 77 was changed

8/1/2010 - The description for Bill Type Code 11 was changed
8/1/2010 - The description for Bill Type Code 12 was changed
8/1/2010 - The description for Bill Type Code 13 was changed
8/1/2010 - The description for Bill Type Code 71 was changed
8/1/2010 - The description for Bill Type Code 73 was changed
8/1/2010 - The description for Bill Type Code 85 was changed

8/1/2010 - The description for Revenue code 0330 was changed
8/1/2010 - The description for Revenue code 0360 was changed
8/1/2010 - The description for Revenue code 0490 was changed
8/1/2010 - The description for Revenue code 0510 was changed
8/1/2010 - The description for Revenue code 0520 was changed

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
		11/21/2010 - For the following CPT/HCPCS codes either the short description and/or the long description was changed. Depending on which description is used in this LCD, there may not be any change in how the code displays in the document: 36468 descriptor was changed in Group 1 36475 descriptor was changed in Group 1 36476 descriptor was changed in Group 1 36478 descriptor was changed in Group 1 37765 descriptor was changed in Group 1	

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Associated Documents

Attachments N/A

Related Local Coverage Documents Article(s) A44614 - Varicose Veins of the Lower Extremity, Treatment of - Supplemental Instructions Article opens in new window

Related National Coverage Documents N/A

Public Version(s) Updated on 11/20/2014 with effective dates 12/01/2014 - N/A Updated on 08/29/2014 with effective dates 09/01/2014 - 11/30/2014 Updated on 06/16/2014 with effective dates 07/01/2014 - 08/31/2014 Updated on 08/27/2013 with effective dates 10/25/2013 - 06/30/2014 Some older versions have been archived. Please visit the MCD Archive Site opens in new window to retrieve them. Back to Top

Keywords

N/A Read the **LCD Disclaimer opens in new window** Back to Top

Developmental Coordination Disorder

Question: Should developmental coordination disorder be removed from the Prioritized List?

Question source: Alison Little, MD, MPH, OHP Medical Director

Issue: Developmental co-ordination disorder (ICD-9 315.4) is also known as clumsiness syndrome, dyspraxia syndrome, or specific motor development disorder. This condition has been reviewed several times by the HSC/HERC. The last review of this code was part of a large scale review of codes on the Excluded List by DMAP and HERC staff, at which time it was moved from the Excluded List to two dysfunction lines. This review was not in-depth and did not include a review of the evidence or effectiveness of treatment. The medical plans are asking that it be replaced on the Non-Covered List.

Currently, 315.4 is currently on 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. The equivalent ICD-10 code, F82 (Specific developmental disorder of motor function) is also on these lines. ICD-10 F82 has the same sub-diagnoses (clumsy child syndrome, developmental coordination disorder, developmental dyspraxia) as ICD-9 315.4.

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.
MOTION: Delete the Coordination Disorder guideline from Line 336. Motion carries 4-0.

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.

HERC Staff Recommendation

1) 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”

Unspecified Developmental Diagnoses

Question:

1) Should ICD-9 315.9 (Unspecified delay in development) continue to be on the Prioritized List?
2) Should ICD-9 348.9 (Unspecified condition of brain) continue to be on the Prioritized list?

Question source: Alison Little, MD, OHP medical director

Issue: ICD-9 315.9 is currently on 2 dysfunction lines. The ICD-10 equivalents are on the Recommended for Non-Coverage Table: F89 (Unspecified disorder of psychological development) and F81.9 (Developmental disorder of scholastic skills, unspecified). The other codes in the 315 series specify various learning disorders.

ICD-9 348.9 is currently on all 4 dysfunction lines. The ICD-10 equivalent, G93.9 (Disorder of brain, unspecified) is on the Recommended for Non-Coverage Table. ICD-9 348.9 has many subdiagnoses, including cerebellar deficiency syndrome, lesion of brain, and mass lesion of brain. However, most of conditions can be coded with other, more specific ICD-9 codes. The other subdiagnoses include disorder of brain or non-specific brain syndrome.

There is no mention of these codes in the HOSC minutes.

From Dr. Little:

> One [code] that is being used is 315.9, unspecified delay in development. Any toddler who is below the median in developmental tasks is qualifying for 30 visits of OT.
>
> I am seeing lots of sensory integration disorder, and because it doesn't have a code (that I have been able to find), it comes in with 348.9, unspecified condition of the brain, as do many vague, mild developmental delays. It is currently on all the dysfunction lines.

From Dr. John Kolsbun, Allcare

> We discussed this situation within AllCare. We have found that these two codes are being utilized for payment for a wide range of conditions, many of which are clearly not intended to be paid for. Our feeling at AllCare is that these two codes could be eliminated, and that if a member is truly in need of supplies or services, that more appropriate coding can be utilized to get payment for these services.

HERC staff recommendations:

1) Remove ICD-9 315.9 (Unspecified delay in development) from lines 297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS and 381 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
    a. Place ICD-9 315.9 on the DMAP "Undefined" List
2) Remove ICD-9 348.9 (Unspecified condition of brain) from lines 75 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES, 297, 349 NEUROLOGICAL DYSFUNCTION IN COMMUNICATION CAUSED BY CHRONIC CONDITIONS and 318

Place ICD-9 348.9 on the DMAP "Undefined" List

Section 5.0

Guidelines

Ventral Hernia Guideline Issue Summary

Question: How should the complicated hernia guideline be modified with regard to ventral hernias with obstruction?

Question source: Gael Martin, Government Program Supervisor for Health Care Services, Moda Health

Issue:

Guideline note 24, which defines complicated hernias, is confusing about the intent with regard to ventral hernias. The goal of excluding ventral hernias from the language was because many of them are incarcerated (irreducible) by definition. For ventral hernias, incarceration is common and is not dangerous; in contrast, for many other types of hernias, incarceration is a predisposing step toward obstruction and gangrene. If a ventral hernia were to somehow cause obstruction or gangrene, this would, of course, be intended for coverage.

Current Prioritized List Status

Line: 172
Condition: COMPLICATED HERNIAS; UNCOMPLICATED INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER;
PERSISTENT HYDROCELE (See Guideline Notes 24,63,64,65)
Treatment: REPAIR
ICD-9: 550.00-550.93,551.00-551.29,551.8-551.9,552.00-552.29,552.8-552.9,603.0,603.8-603.9
CPT: 44050,44120,49491-49572,49582,49587,49590,49650-49659,55040-55060,64505-64530,96127,98966-98969,
99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-99412,99429-99449,99468-
99480,99487-99498,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463,G0466,G0467

Line: 530
Condition: UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN INGUINAL HERNIA IN CHILDREN AGE 18
AND UNDER OR DIAPHRAGMATIC HERNIA) (See Guideline Notes 64,65)
Treatment: REPAIR
ICD-9: 550.90-550.93,553.00-553.29,553.8-553.9
CPT: 44050,49250,49505,49520,49525-
49550,49555,49560,49565,49568,49570,49580,49585,49590,49650-49659,
55540,96127,98966-98969,99051,99060,99070,99078,99184,99201-99239,99281-99285,99291-99404,99408-
99412,99429-99449,99468-99480,99487-99498,99605-99607
HCPCS: G0396,G0397,G0406-G0408,G0425-G0427,G0463,G0466,G0467

GUIDELINE NOTE 24, COMPLICATED HERNIAS
Line 172
Complicated hernias (excluding ventral hernias) are included on this line if they are incarcerated (defined as non-reducible by physical manipulation) or have symptoms of obstruction and/or strangulation. Chronic incarceration that does not place the patient at risk for impending strangulation (e.g. such as a large ventral hernia with loss of domain), is included on Line 530

Ventral Hernia Guideline Issue Summary

UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER OR DIAPHRAGMATIC HERNIA).

Line 172 ventral hernia ICD 10 codes

Code	Code description
K43.6	Other and unspecified ventral hernia with obstruction, without gangrene
K43.7	Other and unspecified ventral hernia with gangrene

Line 530 ventral hernia ICD 10 code

Code	Code Description
K43.9	Ventral hernia without obstruction or gangrene

Recommendations:

1) **Modify Guideline Note 24 as follows:**

   GUIDELINE NOTE 24, COMPLICATED HERNIAS
   Line 172, 530
   Complicated hernias ~~(excluding ventral hernias)~~ are included on ~~this line~~ Line 172 if they ~~are incarcerated (defined as non-reducible by physical manipulation) or have~~ cause symptoms of obstruction and/or strangulation. ~~Chronic incarceration that does not place the patient at risk for impending strangulation (e.g. such as a large ventral hernia with loss of domain), is included on Line 530 UNCOMPLICATED HERNIA AND VENTRAL HERNIA (OTHER THAN INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER OR DIAPHRAGMATIC HERNIA).~~ Incarcerated hernias (defined as non-reducible by physical manipulation) are also included on Line 172, excluding ventral hernias. Incarcerated ventral hernias are included on Line 530, because the chronic incarceration of large ventral hernias does not place the patient at risk for impending strangulation.

2) Rename Line 530 UNCOMPLICATED HERNIA (OTHER THAN INGUINAL HERNIA IN CHILDREN AGE 18 AND UNDER OR DIAPHRAGMATIC HERNIA); ~~AND~~ INCARCERATED VENTRAL HERNIA

Other Penile Anomalies

Question: What conditions coded by ICD-9 752.69 (Other penile anomalies) should be covered and what restrictions on any of these diagnoses should be made?

Question source: Allison Little, MD MPH, OHP medical director

Issue: ICD-9 752.69 as many subdiagnoses, some of which are medically important and some are not. This code is currently found on line 438 HYPOSPADIAS AND EPISPADIAS. The ICD-10 equivalent is Q55.69 (Other congenital malformation of penis) which is also found on line 438. Other congenital or acquired conditions of the penis, such as congenital chordee and hidden penis, are found on line 438 and have guidelines which specify when repair is covered.

Many of the subdiagnoses under ICD-9 752.69 have unique codes in ICD-10. These codes were generally placed on line 438 HYPOSPADIAS AND EPISPADIAS and line 667 GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY. There is currently no guideline note delineating when these codes should be included on the upper or lower line.

Subdiagnoses of ICD-9 752.69

Diagnosis	**ICD-10 Code**	**ICD-10 code Placement**
Aplasia of penis	Q55.5 Congenital absence and aplasia of penis	**438** HYPOSPADIAS AND EPISPADIAS
Congenital absence of penis	Q55.5	**438**
Congenital anomaly of penis	Q55.69 Other congenital malformation of penis	**438**
Congenital familial idiopathic priapism		
Congenital hypoplasia of penis	Q55.62 Hypoplasia of penis	**667** GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
Congenital lateral curvature of penis	Q55.61 Curvature of penis (lateral)	**438** **667**
Congenital penile adhesion		
Congenital penile torsion	Q55.63 Congenital torsion of penis	**438** **667**
Diphallus		
Finding of appearance of penis		
Hooded penis		
Paraspadias	Q54.9 Hypospadias, unspecified	**438** **667**
Rotated penis		
Short preputial frenulum		
Webbed penis		

The specific medical director question which resulted in this review regarded congenital penile torsion. In this anomaly, the penile shaft is rotated. In one review, repair of this anomaly was only recommended if accompanied by congenital chordee or hypospadias. Otherwise, repair

was felt to be cosmetic and appeared to have no relation to penile function. Congenital penile torsion has its own code in ICD-10 (Q55.63).

Priapism (ICD-9 607.3) is located on line 331 FUNCTIONAL AND MECHANICAL DISORDERS OF THE GENITOURINARY SYSTEM INCLUDING BLADDER OUTLET OBSTRUCTION.

Utilization:
During CY 2013 there were 3792 units or service billed for CCO/MCO vs 123 for FFS, representing 317 unique individuals. $1.1 million was billed, with about $325,000 allowed.

Current guidelines for conditions on line 483

GUIDELINE NOTE 73, CONGENITAL CHORDEE

Line 438

Congenital chordee (ICD-10-CM Q54.4/ICD-9-CM 752.63) is included on Line 438 only for severe cases (35 degrees of curvature or greater) and for all cases associated with hypospadias.

GUIDELINE NOTE 89, REPAIR OF HIDDEN PENIS

Line 438

Repair of hidden penis (ICD-10-CM Q55.64/ICD-9-CM 752.65) is only covered if the patient has documented urinary retention, repeated urinary tract infections, meatitis, or balanitis.

Expert Input: Dr. Steven Skoog, OHSU Pediatric Urology

Aplasia of the penis requires repair, but occurs very rarely. Hypoplasia should be covered if associated with hypospadias. Priapism is a surgical emergency, regardless of the cause, and must be treated. The diagnoses that results in curvature can result in voiding problems. Lateral curvature diagnoses should be covered if more than 35 degrees of curvature of if the child has voiding issues. Ventral curvature is chordee and should have the requirements in the current guideline. Torsion should be covered if more than 60 degree or if associated with chordee or hypospadias. Penile adhesions are related to the foreskin. The congenital type is normal and self-resolves. Acquired adhesions are related to circumcisions, dense adhesions results in curvature and can lead to infection. Treat adhesions with topical steroids, rarely a surgical issue. Hooded penis/concealed penis/hidden penis/webbed penis—all the same issue. Recommends using the current guideline restrictions for hidden penis.

Other Penile Anomalies

HERC staff recommendation

1) Add ICD-9 752.69 (Other penile anomalies) to line 667 GENITOURINARY CONDITIONS WITH NO OR MINIMALLY EFFECTIVE TREATMENTS OR NO TREATMENT NECESSARY
2) Adopt a new guideline regarding repair of anomalies of penis
    a. Delete current GN73 and GN89

GUIDELINE NOTE XXX, PENILE ANOMALIES

Lines 438, 667

Anomalies of the penis (ICD-9 752.63, 752.65, 752.69/ICD-10 Q54.4, Q55.5, Q55.6x) are included on line 438 only when they

1) Are associated with hypospadias, OR
2) Result in documented urinary retention, OR
3) Result in repeated urinary tract infections, OR
4) Result in recurrent infections such as meatitis or balanitis, OR
5) Involve 35 degrees of curvature or greater for conditions resulting in lateral or ventral curvature, OR
6) Involve 60 degrees of rotation or greater for conditions resulting in penile torsion, OR
7) Involve aplasia/congenital absence of the penis.

