Health Evidence Review Commission's Health Technology Assessment Subcommittee

September 22, 2014

1:00 PM

Meridian Park Hospital
Community Health Education Center, Room 104
19300 SW 65th Avenue, Tualatin, OR 97062

Section 1.0

Call to Order

AGENDA

HEALTH TECHNOLOGY ASSESSMENT SUBCOMMITTEE (HTAS)

Meridian Park Hospital Health
Education Center, Room 104
Tualatin, Oregon
September 22, 2014 from 1:00 pm - 4:00 pm

All agenda items are subject to change and times listed are approximate

Public comment on listed topics will be taken at the time that topic is discussed and may be limited depending on the number of individuals providing testimony

#	Time	Item	Presenter	Action Item
1	1:00 PM	Call to Order	Jim MacKay	
2	1:05 PM	Review of July minutes	Jim MacKay	X
3	1:10 PM	Alternatives to transurethral resection of the prostate (TURP).	Wally Shaffer	X
4	2:10 PM	Advanced imaging in the staging of prostate cancer	Wally Shaffer	X
5	3:10 PM	Review results of topic monitoring	Alison Little	X
6	3:50 PM	Confirm next meeting:	Jim MacKay	
7	3:55 PM	General Public Comment		
8	4:00 PM	Adjournment	Jim MacKay	

MINUTES

Health Technology Assessment Subcommittee
Meridian Park Community Health Education Center
19300 SW 65th Avenue, Tualatin, OR
July 28, 2014
1:00-3:00pm

Members Present: James MacKay, MD, Chair Pro Tem; Gerald Ahmann, MD, PhD; George Waldmann, MD; Timothy Keenen, MD.

Members Absent: None.

Staff Present: Darren Coffman; Wally Shaffer, MD, MPH; Rachel Seltzer (Preventive Medicine resident at OHSU), Jason Gingerich.

Also Attending: Alison Little, MD (CEBP); Erika Zoller (CEBP); Jim Murray (Hill-Rom), David Sibell (OHSU), Enoch Huang, MD (Adventist Health); Ann Demaree, RN (Healogics & Oregon Bioscience Association)

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1. CALL TO ORDER

Jim MacKay called the meeting of the Health Technology Assessment Subcommittee (HTAS) to order at 1:00 pm.

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2. MINUTES REVIEW

No changes were made to the April 2014 minutes.
Minutes approved 4-0.

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3. REVIEW OF PUBLIC COMMENTS

A) Indications for Hyperbaric Oxygen Therapy

Alison Little reviewed the public comments and the staff-recommended responses. The subcommittee discussed the indication of acute sensorineural hearing loss, asking about the cost versus lifetime hearing aids and the durability of the results. Huang said that the results would be expected to last until another acute event, as the current theory is that this condition is caused by an ischemic event affecting receptor cells. Little said that the evidence showed results taken from a time immediately after treatment to three months after treatment. Huang said he has spoken with otorhinolaryngologists who said such a modest improvement to a minimal hearing loss would be clinically significant, contradicting the Cochrane review. Waldmann asked about Cochrane's basis for saying the change was not significant. Little said that the 8 trials reported mixed results but showed a benefit in the metaanalysis and that there was no reason given for not finding the results clinically significant. After discussion, the subcommittee chose not to make

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any change to the coverage guidance for this indication, but members offered to review further evidence if it becomes available.

Little reviewed the comments and resposes on carbon monoxide poisoning. MacKay confirmed that the Oregon Health Plan does cover this indication. Shaffer said that this is true but that staff has requested clarity on the HTAS position on continued coverage for this condition. After discussion, the subcommittee reworded the draft presented as a handout to the meeting materials to indicate that it (along with air or gas embolism, decompression illness and cyanide poisoning) is presumed to be appropriate for coverage but has been excluded from the coverage guidance recommendation. The group also agreed to delete the row for this indication from the GRADE-informed framework and guidance development framework. The subcommittee also struck the indication of progressive necrotizing infections, as these are not easily distinguished from gas gangrene at the time of treatment, though Shaffer said they are distinguished in the studies. Huang said gas gangrene is treated in the hyperbaric medicine field similarly to other necrotizing infections.

Shaffer raised a concern about refractory osteomyelitis. This indication was not included in any of the public comments, but this was raised earlier by Huang. He said that other payers cover this indication, but he suggested the topic may be appropriate for further discussion. Huang said as a practitioner he would like to have it covered but unfortunately the evidence isn't strong, and new evidence may not become available. Still, many payers are covering it and the Undersea and Hyperbaric Medical Society recommends it, though it can be overused. A forthcoming clinical practice guideline may provide clarity on which patients would benefit from treatment. After brief discussion the subcommittee made no changes.

MacKay raised the indication of thermal burns. Huang said that there currently isn't sufficient evidence according to the HERC critieria but that he is working on a GRADE evidence review with a national group and may present new information when the work is complete.

A motion was made to approve the draft coverage guidance and public comment disposition as modified during the meeting and forward to HERC. **Motion approved 4-0.**

HERC COVERAGE GUIDANCE

Hyperbaric oxygen therapy is recommended for coverage (*strong recommendation*) for diabetic wounds of the lower extremities in patients who meet all of the following criteria:

- Patient has Type 1 or Type 2 diabetes and has a lower extremity wound that is due to diabetes, and
- Patient has a wound classified as Wagner grade III or higher, and
- Patient has failed an adequate course of standard wound therapy including arterial assessment, with no measurable signs of healing after at least thirty days.