Otherwise, these diagnoses are included on line 667.

~~**GUIDELINE NOTE 73, CONGENITAL CHORDEE**~~

~~*Line 438*~~

~~Congenital chordee (ICD-10-CM Q54.4/ICD-9-CM 752.63) is included on Line 438 only for severe cases (35 degrees of curvature or greater) and for all cases associated with hypospadias.~~

~~**GUIDELINE NOTE 89, REPAIR OF HIDDEN PENIS**~~

~~*Line 438*~~

~~Repair of hidden penis (ICD-10-CM Q55.64/ICD-9-CM 752.65) is only covered if the patient has documented urinary retention, repeated urinary tract infections, meatitis, or balanitis.~~

Review
Special Issue: Penile Anomalies in Children
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Abnormalities of Penile Curvature: Chordee and Penile Torsion

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Congenital chordee and penile torsion are commonly observed in the presence of hypospadias, but can also be seen in boys with the meatus in its orthotopic position. Varying degrees of penile curvature are observed in 4–10% of males in the absence of hypospadias. Penile torsion can be observed at birth or in older boys who were circumcised at birth. Surgical management of congenital curvature without hypospadias can present a challenge to the pediatric urologist. The most widely used surgical techniques include penile degloving and dorsal plication. This paper will review the current theories for the etiology of penile curvature, discuss the spectrum of severity of congenital chordee and penile torsion, and present varying surgical techniques for the correction of penile curvature in the absence of hypospadias.

KEYWORDS: penis, chordee, torsion, child, surgery

INTRODUCTION

Ideally, a penis should be straight; i.e., the corpora straight, the skin sufficiently lax to avert traction, and the glans with no element of torsion. Penile curvature, including chordee and penile torsion, can be found in boys with and without hypospadias. While the causes of chordee are evident in boys with hypospadias, its precise etiology, as well as that of torsion, in the absence of hypospadias, remain incompletely understood. Recent studies have furthered our understanding of the possible etiology and previously proposed explanations have been revised, which largely resulted in changes in surgical techniques. The current surgical strategies are largely successful in correcting the penis with abnormal curvature.

EPIDEMILOGY

Penile curvature is a spectrum of disease most commonly associated with hypospadias, but is not uncommon in boys with an orthotopic meatus. The prevalence of hypospadias in the general population is approximately 1 in 300[1] and as many as one-fourth will have chordee[1]. In the U.S., the nationwide Birth Defects Monitoring Program (BDMP) reported a doubling in the rates of hypospadias since the 1970s to about 4 per 1000 in 1993[2]. Given that chordee occurs in the absence of hypospadias and that some boys are not diagnosed until later in life when the foreskin is retracted, the true incidence of chordee

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Section 6.0

Previously Discussed Items

Back Line Reorganization Outstanding Issues

Issue: The back line reorganization plan was approved at the March, 2015 VBBS/HERC meetings. However, several issues remain incompletely resolved or not addressed or have arisen since the last meeting.

Outstanding Back Issues:

1) The non-urgent surgical line title requires clarification. This will clarify how this line differs from line 351 CONDITIONS OF THE BACK AND SPINE WITH URGENT SURGICAL INDICATIONS
    a. Recommendation: Rename the lower surgical line Line 532 CONDITIONS OF THE BACK AND SPINE WITHOUT URGENT SURGICAL INDICATIONS
2) Placement of CPT 62310 (Injection(s), of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, includes contrast for localization when performed, epidural or subarachnoid; cervical or thoracic)
    a. Currently Ancillary
    b. Back line review moved to Services Recommended for Non-Coverage Table
    c. Recommendation: Add CPT 62310 to lines 75 NEUROLOGICAL DYSFUNCTION IN BREATHING, EATING, SWALLOWING, BOWEL, OR BLADDER CONTROL CAUSED BY CHRONIC CONDITIONS; ATTENTION TO OSTOMIES and 297 NEUROLOGICAL DYSFUNCTION IN POSTURE AND MOVEMENT CAUSED BY CHRONIC CONDITIONS
        i. Matches other placements of 62311 (the lumbar equivalent)
3) Intrathecal/epidural medication pumps
    a. CPT 62360-62362 (Implantation or replacement of device for intrathecal or epidural drug infusion) were added to all three surgical lines (351,366 and 532). These codes are currently not on any back lines and it has been the intent of the HSC/HERC to not cover this treatment for back pain. These codes are also on various chemotherapy and dysfunction lines.
        i. Remove CPT 62360-62362 from lines 351, 366 and 532
    b. CPT 62355 (Removal of previously implanted intrathecal or epidural catheter) and 62365 (Removal of subcutaneous reservoir or pump, previously implanted for intrathecal or epidural infusion) are currently on lines 351, 366 and 532
        i. Remove CPT 62355 and 62365 and keep on their current placement on a complications line
    c. Guideline note 72 was not reviewed as part of the back lines reorganization
        i. CPT 62367-62368 were added to lines 351, 366 and 532. CPT 62369-62370 also refer to electronic analysis of intrathecal pumps and are on these back surgical lines
        ii. Recommendation is modify GN72 as shown below

            GUIDELINE NOTE 72, ELECTRONIC ANALYSIS OF INTRATHECAL PUMPS

            Lines ~~374,545,~~ 351, 366, 532, 612

            Electronic analysis of intrathecal pumps, with or without programming (CPT codes 62367-~~62368~~62370), is included on these lines only for pumps implanted prior to April 1, 2009.
4) Epidural steroid injection guideline
    a. Clarify the definition of radiculopathy
    b. Consider adding active therapy modalities as a requirement for injections

   c. See staff recommendations after following review
5) Diagnostic Guideline D4
   a. Errors in asterisks
   b. Changes to footnotes

Back Line Reorganization Outstanding Issues

Epidural steroid injections

There were several outstanding questions regarding the epidural steroid injection guideline.

1) Whether to include radicular pain as an indication for epidural steroid injections.
2) Whether to require some type of active therapy, i.e. use the injection to allow patients to be more active/involved with PT, etc. rather than just passively relying on the injection for pain relief

Evidence

1) **AHRQ 2015**, meta-analysis of percutaneous interventions for low back pain
    a. N=78 RCTs for epidural injections
    b. Definition of radicular pain differed among studies. The review authors defined radiculopathy as presence of leg pain (typically worse than back pain), with or without sensory deficits or weakness, in a nerve root distribution. A number of studies used the term "sciatica," which was classified as radiculopathy.
    c. For epidural corticosteroid injections versus placebo interventions for radiculopathy, the only statistically significant effects were on mean improvement in pain at immediate-term follow-up (weighted mean difference [WMD] –7.55 on a 0 to 100 scale, 95% CI –11.4 to –3.74) (strength of evidence [SOE]: moderate), mean improvement in function at immediate-term follow-up when an outlier trial was excluded (standardized mean difference [SMD] –0.33, 95% CI –0.56 to –0.09) (SOE: low), and risk of surgery at short-term follow-up (relative risk [RR] 0.62, 95% CI 0.41 to 0.92) (SOE: low). The magnitude of effects on pain and function was small, did not meet predefined thresholds for minimum clinically important differences, and there were no differences on outcomes at longer-term follow-up. Trials of epidural corticosteroid injections for radiculopathy versus nonplacebo interventions did not clearly demonstrate effectiveness (SOE: insufficient to low).
    d. Evidence was limited for epidural corticosteroid injections versus placebo interventions for spinal stenosis (SOE: low to moderate) or nonradicular back pain (SOE: low), but showed no differences in pain, function, or likelihood of surgery.
    e. **Conclusions:** Epidural corticosteroid injections for radiculopathy were associated with immediate improvements in pain and might be associated with immediate improvements in function, but benefits were small and not sustained, and there was no effect on long-term risk of surgery. Evidence did not suggest that effectiveness varies based on injection technique, corticosteroid, dose, or comparator. Limited evidence suggested that epidural corticosteroid injections are not effective for spinal stenosis or nonradicular back pain.
2) Summary of evidence from the CEBP table presented at the March 2015 meeting
    a. Epidural steroid injections for non-radicular back pain had insufficient evidence of effectiveness and was not recommended for coverage
    b. Epidural steroid injections for radicular low back pain due to herniated lumbar disc had moderate evidence of effectiveness for short term benefit and was recommended for coverage with a weak recommendations
3) Coverage guidance "box language" on epidural steroid injections for low back pain
    a. For radicular low back pain, epidural steroid injections are recommended for coverage for patients with persistent radiculopathy due to herniated lumbar disc; it is recommended that shared decision-making regarding epidural steroid

injection include a specific discussion about inconsistent evidence showing moderate short-term benefits, and lack of long-term benefits. If an epidural steroid injection does not offer benefit, repeated injections are not recommended for coverage.

b. Epidural steroid injections are not recommended for coverage for central spinal canal stenosis.

HERC staff summary:
The evidence base for epidural steroid injections defines radiculopathy as radicular pain with or without weakness or sensory deficits. The current guideline wording includes only weakness and sensory deficits as covered indications, which does not match the evidence base. There is no requirement for participation in physical therapy or other active treatment modality along with the injection in the current guideline. It was the intent of the Back Lines Reorganization Taskforce that epidural steroid injections only be included for coverage if such injections allowed more active participation in rehabilitation activities.

HERC staff recommendations

1) Modify GN105 as shown below
   a. Modify the definition of radiculopathy to correspond with the definition used in the studies used for determining the effectiveness of this therapy
   b. Require participation in physical therapy or similar active treatment modality

GUIDELINE NOTE 105, EPIDURAL STEROID INJECTIONS FOR LOW BACK PAIN

Line MMM

Epidural lumbar steroid injections (CPT 62311, 64483, 64484) are included on this line for patients with persistent radiculopathy due to herniated lumbar disc, where radiculopathy is defined as pain, weakness, or sensory deficits in a nerve root distribution. ~~showing objective evidence of one or more of the following:~~

~~A) Markedly abnormal reflexes~~
~~B) Segmental muscle weakness~~
~~C) Segmental sensory loss~~
~~D) EMG or NCV evidence of nerve root impingement~~

One epidural steroid injection is included on ~~these lines~~ this line; a second epidural steroid injection may be provided after 3-6 months only if objective evidence of 3 months of sustained pain relief was provided by the first injection. It is recommended that shared decision-making regarding epidural steroid injection include a specific discussion about inconsistent evidence showing moderate short-term benefits, and lack of long-term benefits. Epidural lumbar steroid injections are not included on ~~these lines~~ this line for spinal stenosis or for patients with low back pain without radiculopathy. Epidural steroid injections are only included on this line when the patient is also participating in an active therapy such as physical therapy or home exercise therapy.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-percutaneous-low-back.aspx

Back Line Reorganization Outstanding Issues

Diagnostic Guideline D4 Corrections

1) HERC staff recommendations:
    a. Modify D4 as shown below
        i. Asterisks in the 6th entry are in an incorrect position
        ii. Asterisks in the last entry are incorrect
        iii. Definition of radiculopathy should be changed to match the definition adopted for GN105
        iv. The 3rd footnote should be modified to remove inference that epidural steroid injections are appropriate for spinal stenosis

DIAGNOSTIC GUIDELINE D4, ADVANCED IMAGING FOR LOW BACK PAIN

In patients with non-specific low back pain and no "red flag" conditions [see Table D4], imaging is not a covered service; otherwise work up is covered as shown in the table.
Electromyelography (CPT 96002-4) is not covered for non-specific low back pain.

Table D4
Low Back Pain - Potentially Serious Conditions ("Red Flags") and Recommendations for Initial Diagnostic Work-up

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
Cancer	• History of cancer with new onset of LBP	MRI	ESR
	• Unexplained weight loss • Failure to improve after 1 month • Age >50 years • Symptoms such as painless neurologic deficit, night pain or pain increased in supine position	Lumbosacral plain radiography	
	• Multiple risk factors for cancer present	Plain radiography or MRI	
Spinal column infection	• Fever • Intravenous drug use • Recent infection	MRI	ESR and/or CRP
Cauda equina syndrome	• Urinary retention • Motor deficits at multiple levels • Fecal incontinence • Saddle anesthesia	MRI	None
Vertebral compression fracture	• History of osteoporosis • Use of corticosteroids • Older age	Lumbosacral plain radiography	None
Ankylosing spondylitis	• Morning stiffness • Improvement with exercise • Alternating buttock pain • Awakening due to back pain during the second part of the night • Younger age	Anterior-posterior pelvis plain radiography	ESR and/or CRP, HLA-B27
Nerve compression/ disorders (e.g. herniated disc with radiculopathy)	• Back pain with leg pain in an L4, L5, or S1 nerve root distribution present < 1 month • Positive straight-leg-raise test or crossed straight-leg-raise test	None	None
	• Radiculopathic** signs** present >1 month • Severe/progressive neurologic deficits (such as foot drop), progressive motor weakness	MRI***	Consider EMG/NCV
Spinal stenosis	• Radiating leg pain • Older age • Pain usually relieved with sitting (Pseudoclaudication a weak predictor)	None	None

Possible cause	Key features on history or physical examination	Imaging*	Additional studies*
	• Spinal stenosis symptoms present >1 month	MRI**	Consider EMG/NCV

* Level of evidence for diagnostic evaluation is variable

** Radiculopathic signs are defined for the purposes of this guideline ~~is defined~~ as ~~the presence of as in Guideline Note 37 with any of the following:~~ pain, weakness, or sensory deficits in a nerve root distribution

~~A. Markedly abnormal reflexes~~
~~B. Segmental muscle weakness~~
~~C. Segmental sensory loss~~
~~D. EMG or NCV evidence of nerve root impingement~~
~~E. Cauda equina syndrome,~~
~~F. Neurogenic bowel or bladder~~
~~G. Long tract abnormalities~~

*** Only if patient is a potential candidate for surgery or, if indicated, lumbar epidural steroid injection

Red Flag: Red flags are findings from the history and physical examination that may be associated with a higher risk of serious disorders. CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; NCV = nerve conduction velocity.

Extracted and modified from Chou R, Qaseem A, Snow V, et al: Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007; 147:478-491.

The development of this guideline note was informed by a HERC coverage guidance. See http://www.oregon.gov/oha/herc/Pages/blog-adv-imaging-low-back.aspx

Technology Assessment

Technology Assessment Program

Pain Management Injection Therapies for Low Back Pain

Final
March 20, 2015

Prepared for:

Agency for Healthcare Research and Quality
540 Gaither Road
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Pain Management Injection Therapies for Low Back Pain

Technology Assessment Report

Project ID: ESIB0813

March 20, 2015

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This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2012-00014-I). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

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Persons using assistive technology may not be able to fully access information in this report. For assistance contact TAP@ahrq.hhs.gov

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Key Informants

In designing the study questions, the Evidence-based Practice Center (EPC) consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.
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In place of a Technical Expert Panel, CMS provided input to the Key Questions and scope of the report.

Peer Reviewers

Prior to publication of the final evidence report, the EPC sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Pain Management Injection Therapies for Low Back Pain

Structured Abstract

Objectives. Low back pain is common and injections with corticosteroids are a frequently used treatment option. This report reviews the current evidence on effectiveness and harms of epidural, facet joint, and sacroiliac corticosteroid injections for low back pain conditions.

Data Sources. A prior systematic review (searches through July 2008), electronic databases (Ovid MEDLINE, Scopus, and the Cochrane Libraries from January 2008 through October 2014), reference lists, and clinical trials registries.

Review Methods. Using predefined criteria, we selected randomized trials of patients with lumbosacral radiculopathy, spinal stenosis, nonradicular back pain, or chronic postsurgical back pain that compared effectiveness or harms of epidural, facet joint, or sacroiliac corticosteroid injections versus placebo or other interventions. We also included randomized trials that compared different injection techniques and large (sample sizes >1000) observational studies of back injections that reported harms. The quality of included studies was assessed, data were extracted, and results were summarized qualitatively and using meta-analysis on outcomes stratified by immediate- (1 week to ≤2 weeks), short- (2 weeks to ≤3 months), intermediate- (3 months to <1 year), and long-term (>1 year) followup.

Results. Seventy-eight randomized trials of epidural injections, 13 trials of facet joint injections, and one trial of sacroiliac injections were included. For epidural corticosteroid injections versus placebo interventions for radiculopathy, the only statistically significant effects were on mean improvement in pain at immediate-term followup (weighted mean difference [WMD] –7.55 on a 0 to 100 scale, 95% CI –11.4 to –3.74) (strength of evidence [SOE]: moderate), mean improvement in function at immediate-term followup when an outlier trial was excluded (standardized mean difference [SMD] –0.33, 95% CI –0.56 to –0.09) (SOE: low), and risk of surgery at short-term followup (relative risk [RR] 0.62, 95% CI 0.41 to 0.92) (SOE: low). The magnitude of effects on pain and function was small, did not meet predefined thresholds for minimum clinically important differences, and there were no differences on outcomes at longer-term followup. Evidence on effects of different injection techniques, patient characteristics, or comparator interventions estimates was limited and did not show clear effects. Trials of epidural corticosteroid injections for radiculopathy versus nonplacebo interventions did not clearly demonstrate effectiveness (SOE: insufficient to low).

Evidence was limited for epidural corticosteroid injections versus placebo interventions for spinal stenosis (SOE: low to moderate) or nonradicular back pain (SOE: low), but showed no differences in pain, function, or likelihood of surgery.

Studies found no clear differences between various facet joint corticosteroid injections (intra-articular, extra-articular [peri-capsular], or medial branch) and placebo interventions (SOE: low to moderate). There was insufficient evidence from one very small trial to determine effects of peri-articular sacroiliac joint corticosteroid injections injection (SOE: insufficient).

Serious harms from injections were rare in randomized trials and observational studies, but harms reporting was suboptimal (SOE: low).

Conclusions: Epidural corticosteroid injections for radiculopathy were associated with immediate improvements in pain and might be associated with immediate improvements in function, but benefits were small and not sustained, and there was no effect on long-term risk of surgery. Evidence did not suggest that effectiveness varies based on injection technique, corticosteroid, dose, or comparator. Limited evidence suggested that epidural corticosteroid injections are not effective for spinal stenosis or nonradicular back pain and that facet joint corticosteroid injections are not effective for presumed facet joint pain. There was insufficient evidence to evaluate effectiveness of sacroiliac joint corticosteroid injections.

Section 7.0

Coverage Guidances-EbGS

HERC Coverage Guidance

Coronary Artery Revascularization for Stable Angina

Oregon Health Evidence Review Commission

May 7, 2015

Oregon Health Authority

Oregon Health & Science University

Center For Evidence-based Policy

Revascularization
Primary evidence sources

Dolor, R.J., Melloni, C., Chatterjee, R., Allen LaPointe, N.M., Williams, J.B., Coeytaux, R.R., et al. (2012). *Treatment strategies for women with coronary artery disease*. Rockville, MD: AHRQ. Accessed on October 2, 2014, from http://effectivehealthcare.ahrq.gov/ehc/products/218/1227/CER66_Treatment-Coronary-Artery-Disease_FinalReport_20120816.pdf

Greenhalgh, J., Hockenhull, J., Rao, N., Dundar, Y., Dickson, R. C., & Bagust, A. (2010). Drug-eluting stents versus bare metal stents for angina or acute coronary syndromes. *The Cochrane Database of Systematic Reviews,* Issue 5. Accessed on March 6, 2015, from DOI:10.1002/14651858.CD004587.pub2.

Skinner, J.S., & Cooper, A. (2011). Secondary prevention of ischemic cardiac events. *BMJ Clinical Evidence*, 8 (206), 1-66. Accessed on March 6, 2015, from http://www.ncbi.nlm.nih.gov/pubmed/21875445

Revascularization
Additional evidence sources

Windecker, S., Stortecky, S., Stefanini, G.G., da Costa, B.R., Rutjes, A.W., Di Nisio, M., et. al. (2014). Revascularization versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *British Medical Journal (Clinical Research Edition)*, 23(348), g3859. Accessed on March 6, 2015, from DOI: 10.1136/bmj.g3859. *Fair quality*

Pursnani, S., Korley, F., Gopaul, R., Kanade, P., Chandra, N., Shaw, R.E., et. al. (2012). Percutaneous coronary intervention versus optimal medical therapy in stable coronary artery disease: A systematic review and meta-analysis of randomized clinical trials. *Circulation Cardiovascular Interventions*, *5*(4), 476-490. *Good quality*

Thomas, S., Gokhal, R., Boden, W.E., & Devereaux, P.J. (2012). A meta-analysis of randomized control trials comparing percutaneous coronary interventions with medical therapy in stable angina pectoris. *The Canadian Journal of Cardiology, 29*(4), 472-482. Accessed on March 6, 2015, from DOI: 10.1016/j.cjca.2012.07.010. *Good quality*

Revascularization
Clinical Background

Chronic stable angina

- Commonly caused by coronary artery disease
- Discomfort in the chest, jaw, shoulder, back, or arm
- Aggravated by moderate to severe exertion or emotional stress
- Relieved with rest or sublingual nitroglycerin

Revascularization
Clinical Background

Treatments for angina

Percutaneous coronary intervention (PCI)

- Non-surgical treatment to treat narrowing coronary arteries
- Includes balloon angioplasty, bare metal stents, and drug-eluting stents

Coronary artery bypass grafting (CABG)

- Bypass surgery that creates new routes around narrowed and blocked coronary arteries

Revascularization
Clinical Background

Treatments for angina

Optimal medical therapy

- Two or more antianginals (in addition to standard treatment for coronary artery disease)
  - beta-blocker, nitrate, calcium channel blocker, or ranolazine

Revascularization Evidence Summary

PCI vs. OMT

- No improvement in mortality or most other cardiac outcomes with PCI
  - Low quality evidence (multiple conflicting SRs)
- Some new generation drug-eluting stents may reduce mortality
  - Low quality evidence, based on one fair quality meta analysis
- Short-term improvement in quality of life with PCI
  - Low quality evidence, based on 1 RCT

Revascularization
Evidence Summary

CABG vs. OMT

- Improved mortality at five years follow up, short-term risks are higher with CABG
  - low quality evidence, based on multiple SRs
- Benefit present regardless of left ventricular function or gender
- Mortality benefit of CABG may be limited to patients with three-vessel or left main stem disease

Revascularization Evidence Summary

PCI vs. OMT – All-cause mortality

Study (year)	Number of studies (N)	Effect size (95% CI)
Katrisis (2005)	SR, 11 RCTs (N=2,950)	RR 0.94 (0.72 to 1.24)
Ioannidas (2007)	SR, 6 RCTs (N=2,617)	RR 0.95 (0.73 to 1.23)
Trikalios (2009)	SR, 7 RCTs (N=1,991)	RR 0.82 (0.59 to 1.15)
Jeremias (2009)	SR, 17 RCTs (N=8,052)	OR 0.82 (0.68 to 0.99)

No significant differences in PCI vs. OMT in 3 SRs, significant reduction in 1 SR

Revascularization Evidence Summary

New drug-eluting stents vs. OMT – All-cause mortality

Windecker 2014 - network MA fair quality

Eluting stent type	# studies (N)	Rate Ratio (95% CI)
Everolimus	17 RCTs (N=13,272)	0.75 (0.59 to 0.96)
Zotarolimus (Resolute)	4 RCTs (N=2,285)	0.65 (0.42 to 1.00)
Paclitaxel	27 RCTs (N=11,541)	0.92 (0.75 to 1.12)
Sirolimus	39 RCTs (N=19,781)	0.91 (0.75 to 1.10)
Zotarolimus (Endeavor)	8 RCTs (N=8,937)	0.88 (0.69 to 1.10)

Trend toward reduced mortality with new generation drug-eluting stents. No difference in all-cause mortality with early generation drug-eluting stents.

Revascularization
Evidence Summary

PCI vs. OMT – major adverse cardiac events (MACE)

- 3 SRs
  - 11 RCTs, N=2,950 (Katrisis 2005)
  - 6 RCTs, N=2,617 (Ionnidis 2007)
  - 7 RCTs, N=1,991 (Trikalinos 2009)

- No significant difference in non-fatal MI, cardiac death or MI, *need for subsequent revascularization*, or heart failure

Revascularization
Evidence Summary

PCI vs. OMT – Quality of Life

Mark 2009

- 1 RCT (N=951)

- Duke Activity Status Index
  - Significant improvement at 4-months, disappears at 12 and 24-months

- Mental Health Inventory-5
  - No significant differences at any follow-up

Revascularization Evidence Summary

CABG vs. OMT – All-cause mortality

Yusuf 1994

- SR (7 RCTs, N=2,649)
  - Significant short-term increase and long-term reduction in mortality

- 1-year (mortality or MI): RR 1.45 (95% CI 1.18 to 2.03)
- 5 years: RR 0.61 (95% CI 0.48 to 0.77)
- 10 years: RR 0.83 (95% CI 0.70 to 0.98)

Revascularization
Evidence Summary

CABG vs. OMT – All-cause mortality

Jeremias 2009

- SR (8 RCTs, N=3,098)
  - Significant reduction
  - Relative benefits similar in people with normal compared with reduced left ventricular function
  - OR 0.62 (95% CI 0.50 to 0.77)

Revascularization Evidence Summary

CABG vs. OMT – Mortality (sub-groups)

Yusuf 1994

- SR (7 RCTs, N=2649)

- Non-significant reduction
  - Single-vessel disease: 0.54 (95% CI 0.22 to 1.33)
  - Two-vessel disease: 0.84 (95% CI 0.54 to 1.32)

- Significant reduction
  - Three-vessel disease: 0.58 (95% CI 0.42 to 0.80)
  - Left-main stem disease: 0.32 (95% CI 0.15 to 0.70)

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: CORONARY ARTERY REVASCULARIZATION FOR STABLE ANGINA

REVISED DRAFT for VbBS/HERC meeting materials 5/7/2015

HERC COVERAGE GUIDANCE

Coronary revascularization (with percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG)) is recommended for coverage in patients with stable angina whose symptoms are not controlled with optimal medical therapy[1] or who cannot tolerate such therapy *(weak recommendation).*

CABG is recommended for coverage for patients with stable angina who have left main coronary artery stenosis or three-vessel coronary artery stenosis, with or without a trial of optimal medical therapy *(strong recommendation).*

[1]Optimal medical therapy for angina symptom control prior to PCI is defined as two or more antianginals (in addition to standard treatment for coronary artery disease). Antianginals are defined as: beta-blocker, nitrate, calcium channel blocker, or ranolazine.

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCES

Trusted sources

Dolor, R.J., Melloni, C., Chatterjee, R., Allen LaPointe, N.M., Williams, J.B., Coeytaux, R.R., et al. (2012). *Treatment strategies for women with coronary artery disease*. Rockville, MD: AHRQ. Accessed on October 2, 2014, from http://effectivehealthcare.ahrq.gov/ehc/products/218/1227/CER66_Treatment-Coronary-Artery-Disease_FinalReport_20120816.pdf

Greenhalgh, J., Hockenhull, J., Rao, N., Dundar, Y., Dickson, R. C., & Bagust, A. (2010). Drug-eluting stents versus bare metal stents for angina or acute coronary syndromes. *The Cochrane Database of Systematic Reviews,* Issue 5. Accessed on March 6, 2015, from DOI:10.1002/14651858.CD004587.pub2.

Skinner, J.S., & Cooper, A. (2011). Secondary prevention of ischemic cardiac events. *BMJ Clinical Evidence*, 8 (206), 1-66. Accessed on March 6, 2015, from http://www.ncbi.nlm.nih.gov/pubmed/21875445

Additional sources

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The summary of evidence in this document is derived directly from these evidence sources, and portions are extracted verbatim.

EVIDENCE OVERVIEW

Clinical background

Coronary artery disease (CAD) is the presence of atherosclerosis in the epicardial coronary arteries. Atherosclerotic plaques may either rupture and cause acute ischemia or progressively narrow the coronary artery lumen, resulting in chronic stable angina.