Hyperbaric oxygen therapy is recommended for coverage for late radiation tissue injury, and gas gangrene (*strong recommendation*).

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Hyperbaric oxygen therapy is recommended for coverage for compromised surgical flaps and grafts, and for crush injuries (*weak recommendation*).

Hyperbaric oxygen therapy is not recommended for coverage for cerebral palsy, multiple sclerosis or chronic sensorineural hearing loss (*strong recommendation*).

Hyperbaric oxygen therapy is not recommended for coverage for the following conditions (*weak recommendation*):

- Venous ulcers,
- Surgical reconstruction without flaps and grafts,
- Refractory osteomyelitis,
- Acute traumatic brain injury,
- Brain injuries other than acute traumatic brain injury,
- Migraines and cluster headaches,
- Acute sensorineural hearing loss,
- Delayed or non-healing fractures,
- Bell's Palsy,
- Malignant otitis externa,
- Vascular dementia,
- Thermal burns, or
- Acute coronary syndrome.

The following indications are presumed to be appropriate for coverage but are excluded from these coverage guidance recommendations: air or gas embolism, acute carbon monoxide poisoning, decompression illness and cyanide poisoning.

B) Percutaneous Interventions for Cervical Spine Pain

Alison Little reviewed the public comments and the recommended responses from the meeting materials. The subcommittee discussed the comment about epidural steroid injections for herniated disc versus neuroforaminal stenosis. Little said there is very little literature on this treatment so the recommendation relies on guidelines rather than evidence in this case. Keenen said he does not see a big difference between a spondylosis or bone stenosis versus a herniated disc. Little said that the one study we have is with patients with a herniated disc. Sibell confirmed that a herniated disc can cause the stenosis. With either condition, there is nerve impingement visible on an MRI scan. There can be inflammation with either condition and the injection would treat the pain resulting from the inflammation. Sibell agreed, and said it is difficult to find support in the literature for steroid injections for spinal canal stenosis. Based on this discussion, the subcommittee modified the draft coverage guidance to specify documented neuroforaminal stenosis (without infection or neoplasia) and to remove the requirement of herniated disc. Waldmann asked whether epidural steroid injections might help a patient with a tight foramen who does something to inflame the nerve. Sibell said there is no evidence that a steroid injection would reduce the size of the nerve, but it may reduce pain. He said the injection is not about improving function, but about relieving some of the pain symptoms. Sibell and Keenen agreed that patients with objective loss of

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function would be more likely to benefit from surgery; a percutaneous intervention alone would only serve to relieve symptoms and not address the underlying problem while surgery, and potentially early surgery, may be the best opportunity to restore or preserve function. Sibell acknowledged that this conflicts with the North American Spine Society (NASS) comments which suggested that the evidence is stronger for nonosseous central stenosis, but he couldn't find support for that indication in the literature or among colleagues.

In reviewing comment #2 about spinal nerve (root) blocks using a foraminal approach, Sibell clarified that he believes NASS to be referring to transforaminal selective nerve root block with local anesthetic. He said this is different from the medial branch block used to evaluate whether facet joint radiofrequency neurotomy may be appropriate. Little said that selective nerve root blocks were not reviewed in the core sources for this report. Sibell said he is not aware of any evidence about this procedure, though it may have value. Seltzer clarified that there is no potential for conflicting guidance on these codes as the current guidance does not address selective nerve root blocks of this kind and recommends against coverage of epidural steroid injections using a transforaminal approach.

The subcommittee also discussed the comment about the definition of "chronic". Though the study inclusion criteria required chronic pain for 6 months, Sibell and Keenen both said that the patients most likely to benefit may have pain of shorter duration. The subcommittee agreed there was no evidence to support a specific duration but that six weeks seemed reasonable. After discussion, the subcommittee settled on striking the requirement that the pain be chronic but required that the pain last for six weeks before injection.

Sibell also noted that epidural steroid injections are not effective for cervicogenic headache. Little said that there is a study included in the report which confirms this. However, Sibell said facet joint radiofrequency denervation can be effective for occipital pain, which can include cervicogenic headache. The subcommittee added a clarification that epidural steroid injections are not recommended for coverage for headache.

The subcommittee accepted all the other recommended changes as they appeared in the meeting materials.

A motion was made to approve the draft coverage guidance as modified and forward to HERC. **Motion approved 4-0.**

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HERC COVERAGE GUIDANCE

Therapeutic cervical spinal epidural injections are recommended for coverage for cervical spine pain with radiculopathy of six weeks duration (*weak recommendation*) only when all of the following criteria are met:

- documented neuroforaminal stenosis (without infection or neoplasia),
- radicular pain in a corresponding dermatomal distribution,
- pain is intractable and conservative therapy has failed,
- fluoroscopic guidance or CT guidance is utilized,
- interlaminar approach is utilized,
- no more than two injections without clinically meaningful improvement in pain and function, and
- maximum of three injections in six months.

Epidural steroid injections of the cervical spine are not recommended for coverage *(strong recommendation)* for other types of neck pain or for headache.

Therapeutic cervical intraarticular facet joint injections and therapeutic cervical medial branch blocks are not recommended for coverage for facet joint pain (*strong recommendation*).