Angina resulting from progressive narrowing of the coronary arteries is the initial manifestation of ischemic heart disease in approximately one-half of patients. Angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arm. It is typically aggravated by exertion or emotional stress and relieved by nitroglycerin. Angina usually occurs in patients with CAD that involves at least one large epicardial artery. However, angina can also occur in patients with valvular heart disease, hypertrophic cardiomyopathy, and uncontrolled hypertension. It can also be present in patients with normal coronary arteries and myocardial ischemia related to spasm or endothelial dysfunction.

Most angina is a sign of significant CAD—defined angiographically as a stenosis with greater than 70 percent diameter in at least one major epicardial artery segment or with greater than 50 percent diameter in the left main coronary artery. However, some angina is caused by stenotic lesions of lesser diameters, which have much less prognostic significance. Chronic stable angina is classified as pain that classically occurs with moderate to severe exertion, is milder in nature, and is relieved with rest or sublingual nitroglycerin.

Indications

Treatment options for secondary prevention include medical therapy (antiplatelet agents, statins, blood pressure reduction if indicated, beta-blockers and angiotensin converting enzyme inhibitors), coronary artery bypass grafting (CABG) and a number of less invasive methods, including percutaneous transluminal coronary angioplasty (PTCA), in which a small elongated balloon is inflated at the site of the plaque, effectively compacting the deposited material against the vessel wall. This is often accompanied by a coronary artery stent.

Technology description

Coronary artery stents are expandable devices resembling a tubular wire mesh used to 'scaffold' vessels open during PTCA procedures to relieve coronary obstructions in patients. The first of these were metal and are referred to as bare metal stents (BMS). Restenosis (re-narrowing of the treated vessel), which may require a repeat intervention, is a significant limitation of PTCA with the use of stents; rates of restenosis are recorded as ranging between 20 and 50 per cent, depending on the size, location and complexity of the lesion. In order to improve results and reduce restenosis, developments in stent design have been augmented by new drug-eluting technologies. Drug-eluting stents (DES) release anti-proliferative agents from their surface with the objective of limiting cell growth around the stent using cytotoxic, cytostatic and other agents (sirolimus, paclitaxel, everolimus, tacrolimus). Percutaneous coronary intervention (PCI) is an umbrella term that includes PTCA, with and without the additional use of stents.

This report is limited to individuals with stable angina or non-acute coronary heart disease (CHD); it does not address coronary interventions used in the setting of acute coronary syndrome. It is also limited to a comparison to optimal medical therapy to either PCI or CABG. There is a large body of evidence comparing PCI to CABG that is not included in this report.

Oregon utilization

Data from the Dartmouth Atlas of Health Care demonstrate that in Oregon, utilization of PCI is low compared to the national average and in proportion to utilization of CABG.

Table 1. Percutaneous Coronary Interventions (PCI) versus Inpatient Coronary Artery Bypass Grafting (CABG) Utilization per 1,000 Medicare Enrollees in 2012

	Male		Female		Overall	
	PCI	CABG	PCI	CABG	PCI	CABG
Oregon	5.6	3.9	2.9	1.2	4.1	2.4
Washington	6.9	3.5	3.4	1.3	4.9	2.3
National Average	8.4	4.1	4.5	1.4	6.2	2.6
90th Percentile	10.7	5.4	6.1	2.0	8.1	3.4
10th Percentile	5.8	3.1	3.0	0.9	4.3	1.9

Adapted from The Dartmouth Atlas of Health Care Website, http://www.dartmouthatlas.org/

Evidence review

Percutaneous coronary intervention vs. optimal medical therapy in stable coronary heart disease

It is unclear whether PTCA with or without stenting is more effective than medical treatment alone at reducing mortality, cardiac death, composite outcomes including mortality and cardiovascular morbidity, non-fatal MI, need for revascularization, or heart failure in people with non-acute CHD (low quality evidence). Populations and interventions (particularly the use of stents) varied between trials, and results varied by the specific analysis undertaken, outcome assessed, and population included (low-quality evidence).

Four systematic reviews comparing PTCA with or without stenting versus medical treatment alone (Jeremias 2009, Katritsis 2005, Ioannidis 2007, Trikalinos 2009) and three subsequent reports of RCTs included in the reviews (Boden 2009, Malek 2009, Mark 2009) were identified in the initial search of trusted sources. There was a large overlap in the RCTs meta-analyzed in the systematic reviews. However, each review combined different RCTs in their analysis and therefore all four reviews are reported on here.

The first review (Katrisis 2005, search date 2004, 11 RCTs, 2950 people with angiographically documented coronary stenosis in non-acute coronary artery disease settings) compared PTCA versus medical treatment. People with an acute coronary syndrome within the past week were excluded. However, in two RCTs all people had an MI within the past 3 months, but not in the past week. Most RCTs mainly included people with single-vessel or two-vessel disease, but one included people with multi-vessel disease only. The use of stents in people receiving PTCA varied among RCTs, and no RCT used drug-eluting stents. The review found no significant difference between PTCA and medical treatment in mortality (11 RCTs; 95/1476 [6%] with PTCA v 101/1474 [7%] with medical management; RR 0.94, 95% CI 0.72 to 1.24), non-fatal MI (11 RCTs; 87/1476 [6%] with PTCA v 65/1474 [4%] with medical management; RR 1.28, 95% CI 0.94 to 1.75), cardiac death or MI (11 RCTs; 126/1476 [8%] with PTCA v 109/1474 [7%] with medical management; RR 1.17, 95% CI 0.88 to 1.57), need for CABG (11 RCTs; 109/1476 [7.4%] with PTCA v 106/1474 [7.2%] with medical management; RR 1.03, 95% CI 0.80 to 1.33), or need for PTCA during follow-up (11 RCTs; 219/1476 [15%] with PTCA v 243/1474 [16%] with medical management; RR 1.23, 95% CI 0.80 to 1.90). However, there was considerable heterogeneity among trials.

Pre-specified subgroup analyses found that there was no significant difference in the end points considered in RCTs whether stents were available or not, and in trials with follow-up exceeding 2 years there was no difference in end points between PTCA and medical treatment. However, in RCTs with a mean follow-up <2 years, PTCA was associated with significantly higher rates of the composite outcome of cardiac mortality or MI compared with medical treatment (RR 1.82, 95% CI 1.10 to 2.99; absolute numbers not reported), although the confidence intervals overlapped with those from longer-term trials in which the difference was not significant (RCTs with follow-up exceeding 2 years, cardiac mortality or MI; RR 0.99, 95% CI 0.68 to 1.46). The review found that, in the two RCTs that exclusively included people with a relatively recent MI (more than one week but less than three months), PTCA significantly reduced mortality (RR 0.40, 95% CI 0.17 to 0.95) and need for PTCA during follow-up (RR 0.42, 95% CI 0.20 to 0.91;

absolute numbers not reported) compared with medical treatment. The largest RCT (Pocock 2000) identified by the review (1018 people) found that, compared with medical treatment, PTCA improved physical functioning (P <0.001), vitality (P = 0.01), and general health (P = 0.008) at 1 year (proportion of people rating their health "much improved": 33% with PTCA v 22% with medical treatment; P = 0.008), but found no significant difference at 3 years. The improvements were related to breathlessness, angina, and treadmill tolerance. High transfer (27%) to PTCA by people initially randomized to medical treatment may partly explain the lack of significant difference between groups at 3 years. The review found no significant difference between groups for death or MI (including procedure-related events) at 5 years (9% with PTCA v 8% with medical treatment; ARR +1.8%, 95% CI –1.7% to +5.2%).

The second review (Ioannidis 2007, search date 2007, 6 RCTs and 1 sub study, 2617 people that were stable and had an occluded coronary artery, 1–45 days from the onset of acute MI symptoms [mean 8 days], most RCTs with a mean ejection fraction between 44% and 53%, 1 RCT with a mean ejection fraction of 36%) compared PTCA versus medical treatment. Three RCTs had long-term follow up (mean: range 34–50 months), while the others were limited to 4 to 12 months. Three RCTs used stents in people receiving PTCA. The review found no significant difference between PTCA and medical treatment in mortality (99/1310 with PTCA v 106/1317 with medical management; RR 0.95, 95% CI 0.73 to 1.23; P = 0.69), non-fatal MI (70/1310 with PTCA v 55/1317 with medical management; RR 1.26, 95% CI 0.86 to 1.78; P = 0.19), death or MI (161/1310 with PTCA v 141/1317 with medical management; RR 0.99, 95% CI 0.57 to 1.70; P = 0.96), or heart failure (51/1310 with PTCA v 67/1317 with medical management; RR 0.67, 95% CI 0.36 to 1.22; P = 0.19). The review found no significant heterogeneity among RCTs for any of the summary effects (P >0.10 for all outcomes).

The third review (Jeremias 2009, search date 1997–2008), which included RCTs of coronary revascularization versus medical treatment in people with non-acute coronary artery disease, included a total of 28 RCTs, of which 17 RCTs were confined to PTCA versus medical treatment with a further 2 RCTs randomizing to PTCA, CABG, and medical treatment. In total, 8052 people were included in the trials comparing percutaneous coronary intervention (PCI) versus medical therapy, and the RCTs ranged in follow-up from 1 to 10.2 years. The population in the RCTs included people with stable angina, exercise-induced ischemia, post-thrombolytic therapy for MI, asymptomatic single vessel coronary artery disease, and ischemia post MI, among others. Most RCTs compared balloon angioplasty without stenting versus medical treatment, although in 5 RCTs bare metal stents were implanted in 72% to 100% of cases. The review found that PTCA significantly reduced all-cause mortality compared with medical treatment (OR 0.82, 95% CI 0.68 to 0.99; results presented graphically; absolute numbers not reported).

The fourth review (Trikalinos 2009, search date 2008, people with symptomatic or asymptomatic non-acute coronary artery disease) first compared PTCA without stents versus medical management (7 RCTs, number of people [median] 201, follow-up [median] 60 months, age [mean] 56 years, percentage men [median] 85%, 0% with multivessel disease). The review found no significant difference between PTCA and medical treatment in mortality (7 RCTs, 1991 people; RR 0.82, 95% CI 0.59 to 1.15), non-fatal MI (7 RCTs, 1991 people; RR 1.09, 95% CI 0.59 to 1.99), CABG (5 RCTs, 1646 people; RR 1.10, 95% CI 0.81 to 1.49), and any revascularization (7 RCTs, 1991 people; RR 1.08, 95% CI 0.74 to 1.56; absolute numbers not

reported for any outcome). Significant heterogeneity among RCTs was found for the outcomes of non-fatal MI and any revascularization. The review also compared PTCA with bare metal stents versus medical management (4 RCTs, number of people [median] 1134, follow-up [median] 30 months, age [mean] 60 years, percentage men [median] 83%, 60% with multivessel disease). The review found no significant difference between PTCA with bare metal stents and medical treatment in mortality (3 RCTs, 4518 people; RR 0.96, 95% CI 0.79 to 1.18), non-fatal MI (4 RCTs, 4619 people; RR 1.18, 95% CI 0.97 to 1.43), CABG (2 RCTs, 2267 people; RR 0.97, 95% CI 0.63 to 1.50), and any revascularization (3 RCTs, 4518 people; RR 0.78, 95% CI 0.58 to 1.05; absolute numbers not reported for any outcome). Significant heterogeneity among RCTs was found for the outcome of any revascularization. No RCTs directly compared PTCA with drug-eluting stents versus optimal medical therapy.

The first subsequent report (Boden 2009, 2287 people with initially severe angina [CCS grade 4] stabilized medically and at least 70% stenosis in at least one proximal epicardial coronary artery, and either objective evidence of myocardial ischemia or at least one coronary stenosis of at least 80% and classic angina without provocative testing) reported prespecified tertiary outcomes of one RCT included in a systematic review. The initial report of the RCT (the COURAGE trial) had reported on primary and major secondary end points. This report assessed the impact of PCI when added to optimal medical therapy on major, cause-specific cardiovascular outcomes (i.e., prespecified tertiary end points) during long-term follow-up. PTCA was attempted in 1077 of the 1149 people randomized to PTCA and 94% received at least one stent, the majority being bare metal stents. The RCT found no significant difference between PTCA and medical treatment in cardiac death (39/1149 [3.4%] with PTCA v 44/1138 [3.9%] with medical treatment; HR 0.87, 95% CI 0.56 to 1.33; P = 0.51), the composite outcome of cardiac death and MI (172/1149 [15.0%] with PTCA v 162/1138 [14.2%] with medical treatment; HR 1.07, 95% CI 0.86 to 1.33; P = 0.62), the composite outcome of cardiac death, MI, and acute coronary syndrome (270/1149 [23.5%] with PTCA v 257/1138 [22.6%] with medical treatment; HR 1.07, 95% CI 0.91 to 1.27; P = 0.60), the composite outcome of cardiac death, MI, and stroke (188/1149 [16%] with PTCA v 173/1138 [15%] with medical treatment; HR 1.10, 95% CI 0.89 to 1.35; P = 0.45), and the composite outcome of cardiac death, MI, acute coronary syndrome, and stroke (313/1149 [27.2%] with PTCA v 305/1138 [26.8%] with medical treatment; HR 1.05, 95% CI 0.89 to 1.22; P = 0.51).