Facet joint radiofrequency neurotomy is recommended for coverage *(weak recommendation)* only when all the following criteria are met:

- at least 3 months of moderate to severe pain with functional impairment,
- pain is predominantly axial and not associated with radiculopathy,
- conservative therapy has failed, and
- complete or nearly complete pain relief (80% or greater) following fluoroscopically guided, low-volume local anesthetic blocks of the medial branch nerves, performed on two separate occasions using two commonly-used agents with different anticipated durations of action.

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4. PUBLIC COMMENT

There was no public comment.

5. STAFF REPORT

Coffman reported that the process improvement report mentioned at the last meeting has been delayed but will be discussed at a planned retreat in October, and that any changes to HTAS would be postponed until after that retreat. He encouraged HTAS members to attend, as it may help them better understand the work of the entire HERC and its other subcommittees.

6. ADJOURNMENT

The meeting was adjourned at 3:00 pm. The next meeting is scheduled for September 22, 2014 from 1:00-4:00pm in Room 104 of the Meridian Park Hospital Community Health Education Center in Tualatin.

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Section 2.0

Coverage Guidances

HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: SURGICAL ALTERNATIVES TO TRANSURETHRAL RESECTION OF THE PROSTATE FOR LOWER URINARY TRACT SYMPTOMS IN MEN

DRAFT FOR HTAS MEETING 9/22/2014

HERC Coverage Guidance

For men with lower urinary tract symptoms (LUTS) due to benign prostate enlargement, coverage of surgical procedures is recommended only if symptoms are severe, or if drug treatment and conservative management options have been unsuccessful or are not appropriate. (*strong/weak recommendation*)

The following are coverage recommendations regarding surgical alternatives to transurethral resection of the prostate (TURP):

Recommended for coverage (*strong recommendation*):

- HoLEP (Holmium: YAG Laser Enucleation of Prostate)
- Thulium laser resection
- TUVP (Transurethral Vaporization of Prostate)
- Bipolar TUVP
- TUIP (Transurethral Incision of the Prostate)
- TUVRP (Transurethral Vaporesection of the Prostate)
- Bipolar TURP

Recommended for coverage (*weak recommendation*):

- TUNA (Transurethral Needle Ablation of Prostate)

Not recommended for coverage (*weak recommendation*):

- HoLRP
- Botulinum toxin
- HIFU (High Intensity Focused Ultrasound)
- TEAP (Transurethral Ethanol Ablation of the Prostate)
- Prostatic artery embolization
- Prostatic urethral lifts

Not recommended for coverage (*strong recommendation*):

- Laser coagulation
- Laser vaporization
- TUMT (Transurethral Microwave Thermotherapy)
- Bipolar TURVP

Note: Definitions for strength of recommendation are provided in Appendix B 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

National Institute for Health and Clinical Excellence. (2010). *Management of lower urinary tract symptoms in men.* London: National Institute for Health and Clinical Excellence. Retrieved from http://publications.nice.org.uk/lower-urinary-tract-symptoms-cg97

National Institute for Health and Clinical Excellence. (2013). *Interventional procedure guidance 453: Prostate artery embolisation for benign prostatic hyperplasia.* London: National Institute for Health and Clinical Excellence. Retrieved from http://www.nice.org.uk/nicemedia/live/13705/63679/63679.pdf

National Institute for Health and Clinical Excellence. (2014). *Interventional procedure guidance 475: Insertion of prostatic urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia*. Retrieved from http://www.nice.org.uk/nicemedia/live/13967/66323/66323.pdf

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

EVIDENCE OVERVIEW

Clinical background

Lower urinary tract symptoms (LUTS) comprise storage, voiding and post-micturition symptoms affecting the lower urinary tract. There are many possible causes of LUTS such as abnormalities or abnormal function of the prostate, urethra, bladder or sphincters. In men, the most common cause is benign prostate enlargement (BPE), which obstructs the bladder outlet.

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BPE happens when the number of cells in the prostate increases, a condition called benign prostatic hyperplasia. Other conditions that can cause LUTS include detrusor muscle weakness or overactivity, prostate inflammation (prostatitis), urinary tract infection, prostate cancer and neurological disease. This guidance document addresses the surgical management of LUTS in men.

LUTS are a major burden for the aging male population. Age is an important risk factor for LUTS and the prevalence of LUTS increases as men get older. Troublesome LUTS can occur in up to 30% of men older than 65 years. There has been an increase in the use of pharmacotherapy for LUTS over the last 25 years, with a considerable decline in surgical rates. However, endoscopic resections of the male bladder outlet remain a common procedure, and although it is often effective in reducing symptoms in men, it is associated with considerable morbidity and a significant overall annual cost. In addition, a significant proportion of men (25–30%) do not benefit from prostatectomy and have poor post-surgical outcome with no improvement of symptoms.

The management options for male LUTS include conservative management, drug therapies and surgery. The decision to opt for a particular type of therapy is dependent on patient choice and clinical considerations, such as severity of symptoms, degree of prostatic enlargement and the response to any preceding treatment. It also takes into account the risk/benefit balance of each therapy.