The second and third subsequent reports were follow-ups from RCTs included in three systematic reviews (Malek 2009, Mark 2009). Malek 2009 compared PTCA with stenting versus optimal medical therapy in people with total occlusion of the infarct-related artery (793 left anterior descending [LAD group], 1408 left circumflex or right coronary artery [non-LAD group]). On days 3 to 28 (minimum of 24 hours) after MI, people were randomized to PTCA and stenting with optimal medical therapy (1101 people) or to optimal medical therapy alone (1100 people). People with LAD infarct-related artery were significantly older than people with non-LAD infarct-related artery (mean: 59.5 years with LAD v 58.1 years with non-LAD; P = 0.005) and the proportion of men was significantly lower (591/793 [75%] with LAD v 1126/1408 [80%] with non-LAD; P = 0.003). The RCT found that the 5-year cumulative primary composite outcome of first occurrence of MI, admission to hospital for heart failure, or all-cause mortality occurred more frequently in people with LAD infarct-related artery compared with people with non-LAD infarct-

related artery (19.5% with LAD v 16.4% with non-LAD; HR 1.34, 99% CI 1.00 to 1.81; P = 0.01). The RCT found that in people with LAD infarct-related artery, PTCA did not significantly reduce the primary outcome compared with medical treatment (22.7% with PTCA v 16.4% with medical treatment; HR 1.35, 99% CI 0.86 to 2.31; P = 0.09). Similarly, it found that in people with non-LAD infarct-related artery, PTCA did not significantly reduce the primary outcome compared with medical treatment (16.9% with PTCA v 15.8% with medical treatment; HR 1.03, 99% CI 0.70 to 1.52; P = 0.83). It also reported that there was no significant difference between people with LAD infarct-related artery and people with non-LAD infarct related artery for the secondary outcomes of death or non-fatal re-infarction, fatal and non-fatal reinfarction, or admission to hospital for heart failure or stroke. It reported that there was no significant difference for PTCA versus medical treatment for these secondary outcomes in either people with LAD infarct-related artery or in people with non-LAD infarct-related artery.

Mark 2009 (a substudy of 951 of 2166 people in original trial enrolled in the quality-of-life assessment, 3–28 days post MI) compared PTCA versus medical treatment for the outcome of quality of life at 4, 12, and 24 months' follow-up. The RCT found that PTCA significantly improved quality of life as assessed on the Duke Activity Status Index at 4 months' follow up compared with medical treatment (P = 0.008), whereas there was no significant difference between groups at 12 months' (P = 0.36) or 24 months' follow-up (P = 0.29). It found that there was no significant difference for PTCA versus medical treatment in quality of life as assessed by the Mental Health Inventory 5 at any follow-up.

This information is summarized in Table 1.

Table 1. Percutaneous coronary interventions vs. optimal medical therapy

Review or Trial	Outcomes	Sub-group Information
Katrisis 2005 (SR – no DES)	No difference in: · Mortality · Non-fatal MI · Composite of cardiac death or MI · Need for CABG · Need for PTCA	No difference with or without stents Mean F/U < 2 years: higher rates of composite in PTCA Recent (< 3 mos, > 1 week) MI: lower mortality, need for PTCA in PTCA F/U > 5 years: no diff in death or MI
Ioannidis 2007 (SR)	No difference in: · Mortality · Non-fatal MI · Composite of cardiac death or MI · Heart failure	
Jeremias 2009 (SR – no DES)	PTCA reduced all-cause mortality	

Trikalinos 2009 (SR – no DES)	No difference in: · Mortality · Non-fatal MI · Any revascularization · CABG	Same results comparing PTCA without stents and with bare metal stents
Boden 2009 (RCT – most stented, some DES)	No difference in: · Cardiac death · Composite of cardiac death or MI · Composite of cardiac death, MI or ACS · Composite of cardiac death, MI or stroke · Composite of cardiac death, MI, ACS or stroke	
Malek 2009 (RCT – recent MI, most stented)	No difference in: · Composite (5 year F/U) of MI, admit to hospital for heart failure, or all-cause mortality · Death or non-fatal reinfarction · Any reinfarction · Admit to hospital for heart failure or stroke	Same results comparing LAD and non-LAD infarct related arteries
Mark 2009 (RCT – recent MI, most stented)	PTCA improved quality of life at 4 months, but not 12 or 24 months	
TIME Investigators 2001 (RCT)	PTCA reduced all adverse cardiac events and angina severity No difference in deaths or non-fatal MI	Patients > 75
Dolor 2012 (SR)	PCI reduced composite of death, MI or repeat revascularization at 5 year F/U	Women

Subgroups

Age

One systematic review (Jeremias 2009) which included one RCT (TIME investigators 2001) was identified. The RCT (305 people aged >75 years, 44% female, with chronic refractory angina) compared PTCA versus medical treatment alone. It found that PTCA reduced all adverse cardiac events (death, non-fatal MI, hospital admissions for ACS) and decreased anginal severity compared with medical treatment, but had no significant effect on deaths or non-fatal MI after 6 months (adverse cardiac events, AR: 19% with PTCA v 49% with medical treatment; P <0.0001; change in angina class: –2.0 with PTCA v –1.6 with medical treatment; P <0.0001;

deaths, AR: 9% with PTCA v 4% with medical treatment; P = 0.15; non-fatal infarctions, AR: 8% with PTCA v 12% with medical treatment; P = 0.46).

Gender

One SR examined treatment of women with coronary disease (Dolor 2012). For women with stable angina, meta-analysis of three good quality studies (all women less than age 75) showed a reduction in the composite outcome of death/MI/repeat revascularization at 5 years for revascularization with PCI compared to optimal medical therapy (OR 0.64; CI, 0.47 to 0.89; p=0.008, moderate SOE). In one of these trials, patients had multivessel disease.

Evidence from additional sources

Because the initial search of trusted sources may not have identified the most recent and relevant information, staff undertook an additional MEDLINE search through February 2015, duplicating the strategy used in Dolor 2012 but without specifying women. This search identified three relevant reviews. Two of the three are of good quality, and found no benefit to PCI over medical therapy for management of stable angina, but their search dates ended in November 2011 and January 2012, respectively. The most recent review, of fair quality, found a benefit in overall mortality only with new generation drug eluting stents, as well as a reduction in revascularization and a nonsignificant reduction in subsequent MI. Findings are described in detail below.

Thomas and colleagues (2013) performed a systematic review and study-level meta-analysis of randomized controlled trials of patients with stable angina comparing PCI vs medical therapy for each of the following individual outcomes: all-cause mortality, cardiovascular (CV) mortality, myocardial infarction (MI), and angina relief. Staff rated this systematic review as good quality. Authors searched bibliographic databases through November 2011, and included ten prospective randomized controlled trials encompassing a total of 6,752 patients. This review did not detect differences between PCI vs medical therapy for all-cause mortality (663 events; relative risk [RR], 0.97 [confidence interval (CI), 0.84-1.12]; I^2 = 0%), CV mortality (214 events; RR, 0.91 [CI, 0.70-1.17]; I^2 = 0%), MI (472 events; RR, 1.09 [CI, 0.92-1.29]; I^2 = 0%), or angina relief at the end of follow-up (2016 events; RR, 1.10 [CI, 0.97-1.26]; I^2=85%). PCI was not associated with reductions in all-cause or CV mortality, MI, or angina relief. Considering the cost implication and the lack of clear clinical benefit, authors conclude that these findings continue to support existing clinical practice guidelines that medical therapy be considered the most appropriate initial clinical management for patients with stable angina.

A second systematic review and meta-analysis (Pursnani 2012) searched through January 2012 for randomized clinical trials comparing revascularization with PCI to optimal medical therapy (OMT) in patients with stable coronary artery disease. Staff also rated this a good quality review. The primary outcome was all-cause mortality, and secondary outcomes included cardiovascular death, nonfatal myocardial infarction, subsequent revascularization, and freedom from angina. Primary analyses were based on longest available follow-up with secondary analyses stratified by trial duration, with short-term (≤1 year), intermediate (1-5 years), and long-term (≥5 years) time points. Authors identified 12 randomized clinical trials enrolling 7,182 participants. For the primary analyses, when compared with OMT, PCI was associated with no significant improvement in mortality (risk ratio [RR], 0.85; 95% CI, 0.71-1.01), cardiac death (RR, 0.71;

95% CI, 0.47-1.06), nonfatal myocardial infarction (RR, 0.93; 95% CI, 0.70-1.24), or repeat revascularization (RR, 0.93; 95% CI, 0.76-1.14), with consistent results over all follow-up time points. Sensitivity analysis restricted to studies in which there was >50% stent use showed attenuation in the effect size for all-cause mortality (RR, 0.93; 95% CI, 0.78-1.11) with PCI. However, for freedom from angina, there was a significant improved outcome with PCI, as compared with the OMT group (RR, 1.20; 95% CI, 1.06-1.37), evident at all of the follow-up time points.

A network meta-analysis by Windecker and colleagues (2014) was the most recent and comprehensive review, although it was rated of fair quality by staff due to indirectness of evidence. Randomized controlled trials from 1980 through June 2013 were included if they had a clinical follow-up duration of at least six months and had randomized at least 100 patients per trial arm. Patients had to be randomized to medical treatment, coronary artery bypass grafting, or percutaneous coronary intervention using balloon angioplasty, bare metal stents, early generation stent systems (paclitaxel eluting Taxus stent [Boston Scientific, Natick, MA], sirolimus eluting Cypher stent [Cordis, Miami Lakes, FL], zotarolimus eluting Endeavor stent [Medtronic Cardiovascular, Santa Rosa, CA]) or new generation stent systems (zotarolimus eluting Resolute stent [Medtronic Cardiovascular, Santa Rosa, CA] and everolimus eluting Xience/Promus stent [Abbott Vascular, Santa Clara, CA and Boston Scientific, Natick, MA]) approved by the FDA. The review excluded trials in patients with acute myocardial infarction (ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction) and symptom onset less than 72 hours, trial arms with polymer or carbon coated bare metal stents, and trial arms with non-FDA approved drug eluting stents. Authors considered studies in general to be of high quality. Ninety five trials including 93,553 randomized patients and 5,346 accumulated events contributed to the analysis of all cause mortality for all interventions including CABG.

Percutaneous coronary intervention with the new generation everoliumus eluting stent, but no other percutaneous coronary intervention technology, was associated with reduced mortality compared with medical treatment (0.75, 0.59 to 0.96 17 trials, N = 13,272). There was also a trend toward reduced mortality with the new generation zotarolimus eluting (Resolute) stent (0.65, 0.42 to 1.00 four trials, N = 2,285). The estimated rate ratios for mortality were below 1, but inconclusive for revascularization with balloon angioplasty (0.85, 0.68 to 1.04, 29 trials, N = 7,609), bare metal stents (0.92, 0.79 to 1.05, 50 trials, N = 16,042), and early generation drug eluting stents (paclitaxel eluting: 0.92, 0.75 to 1.12, 27 trials, N = 11,541; sirolimus eluting: 0.91, 0.75 to 1.10, 39 trials, N = 19,781; zotarolimus eluting [Endeavor]: 0.88, 0.69 to 1.10, 8 trials, N = 8,937).

In the analysis of myocardial infarction, 5,796 events were reported during 243,031 patient years. All percutaneous coronary interventions, except bare metal stent (1.04, 0.84 to 1.27) and paclitaxel eluting stent (1.18, 0.88 to 1.54), showed evidence for a relevant but inconclusive reduction of myocardial infarction, with point estimates below 1 for balloon angioplasty (0.88, 0.70 to 1.11), sirolimus eluting stent (0.94, 0.71 to 1.22), zotarolimus eluting (Endeavor) stent (0.80, 0.56 to 1.10), zotarolimus eluting (Resolute) stent (0.82, 0.52 to 1.26), and everolimus eluting stent (0.75, 0.55 to 1.01).

Revascularization using coronary stents was associated with a reduction in subsequent revascularization for bare metal stent (0.44, 0.59 to 0.82), paclitaxel eluting stent (0.44, 0.35 to 0.55), sirolimus eluting stent (0.29, 0.24 to 0.36), zotarolimus eluting (Endeavor) stent (0.38, 0.29 to 0.51), zotarolimus eluting (Resolute) stent (0.26, 0.17 to 0.40), and everolimus eluting stent (0.27, 0.21 to 0.35). Revascularization with balloon angioplasty showed similar risks of subsequent revascularization compared with medical treatment (0.97, 0.82 to 1.16).

In summary, this network meta-analysis (Windecker 2014) found that percutaneous coronary intervention with the new generation everoliums eluting stents reduced mortality compared to medical management. The new generation zotarolimus eluting (Resolute) stent had only four trials contributing data, but also showed a trend toward reduced mortality. No other percutaneous coronary intervention technology was associated with reduced mortality when compared with medical management. All percutaneous coronary interventions, except bare metal stent and paclitaxel eluting stent, showed evidence for a relevant but inconclusive reduction of myocardial infarction. Revascularization using coronary stents was associated with a reduction in subsequent revascularization by 56-74%.

Summary

In summary, based on multiple trusted source and good quality systematic reviews, there is no clear advantage of an initial routine strategy of PTCA with or without stenting compared with medical treatment to reduce mortality and MI in patients with stable coronary disease and no recent MI. The exception, based on one recent fair quality meta-analysis, is a finding of reduced mortality with the new generation everolimus drug-eluting stent. There may be short-term improvement based on two RCTs in quality of life, and for women and older individuals, one systematic review suggests PCI may result in a reduction in angina symptoms and adverse cardiac events. Finally, one meta-analysis found that a strategy of PCI reduced need for subsequent revascularization by 56-74% over medical management.

Coronary artery bypass graft vs. optimal medical therapy

Two systematic reviews comparing CABG versus medical treatment were identified. In the first systematic review (Yusuf 1994, search date not reported, 7 RCTs, 2649 people with CHD, mostly male, aged 41–60 years, 80% with ejection fraction >50%, 60% with prior MI; and 83% with 2–3 vessel disease), people assigned to CABG also received medical treatment, and 37% initially assigned to medical treatment underwent CABG in the following 10 years. It found that, compared with medical treatment, CABG significantly reduced mortality at 5 and 10 years (5 years: RR 0.61, 95% CI 0.48 to 0.77; 10 years: RR 0.83, 95% CI 0.70 to 0.98). Most trials did not collect data on quality of life; neither did they report detailed information about long-term medication use. However, at one year, 66% of the medical treatment group and 20% of the CABG group were treated with beta-blockers, and 19% of the medical treatment group and 26% of the CABG group were treated with antiplatelet agents. The review found that, of the 1240 people who had CABG, 40 (3%) died and 88 (7%) had non-fatal MI within 30 days of the procedure. At 1 year, rates of the combined outcome of mortality or MI were significantly higher with CABG compared with medical treatment (12% with CABG v 8% with medical treatment; RR 1.45, 95% CI 1.18 to 2.03).