In general terms the conservative treatments carry the lowest risk but have a lower chance of success and a higher chance of symptom recurrence. Medical therapies with drugs such as alpha blockers and 5 alpha-reductase inhibitors carry a greater risk of interactions and adverse effects but may produce better subjective and objective improvement. Surgical intervention carries the greatest possibility of improvement, particularly in those with severe symptoms but this must be weighed against the risks of surgery, anesthesia and hospitalization.

Transurethral resection of prostate (TURP) has been the mainstay of treatment for symptomatic BPE for many years since it combines high effectiveness with a previously acceptable side effect profile. However, less morbid invasive treatments have been developed. These interventions can be sub-divided into surgical procedures that generally involve removal of prostate tissue requiring general or regional anesthesia and minimally invasive options, which do not require general anesthesia and can be carried out in an outpatient setting.

The interventions considered in this guidance document include the following:

- Holmium:YAG Laser Enucleation of Prostate (HoLEP):
    - Uses Holmium: YAG laser to dissect in the surgical planes and is conceptually the endoscopic equivalent of open prostatectomy.
    - The completely resected prostate lobes are pushed into the bladder, morcellated and removed. The use of the morcellator requires special training.
    - The procedure requires similar operative and anesthetic conditions and post-operative care to TURP, though may take longer.

  - Useful for large prostates which would previously have required an open prostatectomy.
  - Holmium Laser Resection of the Prostate (HoLRP) uses Holmium YAG laser to deliver the energy to the prostate but tissue is removed in a piecemeal fashion similar to undertaking diathermy resection in TURP.
  - Thulium resection uses a Thulium YAG fiber to deliver light of 2000nm wavelength light to vaporize and resect or enucleate tissue. These resection techniques can be undertaken using saline as an irrigating solution, thus reducing the risk of "TURP" syndrome, a rare but serious complication of TURP.
- Laser coagulation techniques:
  - Laser induced necrosis of prostatic tissue is achieved either by surface application of the laser to the prostatic urethra in a technique termed visual laser ablation of the prostate (VLAP) or by inserting specially designed laser fibers into the prostatic tissue via the urethra, termed interstitial laser coagulation (ILC).
  - Typically up to 10 locations can be treated with the procedure lasting 30-60 minutes under local anesthesia.
  - Catheterization is typically required for between three and seven days.
- Laser vaporization techniques:
  - Initially neodinium-yttrium-aluminium-garnet (Nd-YAG – wavelength 1064 nm) was used but this resulted in relatively deep tissue penetration (4mm).
  - Now 532 nm KTP laser is used, generated by passing the Nd-YAG generated beam through a potassium-titanyl-phosphate (KTP) crystal. The light is absorbed by hemoglobin and results in minimal tissue penetration (1mm).
  - Holmium ablation (HoLAP) wavelength 2100nm is a similar technique which results in water absorption of light with tissue penetration of 0.8 mm.
  - Vaporization techniques require similar anesthesia and operating conditions to TURP but with longer operating times.
  - Vaporization technology is rapidly changing (differing wavelengths, power outputs and penetration) and published literature often refers to technology that manufacturers would regard as obsolete.
- Transurethral microwave thermotherapy (TUMT):
  - Microwave energy used to achieve temperatures of 45 - 70°C in the prostate depending on the device and power setting.
  - Treatment lasts 30-60 minutes using local anesthesia and oral analgesia together with sedation for high energy protocols.
  - Requirement for post-operative catheterization varies from 1-12 weeks depending on the protocol used.
- Transurethral vaporization of prostate (TUVP):
  - Utilizes a standard monopolar electro-diathermy device as for TURP.
  - The current is delivered through a grooved ball or modified loop electrode with temperatures up to 300 – 400C. Further modification has allowed the use of bipolar current enabling use of physiological saline as a safer irrigant with tissue effects occurring at lower temperatures (ranging from 40-70C).

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  - Electrode rolled over the prostate to vaporize tissue and coagulate surface reducing blood loss.
  - No tissue is available for histological examination.
- Transurethral needle ablation of prostate (TUNA):
  - Radio frequency energy delivered through two adjustable needles which are inserted into the prostate.
  - Localized heating up to 115°C, causing tissue death.
  - Procedure lasts 30 to 60 minutes under local or regional anesthesia.
  - Indwelling catheter placed for up to 3 days.
- Transurethral incision of the prostate (TUIP):
  - Bilateral or unilateral incisions from bladder neck to verumontanum, usually for small prostates.
  - Indwelling catheters usually left in the urethra for less time compared to TURP.
- Botulinum toxin:
  - Injection of botulinum toxin A directly into the prostate.
  - Does not usually require an anesthetic.
  - This treatment is considered investigational.
- Transurethral vaporesection of the prostate (TUVRP):
  - Thick band-like loop electrode at high power used to resect prostate tissue in a similar manner to TURP but combining vaporization and coagulation at the cutting edge.
- High intensity focused ultrasound (HIFU):
  - Ultrasound energy used to achieve temperatures of up to 80–100 C.
  - Treatment lasts about 60 minutes under general anesthetic or sedo-analgesia as an outpatient procedure.
  - Indwelling catheter required for approximately 2 weeks.
- Transurethral ethanol ablation of the prostate (TEAP):
  - Chemical ablation of prostatic tissue using dehydrated ethanol.
  - Delivery of ethanol into the prostate can be achieved either by injecting via a transperineal, transrectal or transurethral (most common) route.
  - Requirement for an indwelling catheter is longer than standard TURP.
- Open prostatectomy (OP):
  - Surgical removal of the prostate through an incision made in the lower abdomen leaving behind only the capsule of the prostate.
  - Hospital stay and recovery period after surgery is usually longer than for TURP.
  - A general or spinal anesthetic is required.
- Transurethral resection of prostate (TURP):
  - Diathermy current for prostate resection via a loop electrode.
  - Continuous flow endoscope passed down the urethra with non-ionic fluid irrigant (usually glycine 1.5%).
  - Coagulative hemostasis achieved with a ball diathermy electrode.
  - Indwelling catheter for 24-48 hours.
  - Hospital stay approximately 1-3 days.
- Bipolar resection of the prostate (bipolar TURP):