The second systematic review (Jeremias 2009, search date 1977–2008) included RCTs of coronary revascularization (CABG/PCI/mixed) versus medical treatment in people with non-acute coronary artery disease. It included 28 RCTs in total, of which 6 RCTs evaluated CABG (largely with saphenous vein grafts) versus medical treatment (all of which were included in the first review) and it included a further two RCTs evaluating PCI or CABG (the majority with internal thoracic artery graft). The 8 RCTs comparing CABG versus medical treatment included 3098 people, who were mostly male, and follow-up in the RCTs was from 1 to 5 years. The 8 RCTs included people with stable angina, disabling angina, mild stable angina, or free of angina post MI, and no symptoms; the year of publication of the RCTs varied from 1977 to 2004. The review found that CABG significantly reduced all-cause mortality compared with medical treatment (8 RCTs; OR 0.62, 95% CI 0.50 to 0.77; results presented graphically; absolute numbers not reported).

No harms were reported in either SR.

The efficacy of revascularization versus medical treatment has been evaluated in people with stable ischemia in one additional RCT (Davies 1997). The RCT (558 people with ischemia identified by exercise test or ambulatory ECG, who were either asymptomatic or whose angina was able to be controlled with medications) compared three interventions: revascularization (90 selected for CABG, 11 later refused and 1 had the procedure outside the specified time window; 102 selected for PTCA, 8 later refused and 2 had the procedure outside the time window), angina-guided medical treatment, and ischemia-guided medical treatment. In the angina-guided treatment group, drug treatment was sufficient to control angina. In the ischemia-guided group, additional drug therapy was added if ischemia was still present on ambulatory ECG recording. At 2 years, the rate of mortality or MI was lower with revascularization (angina-guided treatment: 12%; ischemia-guided treatment: 9%; revascularization: 5%). The difference between angina-guided treatment and revascularization was significant (P <0.01), but the differences between ischemia-guided treatment and revascularization (P = 0.12) and angina-guided treatment and ischemia-guided treatment (P = 0.3) were not significant. There was a tendency for the benefit of revascularization to be concentrated in those with proximal LAD artery disease, and in those with three-vessel disease compared with one- or two-vessel disease.

Subgroups

Reduced left ventricular function

The Yusuf 1994 systematic review described above found that the relative benefits of CABG were similar in people with normal compared with reduced left ventricular function (death: OR 0.61, 95% CI 0.46 to 0.81, with normal left ventricular function; OR 0.59, 95% CI 0.39 to 0.91, with reduced left ventricular function). The absolute benefit of CABG was greater in people with a reduced left ventricular function because the baseline risk of death was higher.

Multiple vessel disease

Yusuf 1994 found that CABG reduced mortality compared with medical treatment in people with single-vessel, two-vessel, three-vessel, and left main stem disease. Change in mortality was not significant for people with single-vessel and two-vessel disease; however, this may have been because the number of deaths was small. The risk of mortality was 0.54 (95% CI 0.22 to 1.33) with single-vessel disease, 0.84 (95% CI 0.54 to 1.32) with two-vessel disease, 0.58 (95% CI

0.42 to 0.80) with three-vessel disease, and 0.32 (95% CI 0.15 to 0.70) with left main stem disease.

Gender

One SR examined treatment of women with coronary disease (Dolor 2012). For women with stable angina, meta-analysis of two good quality studies showed a reduction in the composite outcome of death/ MI/repeat revascularization at 5 years for revascularization with CABG compared to OMT (OR 0.56; CI, 0.32 to 0.96; p=0.04; low SOE). However, patients in these two trials either had multivessel disease or left ventricular dysfunction.

Evidence from additional sources

Similar to the process used for PCI v OMT, because the initial search of trusted sources may not have identified the most recent and relevant information, staff undertook an additional MEDLINE search through February 2015, duplicating the strategy used in Dolor 2012 but without specifying women. This search identified one relevant network meta-analysis of CABG versus medical management (Windecker 2014), the details of which are described above. In patients with stable symptomatic or asymptomatic coronary artery disease, compared with a strategy of initial medical treatment, revascularization using coronary artery bypass grafting reduced all cause mortality by 20% (rate ratio 0.80, 95% confidence interval 0.70 to 0.91, 22 trials, N = 8,920). Revascularization using coronary artery bypass grafting compared with medical treatment reduced myocardial infarction during the observational period by 21% (0.79, 0.63 to 0.99). Compared with medical treatment, revascularization with coronary artery bypass grafting was effective in reducing subsequent revascularization by 84% (0.16, 0.13 to 0.20).

Summary

In summary, CABG plus medical treatment may be more effective than medical treatment alone at reducing mortality in the long run in people (mostly male) aged 41 to 60 years, most with previous MI and two to three-vessel disease and also in people with non-acute coronary artery disease (low quality evidence). However, it may increase the estimated incidence of the composite outcome of death or MI at 1 year. Further analysis in people (mostly male) aged 41 to 60 years, most with previous MI and two- to three-vessel disease, found that CABG may reduce mortality compared with medical treatment both in people with normal left ventricular function or with reduced left ventricular function, and may reduce mortality in people with three-vessel and left main stem disease, although the effect of CABG in those with single- or two-vessel disease are unclear, as the number of deaths in these groups was small (low-quality evidence).

A recent fair quality network meta-analysis of patients with symptomatic or asymptomatic stable CAD found a significant reduction in mortality, MI, and need for subsequent revascularization with CABG as compared to medical management.

Limitations of the evidence on coronary artery bypass grafting compared to optimal medical therapy

The results of the systematic reviews may not be easily generalized to current practice. People were generally aged 65 years or younger, but >50% of CABG procedures are now performed on people >65 years of age. In addition, almost all were male, and high-risk people (such as those with severe angina and left main coronary artery stenosis) were under represented. Internal thoracic artery grafts were largely confined to two more recent trials. In the first systematic review lipid lowering agents (particularly statins) and aspirin were used infrequently (aspirin used in 3% of people at enrollment, about 22% at 1 year). Only about 50% of people were taking beta-blockers at baseline. The first systematic review (Yusuf 1994) evaluated the efficacy of an initial strategy of CABG compared with medical treatment, although there was considerable crossover to surgery in those assigned to medical treatment; in the three larger trials, 25% by 5 years, 33% by 7 years, and 41% by 10 years. However, some general observations can be made, and those with more-extensive CHD and impaired left ventricular function are likely to derive the greatest absolute benefit with improved survival from CABG. One RCT (Hueb 2007) included in the second systematic review (Jeremias 2001) in those with preserved left ventricular function and multivessel disease more accurately reflects contemporary clinical practice with the use of more arterial conduits, although the mean age of participants was still only 60 years. The RCT was not powered to detect differences in survival, but CABG reduced the need for additional revascularization procedures and improved angina-free survival at 5 years. People with prior CABG have not been studied in RCTs, although they now represent a growing proportion of those undergoing CABG.

EVIDENCE SUMMARY

Evidence suggests that, compared to optimal medical therapy, PCI does not result in improvement in mortality or most other cardiac outcomes (non-fatal MI, need for revascularization, heart failure, composite outcomes), based on low quality evidence (multiple conflicting SRs). However, most studies utilized only PTCA or bare metal stents, and only a few trials included drug eluting stents. A network meta-analysis incorporating new generation drug-eluting stents found evidence that the everolimus eluting stent, but not other modalities, reduces mortality compared to medical treatment (low quality evidence, based on one fair quality metanalysis). Some subgroups appear to have differential outcomes; PCI may result in short-term benefit in mortality in patients with a recent MI (very low quality evidence, based on three conflicting RCTs), as well as in women (moderate quality evidence, based on one SR). In addition, PCI may improve physical functioning and quality of life in the short-term compared to OMT (very low quality evidence, based on one RCT), and for patients over age 75, may reduce anginal severity (very low quality evidence, based on one RCT).

On the contrary, CABG does appear to result in improved mortality compared to OMT, at least at five years follow up, although short-term risks are higher (low quality evidence). This benefit is present regardless of left ventricular function or gender, but may be limited to patients with three-vessel or left main stem disease.

There are a number of limitations to the evidence base, including the fact that most trials were limited to patients age 65 or younger, few trials included DE stents and OMT in many trials was suboptimal compared to current standards. In addition, for CABG trials, most did not utilize internal thoracic artery grafts. Lastly, there was considerable cross-over to surgery in those assigned to OMT (up to 41% by 10 years).

GRADE-INFORMED FRAMEWORK

The 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 carrying out the steps involved in developing recommendations. There are four elements that determine the strength of a recommendation, as listed in the table below. The 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. Balance between desirable and undesirable effects, and quality of evidence, are derived from the evidence presented in this document, while estimated relative costs, values and preferences are assessments of the HERC members.

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
PCI vs. OMT (patients with non-acute coronary heart disease)	No difference in mortality (except with 1 out of 2 new generation drug-eluting stents), MI, MACE. PCI caused reduction in subsequent revascularization by 56-74%	Low based on multiple conflicting SRs*	Moderate	LOW most patients would not want a semi-invasive intervention without some assurance of proven significant benefit	Recommended for coverage in patients with stable angina whose symptoms are not controlled with optimal medical therapy[1] or who cannot tolerate such therapy *(weak recommendation)*	While the evidence is weak, it would be appropriate to cover PCI for symptomatic relief if optimal medical therapy has been tried and is ineffective at controlling symptoms, and coronary anatomy is appropriate. PCI cannot be recommended for coverage for improvement in MACE or mortality given the lack of consistent evidence of benefit for these critical outcomes.
	Possible short-term improvement in physical functioning, QOL, angina	Low based on 2 RCTs[#]				

Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
CABG vs. OMT	Short-term worse mortality, long-term benefit in mortality (benefit possibly limited to three vessel or left main stem disease) 21% reduction in MI and 84% reduction in subsequent revascularization compared with OMT in patients with stable disease	Low based on multiple SRs*	High	MODERATE Long term benefit is appealing but this is a major cardiac surgery and increased short-term mortality is concerning	Recommended for coverage in those with three vessel or left main stem disease *(strong recommendation)* Recommended for coverage in patients with stable angina whose symptoms are not controlled with optimal medical therapy[1] or who cannot tolerate such therapy *(weak recommendation)*	There is low quality evidence but with significant improvements in long-term mortality. CABG is recommended for coverage for those who have failed optimal medical therapy and for those with stable CHD but with appropriate anatomy, regardless of failure of OMT.

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A

POLICY LANDSCAPE

Quality measures

Nine potentially relevant quality measures were identified when searching the National Quality Measures Clearinghouse. Six were measures developed by the Agency for Healthcare Research and Quality, and three were developed by the Canadian Institute for Health Information. Seven of the measures quantified utilization of either PCI or CABG (area rate, volume), while there was one measure for each PCI and CABG documenting the mortality rate associated with the procedure.

Professional society guidelines

The 2012 ACC/AHA/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease addresses diagnosis, risk assessment, treatment and follow up of patients with known or suspected SIHD. While the guideline developers have been meticulous in maintaining and documenting editorial independence, the guideline overall receives a poor rating, primarily because study selection criteria are not specified, and no assessment of study quality is taken into account when developing recommendations.

Treatment is the section of the guideline that pertains to this coverage guidance document. Selected background and recommendations that are pertinent to stable disease from this section are presented below.

Factors That Should Not Influence Treatment Decisions

The 2 medical indications for revascularization are to prevent death and cardiovascular complications and to improve symptoms and quality of life. Nonetheless, the use of revascularization has risen dramatically in the past 3 decades. Much of this increase appears to be for indications for which benefits in survival or symptoms in comparison with noninvasive therapies are unlikely. National data suggest that about 12% of PCIs could be inappropriate because they lack evident potential to improve either survival or symptoms. Several reasons influence patients and physicians to prefer revascularization when the likelihood of benefit is less than the potential risk of the procedure. An ingrained preference for action (i.e., revascularization) over perceived inaction (i.e., medical therapy alone) likely often influences the decision making of both patients and physicians. Moreover, some healthcare professionals are unduly pessimistic about survival with conservative medical therapy and inaccurately optimistic about the survival benefits of revascularization procedures. As indicated earlier, patients often believe mistakenly that PCI has the potential to prevent AMI and prolong survival. In addition, the attendant expense and risk of combined antiplatelet therapy for an uncertain period of time might not be fully considered. Physicians are professionally obligated to provide accurate estimates of the risks, benefits, and costs of various therapeutic options that are based on the best available scientific data. Other factors can induce physicians to recommend revascularization. These include medicolegal concerns (often exaggerated) and feeling compelled to satisfy the expectations of patients and referring physicians (which are sometimes misinformed or unrealistic). Additionally, there are well-

documented regional variations in the use and appropriateness of cardiac procedures that appear to reflect local practice styles. This might partly reflect a mistaken belief by some physicians that “more care is better care”.

Although successful procedures can be psychologically satisfying to the physician and the patient, this does not justify the attendant economic costs and risk of complications of procedures that offer minimal, if any, genuine benefit. Although rarely discussed explicitly, financial incentives seem to affect the willingness of a minority of physicians and institutions to recommend certain procedures or drug therapies. Strong incentives created by the payment system encourage overutilization. Also, a small number of physicians might have financial relationships with the manufacturers of devices or drugs that might represent apparent conflicts that ought to be disclosed to patients. At a higher level, those responsible for the payment system, the manufacturers of devices and drugs, and physicians making clinical decisions must commit to supporting guideline based interventions. Any and all conflicts of interest must be revealed to patients in the process of informed consent before any invasive or noninvasive procedure.