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  - Uses a continuous flow resectoscope with saline irrigation reducing the risks of fluid absorption.
  - The cutting loop is similar to the monopolar loop in shape but has the active and return electrode on the same axis, separated by a ceramic insulator.
  - The two electrodes form an ionized plasma "pocket" which can be used to resect or vaporize tissues.
- Prostate artery embolization
  - Aim is to reduce the blood supply of the prostate gland, causing some of it to undergo necrosis with subsequent shrinkage.
  - The procedure is usually performed with the patient under local anesthetic and sedation. Using a percutaneous transfemoral approach, super-selective catheterization of small prostatic arteries is done using microcatheters.
  - Embolization involves the introduction of microparticles to block these small prostatic arteries. Embolization agents include polyvinyl alcohol (PVA), gelatin sponge and other synthetic biocompatible materials.
- Prostatic urethral lift implants
  - Aim is to secure the prostatic lobes in retracted positions such that the lumen of the urethra is increased.
  - The procedure is designed to cause less tissue injury than surgical resection or thermal ablation, and it is claimed to reduce the risk of complications such as sexual dysfunction and incontinence.
  - The procedure is undertaken transurethrally with the patient under local or
  - general anesthesia. A pre-loaded delivery device is passed through a rigid sheath under cystoscopic visualization. The delivery device is used to compress one lateral lobe of the prostate in an anterolateral direction towards the prostatic capsule. A needle is then advanced through the lobe and capsule, and a monofilament implant with 2 end pieces is deployed. One end of the implant is anchored in the urethra and the other on the outer surface of the prostatic capsule, retracting the prostatic lobe away from the urethral lumen.
  - Multiple implants are usually inserted during the same procedure.

Evidence review

Evidence was identified for the following procedures compared to TURP:

- Bipolar TURP
- Bipolar TUVP
- TUVRP
- TEAP
- TUVP
- TUNA
- Laser
- TUMT
- TUIP
- HOLEP

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- Watchful waiting

In addition, evidence was identified for the following comparisons:

- TUVP vs. Laser
- Laser vs. TUMT
- Laser vs. OP
- Laser vaporization vs. laser coagulation
- TUMT vs. sham
- TUIP vs. HOLEP
- OP vs. HOLEP
- Botulinum toxin vs. placebo

HoLEP vs. TURP

There is no statistically significant difference between HoLEP and TURP in improving symptom scores[1] at 3, 6, 12, 24, 36 and 48 months postoperatively [low to moderate strength of evidence (SOE)]. There is no statistically significant difference between HoLEP and TURP in improving quality of life[2] at 3, 6, 12, 24, 36 and 48 months postoperatively (very low to moderate SOE). HoLEP is more effective than TURP in improving urinary flow rate at 3 months and longest follow up (low to moderate SOE). Fewer men treated with HoLEP compared to TURP experienced blood transfusions (moderate SOE). There is no statistically significant difference between HoLEP and TURP in the number of men experiencing strictures, urinary retention, transurethral resection syndrome (TUR), reoperations, incontinence, infection, retrograde ejaculation or mortality (low SOE).

Thulium laser resection vs. TURP

There is no statistically significant difference between thulium laser resection and TURP in improving symptom scores at 6 and 12 months postoperatively (moderate SOE). There is no statistically significant difference between thulium laser resection and TURP in improving maximum urinary flow at long term follow-up (low SOE). There is no statistically significant difference between thulium laser resection and TURP in improving quality of life scores at 6 or 12 months postoperatively (low to moderate SOE). There is no statistically significant difference between thulium laser and TURP in the number of complications for infection, TUR, urinary retention, transfusion, incontinence or retrograde ejaculation (low SOE).

HoLEP vs. TUIP

No studies comparing HOLEP with TUIP were identified in the review. However, one study that compared HoLEP against using holmium laser for bladder neck incision (HoBNI) was found, and it was the opinion of the guideline development group that HoBNI would have outcomes similar to TUIP.

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[1] Symptom scores were reported either using the International Prostate Symptom Score (IPSS) or the American Urological Association's Symptom Score
[2] Quality of life was measured using the IPSS quality of life question

There is no statistically significant difference between HoLEP and HoBNI in improving symptom scores at 3, 6 and 12 months post-operatively. There is no statistically significant difference between HoLEP and HoBNI in improving quality of life scores at 3, 6 and 12 months postoperatively. There is no statistically significant difference between HoLEP and HoBNI in improving the maximum urinary flow at 3 and 12 months post-operatively. There is no statistically significant difference between HoLEP and HoBNI in the number of patients experiencing strictures, incontinence, reoperation, infection, retention or mortality. (Very low SOE for all outcomes.)