Revascularization to Improve Survival: Recommendations

Left Main CAD Revascularization

CLASS I Recommendations

1. CABG to improve survival is recommended for patients with significant (≥50% diameter stenosis) left main coronary artery stenosis. (Level of Evidence: B)

CLASS IIa Recommendations

1. PCI to improve survival is reasonable as an alternative to CABG in selected stable patients with significant (≥50% diameter stenosis) unprotected left main CAD with: 1) anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g., a low SYNTAX score [≤22], ostial or trunk left main CAD); and 2) clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality ≥5%). (Level of Evidence: B)

CLASS IIb Recommendations

1. PCI to improve survival may be reasonable as an alternative to CABG in selected stable patients with significant (≥50% diameter stenosis) unprotected left main CAD with: a) anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (e.g., low–intermediate SYNTAX score of <33, bifurcation left main CAD); and b) clinical characteristics that predict an increased risk of adverse surgical outcomes (e.g., moderate–severe chronic obstructive pulmonary disease, disability from previous stroke, or previous cardiac surgery; STS-predicted risk of operative mortality >2%). (Level of Evidence: B)

CLASS III Recommendations: Harm

1. PCI to improve survival should not be performed in stable patients with significant (≥50% diameter stenosis) unprotected left main CAD who have unfavorable anatomy for PCI and who are good candidates for CABG. (Level of Evidence: B)

Non–Left Main CAD Revascularization

CLASS I Recommendations

1. CABG to improve survival is beneficial in patients with significant (≥70% diameter) stenoses in 3 major coronary arteries (with or without involvement of the proximal LAD artery) or in the proximal LAD artery plus 1 other major coronary artery. (Level of Evidence: B)

2. CABG or PCI to improve survival is beneficial in survivors of sudden cardiac death with presumed ischemia-mediated ventricular tachycardia caused by significant (≥70% diameter) stenosis in a major coronary artery. (CABG Level of Evidence: B ; PCI Level of Evidence: C)

CLASS IIa Recommendations

1. CABG to improve survival is reasonable in patients with significant (≥70% diameter) stenoses in 2 major coronary arteries with severe or extensive myocardial ischemia (e.g., high-risk criteria on stress testing, abnormal intracoronary hemodynamic evaluation, or >20% perfusion defect by myocardial perfusion stress imaging) or target vessels supplying a large area of viable myocardium. (Level of Evidence: B)

2. CABG to improve survival is reasonable in patients with mild–moderate LV systolic dysfunction (EF 35% to 50%) and significant (≥70% diameter stenosis) multi-vessel CAD or proximal LAD coronary artery stenosis, when viable myocardium is present in the region of intended revascularization. (Level of Evidence: B)

3. CABG with a left internal mammary artery (LIMA) graft to improve survival is reasonable in patients with significant (≥70% diameter) stenosis in the proximal LAD artery and evidence of extensive ischemia. (Level of Evidence: B)

4. It is reasonable to choose CABG over PCI to improve survival in patients with complex 3-vessel CAD (e.g., SYNTAX score >22), with or without involvement of the proximal LAD artery who are good candidates for CABG. (Level of Evidence: B)

5. CABG is probably recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus, particularly if a LIMA graft can be anastomosed to the LAD artery. (Level of Evidence: B)

CLASS IIb Recommendations

1. The usefulness of CABG to improve survival is uncertain in patients with significant (70%) diameter stenoses in 2 major coronary arteries not involving the proximal LAD artery and without extensive ischemia. (Level of Evidence: C)

2. The usefulness of PCI to improve survival is uncertain in patients with 2- or 3-vessel CAD (with or without involvement of the proximal LAD artery) or 1-vessel proximal LAD disease. (Level of Evidence: B)

3. CABG might be considered with the primary or sole intent of improving survival in patients with SIHD with severe LV systolic dysfunction (EF<35%) whether or not viable myocardium is present. (Level of Evidence: B)

4. The usefulness of CABG or PCI to improve survival is uncertain in patients with previous CABG and extensive anterior wall ischemia on noninvasive testing. (Level of Evidence: B)

CLASS III Recommendations: Harm

1. CABG or PCI should not be performed with the primary or sole intent to improve survival in patients with SIHD with 1 or more coronary stenoses that are not anatomically or functionally significant (e.g., <70% diameter non–left main coronary artery stenosis, FFR >0.80, no or only mild ischemia on noninvasive testing), involve only the left circumflex or right coronary artery, or subtend only a small area of viable myocardium. (Level of Evidence: B)

Revascularization to Improve Symptoms: Recommendations

CLASS I Recommendations

1. CABG or PCI to improve symptoms is beneficial in patients with 1 or more significant (≥70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite guideline directed medical therapy (GDMT). (Level of Evidence: A)

CLASS IIa Recommendations

1. CABG or PCI to improve symptoms is reasonable in patients with 1 or more significant (≥70% diameter) coronary artery stenoses and unacceptable angina for whom GDMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences. (Level of Evidence: C)

2. PCI to improve symptoms is reasonable in patients with previous CABG, 1 or more significant (≥70% diameter) coronary artery stenoses associated with ischemia, and unacceptable angina despite GDMT. (Level of Evidence: C)

3. It is reasonable to choose CABG over PCI to improve symptoms in patients with complex 3-vessel CAD (e.g., SYNTAX score >22), with or without involvement of the proximal LAD artery, who are good candidates for CABG. (Level of Evidence: B)

CLASS IIb Recommendations

1. CABG to improve symptoms might be reasonable for patients with previous CABG, 1 or more significant (≥70% diameter) coronary artery stenoses not amenable to PCI, and unacceptable angina despite GDMT. (Level of Evidence: C)

2. Transmyocardial revascularization (TMR) performed as an adjunct to CABG to improve symptoms may be reasonable in patients with viable ischemic myocardium that is perfused by arteries that are not amenable to grafting. (Level of Evidence: B)

CLASS III Recommendations: Harm

1. CABG or PCI to improve symptoms should not be performed in patients who do not meet anatomic (≥50% diameter left main or ≥70% non–left main stenosis diameter) or physiological (e.g., abnormal FFR) criteria for revascularization. (Level of Evidence: C)

The 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease updates the 2012 guideline described above. The areas addressed, where new evidence was found or recommendations were revised, were there following:

- Diagnosis of SIHD
- Treatment: Chelation therapy
- Treatment: Enhanced external counterpulsation
- CAD Revascularization: Revascularization to improve survival

Only the last area pertains to this guidance document, and will be discussed further. The 2012 recommendation was as follows:

Class IIa

CABG is probably recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus, particularly if a LIMA graft can be anastomosed to the left anterior descending (LAD) artery. (Level of Evidence: B)

The 2014 focused update makes the following new recommendation:

Class I

1. A Heart Team approach to revascularization is recommended in patients with diabetes mellitus and complex multivessel CAD. (Level of Evidence: C)

2. CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD), particularly if a LIMA graft can be anastomosed to the LAD artery, provided the patient is a good candidate for surgery. (Level of Evidence: B)

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.

APPENDIX A. GRADE ELEMENT DESCRIPTIONS

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
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—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

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Quality or strength of evidence rating across studies for the treatment/outcome[1]

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 effect estimate: 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 effect estimate 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 effect estimate: 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.

[1] Includes risk of bias, precision, directness, consistency and publication bias

APPENDIX B. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
413.0	Angina decubitus
413.1	Prinzmetal angina
413.9	Other and unspecified angina pectoris
414.0	Coronary atherosclerosis
414.2	Chronic total occlusion of coronary artery
414.8-9	Other specified and unspecified forms of chronic ischemic heart disease
ICD-10 Diagnosis Codes	
I20.1	Angina pectoris with documented spasm
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I20.10	Atherosclerotic heart disease of native coronary artery without angina pectoris
I25.82	Chronic total occlusion of coronary artery
I25.89	Other forms of chronic ischemic heart disease
I25.9	Chronic ischemic heart disease, unspecified
ICD-9 Volume 3 (Procedure Codes)	
36.0	Removal of coronary obstruction and insertion of stent(s)
36.1	Bypass anastomosis for heart revascularization
CPT Codes	
33510-33516	Coronary artery bypass – venous grafting only
33517-33530	Combined arterial-venous grafting for coronary bypass
33533-33548	Arterial grafting for coronary artery bypass
92920-92944	Percutaneous revascularization procedures
HCPCS Level II Codes	
	None

Note: Inclusion on this list does not guarantee coverage

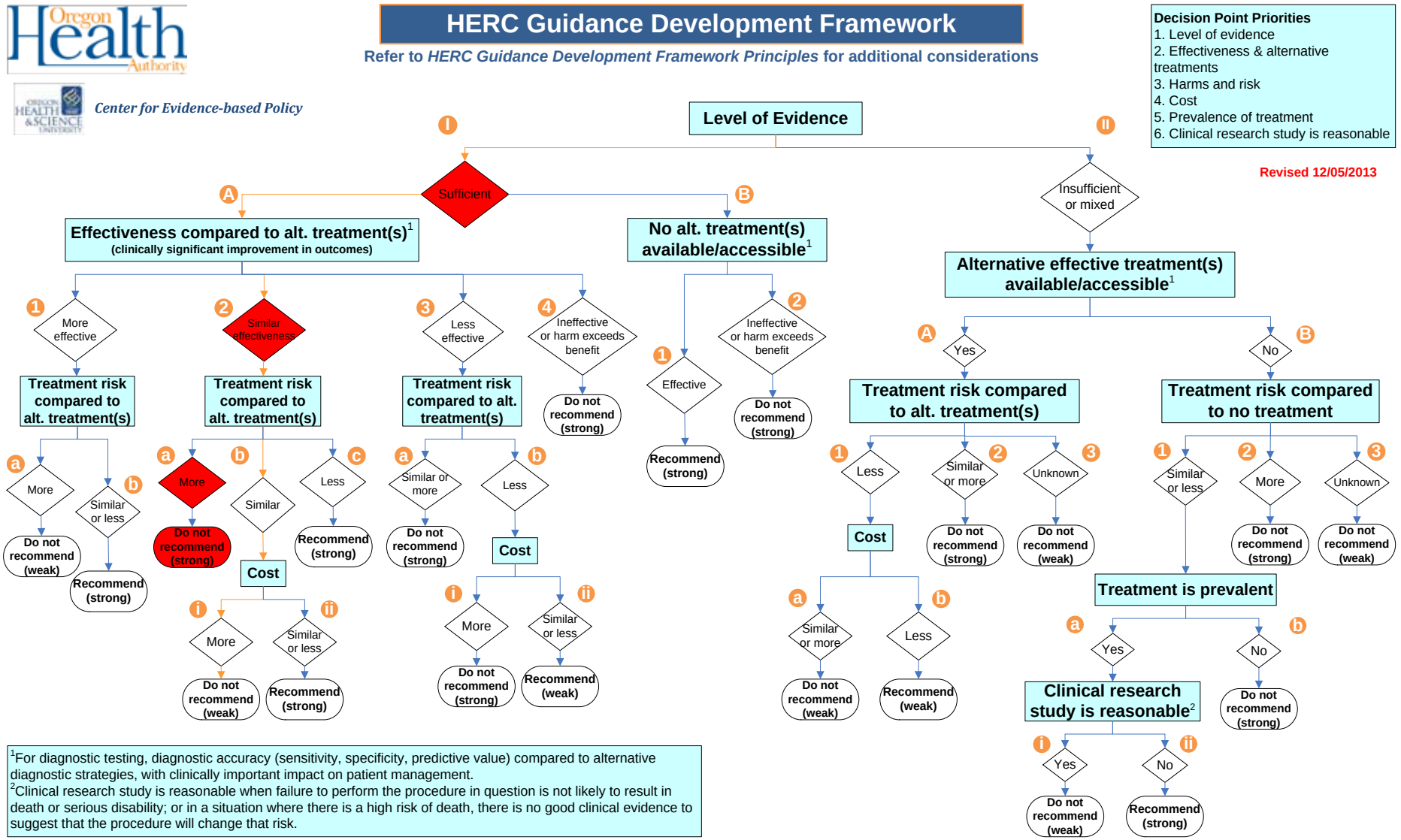
APPENDIX C. HERC GUIDANCE DEVELOPMENT FRAMEWORK

HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.

PCI for chronic stable angina vs. OMT – Based on mortality, MI



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

PCI for chronic stable angina vs. OMT based on quality of life

Oregon Health Authority

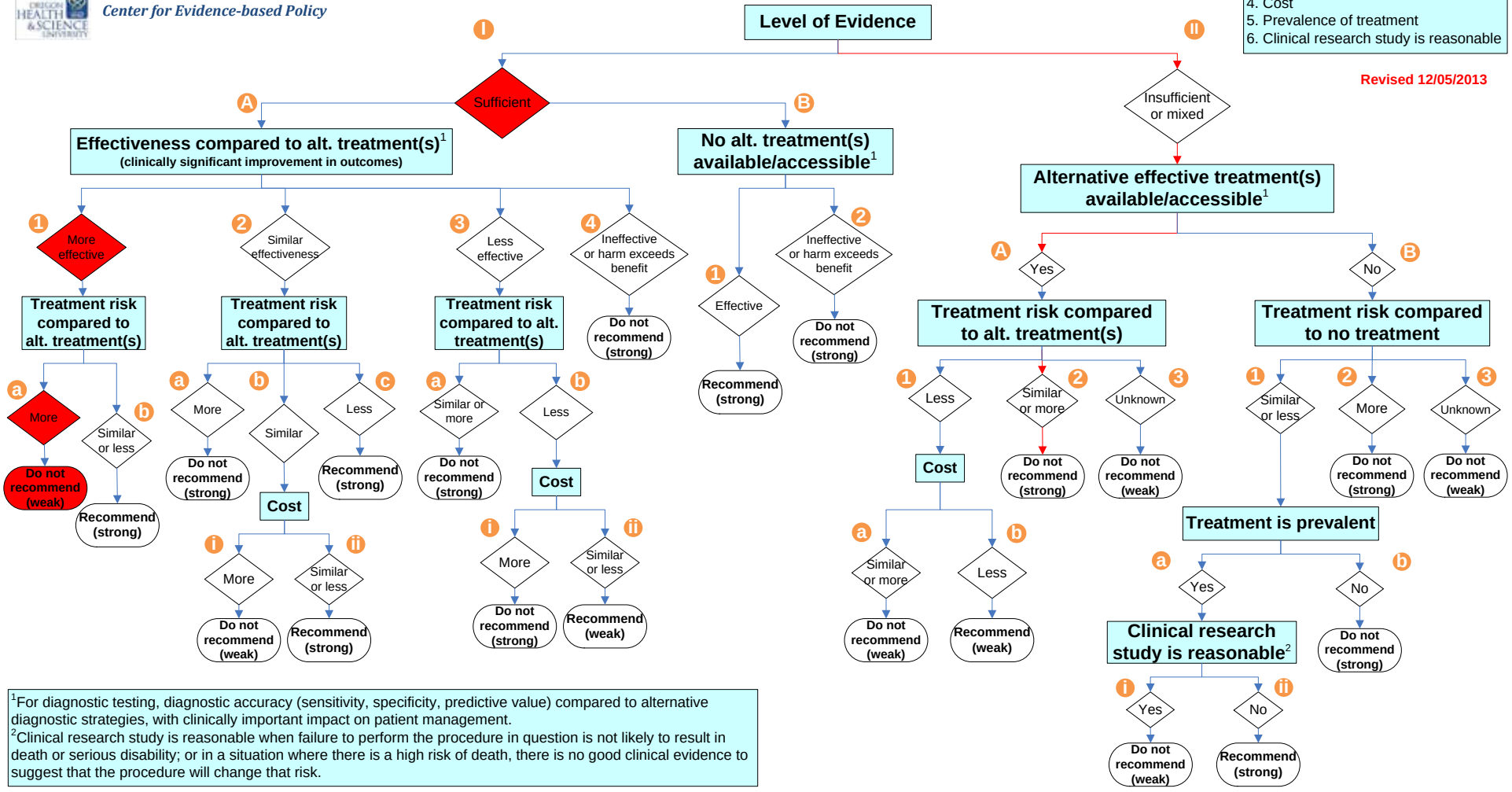
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities
1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

Revised 12/05/2013



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

CABG for chronic stable angina vs. OMT in 3-vessel and left main disease, based on mortality, MI, MACE

Oregon Health Authority

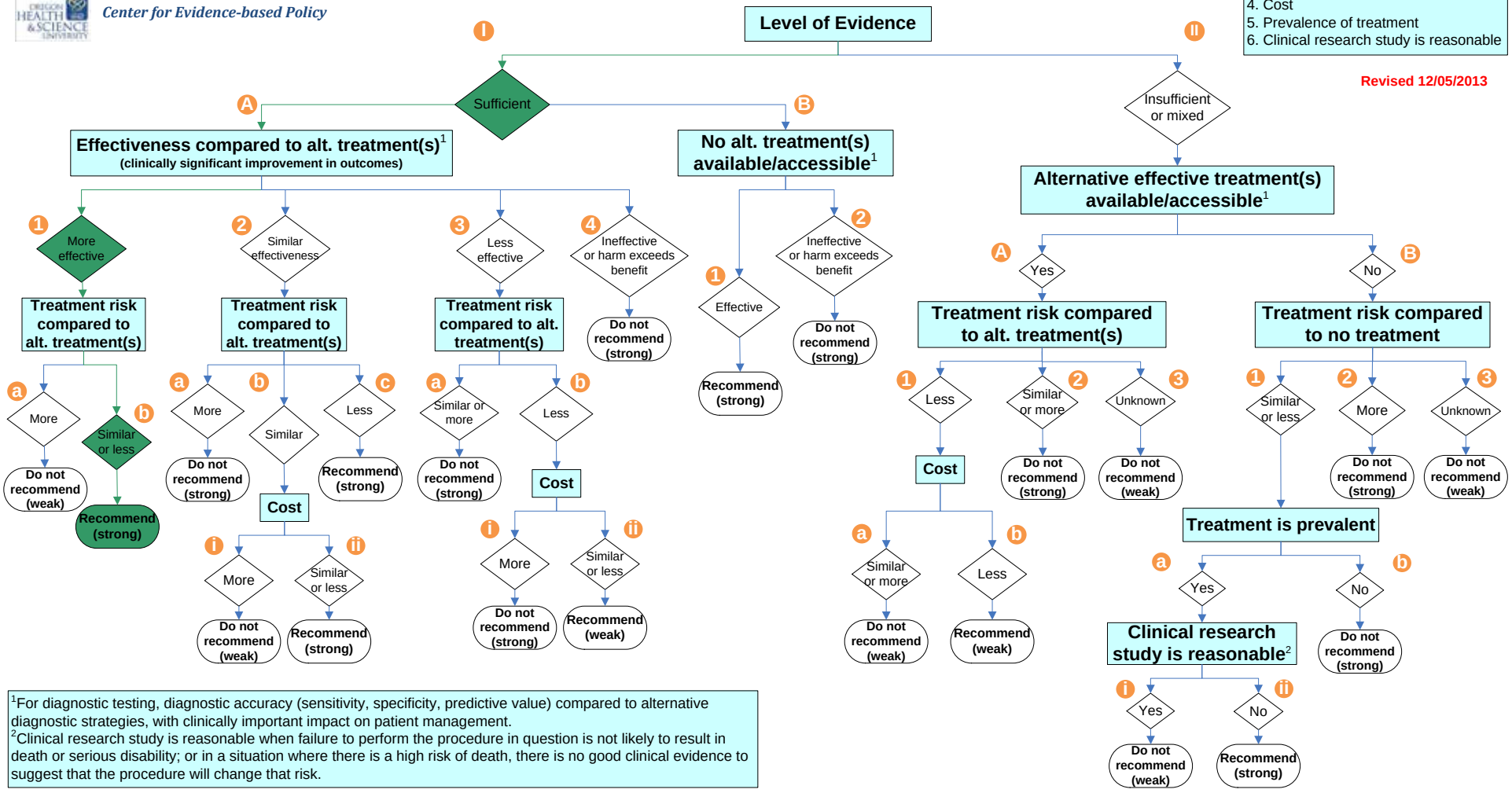
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities
1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

Revised 12/05/2013



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

CABG for chronic stable angina vs. OMT in 1- or 2-vessel, not left main, based on mortality, MI, MACE

Oregon Health Authority

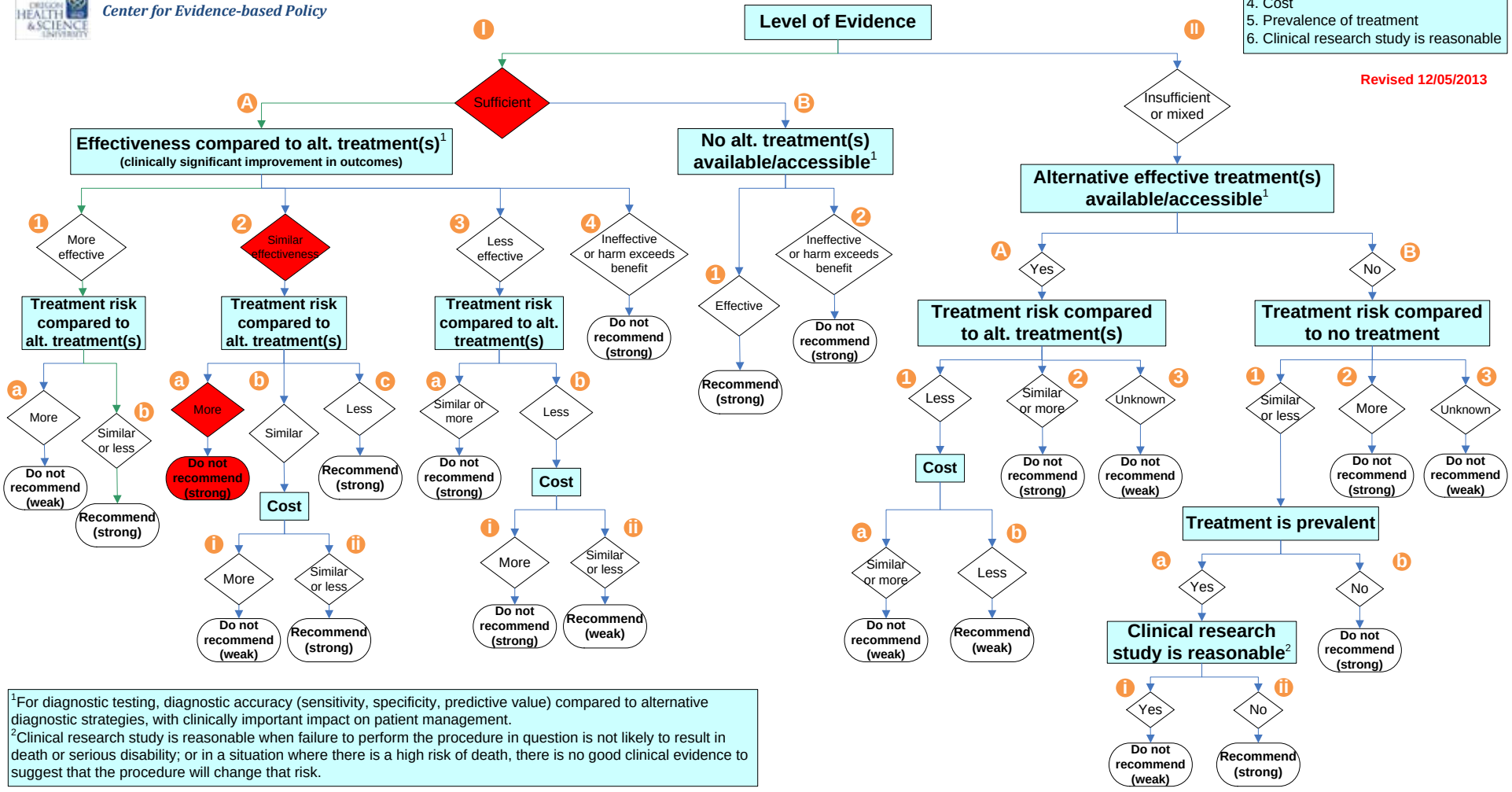
Center for Evidence-based Policy

HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

Decision Point Priorities
1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

Revised 12/05/2013



[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

Coronary Artery Revascularization for Stable Angina – Prioritized List Changes

Current Prioritized List status

ICD-9 Code	**Code Description**	**Current Line(s) / Lists**
413.x	Angina	**193** CHRONIC ISCHEMIC HEART DISEASE
414.0x	Coronary atherosclerosis	**193** CHRONIC ISCHEMIC HEART DISEASE
414.8-414.9	Chronic ischemic heart disease	**193** CHRONIC ISCHEMIC HEART DISEASE
ICD-10 Code		
I20.x	Angina pectoris	**193** CHRONIC ISCHEMIC HEART DISEASE
I25.111-I25.118	Atherosclerotic heart disease of native coronary artery with angina pectoris	**193** CHRONIC ISCHEMIC HEART DISEASE
I25.119	Atherosclerotic heart disease of native coronary artery with unspecified angina pectoris	**Services Recommended for Non-Coverage Table**
I25.701, I25.708, I25.711, I25.721, I25.731, I25.738, I25.751, I25.758, I25.761, I25.768. I25.791, I25.798	Atherosclerosis of autologous/non-autologous vein/artery coronary artery bypass graft(s) with angina pectoris	**193** CHRONIC ISCHEMIC HEART DISEASE
I25.709	Atherosclerosis of coronary artery bypass graft(s), unspecified, with unspecified angina pectoris	**Services Recommended for Non-Coverage Table**
I25.719	Atherosclerosis of autologous vein coronary artery bypass graft(s) with unspecified angina pectoris	**Services Recommended for Non-Coverage Table**
I25.729	Atherosclerosis of autologous artery coronary artery bypass graft(s) with unspecified angina pectoris	**Services Recommended for Non-Coverage Table**
I25.739	Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unspecified angina pectoris	**Services Recommended for Non-Coverage Table**
I25.759	Atherosclerosis of native coronary artery of transplanted heart with unspecified angina pectoris	**Services Recommended for Non-Coverage Table**
I25.769	Atherosclerosis of bypass graft of coronary artery of transplanted heart with unspecified angina pectoris	**Services Recommended for Non-Coverage Table**
I25.799	Atherosclerosis of other coronary artery bypass graft(s) with unspecified angina pectoris	**Services Recommended for Non-Coverage Table**
I25.89	Other forms of chronic ischemic heart disease	**193** CHRONIC ISCHEMIC HEART DISEASE
I25.9	Chronic ischemic heart disease, unspecified	**193** CHRONIC ISCHEMIC HEART DISEASE

Coronary Artery Revascularization for Stable Angina – Prioritized List Changes

CPT codes		
33510-33516	Coronary artery bypass – venous grafting only	**73** ACUTE AND SUBACUTE ISCHEMIC HEART DISEASE, MYOCARDIAL INFARCTION **103** CARDIOMYOPATHY **193** **290** COMPLICATIONS OF A PROCEDURE ALWAYS REQUIRING TREATMENT
33517-33530	Combined arterial-venous grafting for coronary bypass	**73,103,193,290**
33533-33536	Arterial grafting for coronary artery bypass	**73,193,290**
92920-92944	Percutaneous revascularization procedures	**49,73,102,193**

Coronary Artery Revascularization for Stable Angina – Prioritized List Changes

HERC Staff recommendations:

1) Add ICD-10 I25.119, I25.709, I25.719, I25.729, I25.739, I25.759, I25.769, I25.799 (Atherosclerosis with unspecified angina) to line 193
    a. Remove from the Recommended for Non-Coverage Table
2) Adopt the following new guideline for line 193

GUIDELINE NOTE XXX REVASCULARIZATION FOR CHRONIC STABLE ANGINA

Line 193

Coronary revascularization with percutaneous coronary intervention (PCI; CPT 92920-92944) or coronary artery bypass surgery (CABG; CPT 33510-33516, 33517-33530, 33533-33536) is included on this line for patients with stable angina (ICD-9 413.x, 414.0x, 414.8, 414.9/ICD-10 I20.x, I25.111-119, I25.701-9, I25.711-9, I25.721-9, I25.731-9, I25.751-9, I25.761-9, I25.791-9,I25.89, I25.9) whose symptoms are not controlled with optimal medical therapy for angina or who cannot tolerate such therapy.

Optimal medical therapy for angina symptom control prior to PCI is defined as two or more antianginals (beta-blocker, nitrate, calcium channel blocker, or ranolazine) in addition to standard treatment for coronary artery disease.

For those with left main coronary artery stenosis or three-vessel coronary artery stenosis, CABG is included on this line with or without a trial of optimal medical therapy.

HERC Coverage Guidance – Coronary artery revascularization for stable angina
Disposition of Public Comments

Stakeholder	#	Comment	Disposition
	1	No public comments were received for this topic.	