HoLEP vs. OP

There is no statistically significant difference between HoLEP and OP in improving symptom scores at 3, 6, 12, 24, 36, 48 or 60 months postoperatively (low to moderate SOE). Open prostatectomy is more effective than HoLEP in improving quality of life scores at 3 months (low SOE). There is no statistically significant difference between HoLEP and OP in improving quality of life scores at 12 and 24 months postoperatively (low SOE). There is no statistically significant difference between HoLEP and OP in improving the maximum urinary flow at 3 months or at long term follow-up (low SOE). Fewer men treated with HoLEP compared to OP experienced blood transfusions (moderate SOE). There is no statistically significant difference between HoLEP and OP with number of patients who experienced mortality, strictures, incontinence, reoperation or retention (low SOE).

Laser coagulation techniques vs. TURP

Laser coagulation techniques are less effective than TURP in improving symptom scores at 12 months and 2 years post-operatively (low SOE). There is no statistically significant difference between laser coagulation techniques and TURP in improving symptom scores at 3 and 6 months (very low SOE). Laser coagulation techniques are less effective than TURP in improving quality of life at 3, 12 months and at 2 years post-operatively (very low to low SOE). There is no statistically significant difference between laser coagulation techniques and TURP in improving quality of life at 6 months post-operatively (very low SOE). No studies report quality of life at 18 months, 3 years, 4 years and 5 years.

Laser coagulation techniques are less effective than TURP in improving the maximum urinary flow at 3 months or longer follow-up postoperatively (low SOE). There is no statistically significant difference between laser coagulation techniques and TURP in all-cause mortality or number of patients who experienced TUR syndrome and urinary retention (low SOE). More patients treated with laser coagulation techniques compared to TURP experienced urinary tract infection and reoperations (moderate SOE). Fewer patients treated with laser coagulation techniques compared to TURP experienced blood transfusions, strictures, retrograde ejaculation or urinary incontinence (low to moderate SOE).

In acute urinary retention (AUR) patients, there is no statistically significant difference between laser coagulation techniques and TURP in symptom scores or quality of life at 6 months follow up (low SOE). In AUR patients, there is no statistically significant difference between laser coagulation techniques and TURP in all-cause mortality or number of patients who experienced

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TUR syndrome, blood transfusion and urinary retention, urinary tract infections, urinary incontinence or reoperations (very low to moderate SOE).

Laser vaporization techniques vs. TURP

There is no statistically significant difference between laser vaporization techniques and TURP in improving symptom score at 3 months, 6 months, 2 years and at 5 years or longer follow up (very low SOE). Laser vaporization techniques are less effective than TURP in improving symptom score at 1 year and 3 years follow up (very low to low SOE). There is no statistically significant difference between laser vaporization techniques and TURP in improving the International Prostate Symptom Score (IPSS) QoL score at 3 months, 1 year and 5 years or longer follow up (very low to low SOE). Laser vaporization techniques are less effective than TURP in improving IPSS QoL score at 3 years follow up (very low SOE).

Laser vaporization techniques are less effective than TURP in improving Qmax[3] at 3 months follow up but there is no statistically significant difference at longest available follow up (very low to low SOE). Fewer patients treated with laser vaporization techniques compared to TURP experienced transfusions or strictures (moderate SOE).

More patients treated with laser vaporization techniques compared to TURP experienced urinary retention (moderate SOE). There is no statistically significant difference between laser vaporization techniques and TURP in number of patients with all-cause mortality, UTI, reoperation, incontinence, TUR syndrome or retrograde ejaculation (very low to low SOE).

Laser vs. OP

There is no statistically significant difference between laser vaporization and OP in improving symptom scores at 3, 6, 12 or 18 months. There is no statistically significant difference between laser vaporization and OP in improving quality of life at 3 months. OP is more effective than laser vaporization in improving quality of life at 6, 12 and 18 months. There is no statistically significant difference between laser vaporization and OP in improving Qmax. Fewer men treated with laser vaporization than OP needed blood transfusions. There is no statistically significant difference between laser vaporization and OP in men experiencing urinary tract infections or reoperation. (Moderate SOE for all outcomes.)

Laser vs. TUMT

There is no statistically significant difference between TUMT and laser coagulation in improving symptom scores at 6 months postoperatively. There is no statistically significant difference between TUMT and laser coagulation in improving the maximum urinary flow at longer follow-up postoperatively. There is no statistically significant difference between laser coagulation and TUMT with number of patients experiencing urinary retention, strictures, reoperations and

[3] Maximum urinary flow rate, measured as milliliters of urine passed per second (ml/sec).

retrograde ejaculation. More men treated with laser coagulation compared to TUMT experienced urinary tract infections. (Low SOE for all outcomes.)

Laser vs. TUVP

TUVP is more effective than laser vaporization in improving symptoms at 6 months, 2 years and 4 years post-operatively (very low SOE). There is no statistically significant difference between TUVP and laser in improving symptom at 12 months, 3 years and 5 years postoperatively (very low SOE). TUVP was more effective than lasers in improving quality of life at 2, 3, and 4 years post-operatively (very low SOE). There is no statistically significant difference between TUVP and laser in improving quality of life at 6 and 12 months postoperatively (very low SOE). There is no statistically significant difference between laser and TUVP in improving the maximum urinary flow at longer follow-up postoperatively (very low SOE). There is no statistically significant difference between laser and TUVP with number of patients who died or experienced strictures, urinary tract infections and incontinence (very low to moderate SOE). More men treated with laser compared to TUVP experienced urinary retention or had reoperation (very low to moderate). Fewer men treated with laser compared to TUVP experienced retrograde ejaculation (moderate SOE).

Laser vs. laser

Laser vaporization techniques vs. Laser coagulation techniques

There is no statistically significant difference between laser coagulation techniques and laser vaporization techniques in improving symptom at 3, 6, 12 and 24 months post operatively (very low SOE). There is no statistically significant difference between laser coagulation techniques and laser vaporization techniques in improving Qmax at 3 months or longest available follow up (very low to low SOE). There is no statistically significant difference between laser vaporization techniques and laser coagulation techniques in number of patients who experienced transfusion, urinary retention, urinary tract infections, reoperations or developed erectile dysfunction (very low SOE).

HoLRP vs. Visual Laser Ablation of the Prostate (VLAP)

There is no statistically significant difference between HoLRP compared to laser coagulation techniques in number of patients who experienced urinary tract infections or urinary retention (very low SOE).

HoLAP vs. KTP laser vaporization

KTP laser vaporization is more effective than HoLAP in improving symptom scores at 3 months. There is no statistically significant difference between HoLAP and KTP laser vaporization in improving symptom scores at 6 or 12 months. There is no statistically significant difference between HoLAP and KTP laser vaporization in improving quality of life IPSS symptom score at 3, 6 or 12 months. There is no statistically significant difference between HoLAP and KTP laser vaporization in improving Qmax at 3, 6 or 12 months. There is no statistically significant

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difference between HoLAP and KTP laser vaporization in men experiencing incontinence, re-catheterization, reoperation, strictures or urinary tract infections. (Low SOE for all outcomes.)

Transurethral microwave thermotherapy (TUMT)

TUMT vs. sham

TUMT is more effective than sham in improving symptom scores at 3 and 6 months (low to high SOE). TUMT is more effective than SHAM in improving maximum urinary flow rate at 3 months follow-up (moderate SOE). TUMT is more effective than sham in improving maximum urinary flow rate at longer follow-up (low SOE). Fewer men treated with TUMT compared to SHAM experienced reoperations (low SOE). Fewer men treated with SHAM compared to TUMT experienced urinary retention (moderate SOE).

There is no statistically significant difference between TUMT and sham treatment in number of men experiencing strictures, urinary tract infections, urinary incontinence, retrograde ejaculation and mortality (low SOE).

TUMT vs. TURP

TURP is more effective than TUMT in improving symptom scores at 3, 6, 24 and 36 months postoperatively (very low to moderate SOE). There is no statistically significant difference between TURP and TUMT in improving symptom scores at 12, 48 or 60 months postoperatively (very low to low SOE). TURP is more effective than TUMT in improving maximum urinary flow rates at 3 months and longest follow-up postoperatively (moderate SOE). TURP is more effective than TUMT in improving quality of life scores at 24 months post operatively (low SOE). There is no statistically significant difference between TURP and TUMT in improving quality of life scores at 3, 6, 12, 36, 48 or 60 months (very low to moderate SOE). There is no statistically significant difference between TUMT and TURP in number of patients experiencing infection, blood transfusion, TUR syndrome, incontinence or mortality (very low to low SOE). There is no statistically significant difference between TUMT and TURP in number of men experiencing retrograde ejaculation (very low SOE). Significantly fewer men treated with TURP experienced reoperations compared to TUMT (moderate SOE). Significantly fewer men treated with TURP experienced acute retention compared to TUMT (low SOE). Significantly fewer men treated with TUMT experienced strictures compared to TURP (low SOE).

Transurethral vaporization of prostate (TUVP)

TUVP vs. TURP

There is no statistically significant difference between TUVP and TURP in improving symptom score at any follow up interval (very low to moderate SOE). TURP is more effective than TUVP in improving quality of life at 6 months (low SOE). TUVP is more effective than TURP in improving quality of life at 3 years (low SOE). There is no statistically significant difference between TUVP and TURP in improving quality of life (IPSS question) at 3 months, 1 year, 2 years and 5 years or longer follow up (low to very low SOE). There is no statistically significant difference between TUVP and TURP in improving Qmax at 3 months or longer follow up (very

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low to low SOE). Significantly more men treated with TUVP than TURP experience urinary retention (low SOE). Significantly more men treated with TURP than TUVP required blood transfusions (low SOE). There is no statistically significant difference between TUVP and TURP in number of men experiencing UTI, incontinence, retrograde ejaculation, TUR syndrome or strictures (very low to low SOE).

Bipolar TUVP vs. TURP

Bipolar TUVP is more effective than TURP in improving symptom score at 3 months, 6 months and 1 year follow up (very low SOE). Bipolar TUVP is less effective than TURP in improving symptom score at 2 and 3 years follow up (very low SOE). Bipolar TUVP is less effective than TURP in improving Qmax at 3 months and 3 years follow up (very low SOE). There is no statistically significant difference between Bipolar TUVP and TURP in number of men requiring transfusion though the result is borderline in favor of Bipolar TUVP (low SOE). There is no statistically significant difference between Bipolar TUVP and TURP in the number of patients experiencing urinary retention, retrograde ejaculation, TUR syndrome or strictures (very low to low SOE). Catheterization time (days) is significantly shorter for those men treated with Bipolar TUVP compared to TURP (very low SOE). There is no statistically significant difference between Bipolar TUVP and TURP in length of stay (days) though the result is borderline in favor of Bipolar TUVP (very low SOE).

Transurethral needle ablation (TUNA)

TUNA vs. TURP

TUNA is less effective than TURP in improving symptoms scores at 12 months and 2, 3 and 4 years post-operatively (very low to low SOE). There is no statistically significant difference between and TUNA and TURP in improving symptom scores at 3, 18 months and 5 years (very low SOE). There is no statistically significant difference between TUNA and TURP in improving quality of life scores at 3 and 18 months (very low SOE). TUNA is less effective than TURP in improving the maximum urinary flow at 3 months or longer follow-up postoperatively (very low SOE). There is no statistically significant difference between TUNA and TURP in all-cause mortality or number of patients who experienced urinary retention or urinary tract infections (very low to low SOE). Fewer men treated with TUNA compared to TURP experienced blood transfusion, strictures, retrograde ejaculation or urinary incontinence (very low to moderate SOE). More men treated with TUNA compared to TURP had reoperations (very low SOE).

Transurethral incision of the prostate (TUIP)

TUIP vs. TURP

There is no statistically significant difference between TUIP and TURP in improving symptom scores at 3 and 6 months post operatively (low SOE). TUIP is significantly more effective than TURP in improving symptom scores at 24 months post operatively (low SOE). There is no data for TUIP compared TURP at 12 months, or beyond 24 months post operatively in improving symptom scores. TUIP is less effective than TURP in improving quality of life scores at 24 months post operatively (low SOE). There is no data for TUIP compared to TURP in improving

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quality of life scores at 3, 6, 12, 36, 48 or 60 months post operatively. There is no significant difference between TUIP and TURP in improving flow rate (Qmax) at 3 months post operatively (low SOE). There is no significant difference between TUIP and TURP in improving peak flow rate (Qmax) at the longest available follow up period reported (low SOE). There is no statistically significant difference between TUIP and TURP in all-cause mortality, number of patients experienced TUR syndrome, urinary retention, urinary incontinence, urinary tract infections or urinary strictures (low SOE). Significantly fewer men treated with TUIP compared to TURP required blood transfusions or experienced retrograde ejaculations (low to moderate SOE). More men treated with TUIP compared to TURP had reoperations (moderate SOE).

TUIP vs. TURP for AUR patients

In men with AUR, there is no statistically significant difference between TUIP and TURP in all-cause mortality, number of men experienced TUR syndrome, urinary retention, urinary incontinence, urinary tract infections or urinary strictures (very low SOE). In men with AUR, significantly fewer men treated with TUIP compared to TURP required blood transfusions (moderate SOE).

Botulinum toxin in the prostate

Botulinum toxin in prostate vs. placebo

Botulinum toxin injection is more effective than placebo in improving symptom scores at 1 and 2 months post injection. Botulinum toxin injection is more effective than placebo in improving peak flow at the longest available follow up (2 months) post injection. There is no data for botulinum toxin compared to placebo in improving symptom scores at 3, 6, 12, 18 or 24 months and beyond in improving peak flow rates (Qmax). There are no events in urinary incontinence for botulinum toxin compared placebo. (Very low SOE for all outcomes.)

Transurethral vaporesection of the prostate (TUVRP)

TUVRP vs. TURP

There is no statistically significant difference between TUVRP and TURP in improving symptom scores at 3 months, 6 months and 2 years (very low to low SOE). TUVRP is more effective than TURP in improving symptom scores at 1 year (moderate SOE). There is no statistically significant difference between TUVRP and TURP in improving Qmax at 3 months and 2 years (very low SOE). There is no statistically significant difference between TUVRP and TURP in improving quality of life IPSS symptom score at 3 months and 2 years (very low SOE). There is no statistically significant difference between TUVRP and TURP in men experiencing incontinence, reoperation, strictures, urinary tract infections, urinary retention, mortality, TUR syndrome or blood transfusions (very low to low SOE).

Bipolar TUVRP vs. TURP

There is no statistically significant difference between Bipolar TUVRP and TURP in improving symptom score from baseline at 3 months. There is no statistically significant difference between Bipolar TUVRP and TURP in improving IPSS QoL score from baseline at 3 months.

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There is no statistically significant difference between Bipolar TUVRP and TURP in improving Qmax from baseline at 3 months. There is no statistically significant difference between Bipolar TUVRP and TURP in the number of men experiencing urinary retention, UTI and TUR syndrome. (Very low SOE for all outcomes.)

High intensity focused ultrasound (HIFU)

No evidence was identified for this procedure.

Transurethral ethanol ablation of the prostate (TEAP)

TEAP vs. TURP

No studies report symptom score, quality of life or peak flow (Qmax) for TEAP compared to TURP at any time point of follow up. Significantly fewer men had blood transfusions for TEAP compared to TURP. There is no statistically significant difference between TEAP and TURP in number of men who experienced urinary retention, urinary incontinence, urinary tract infections or urinary strictures. (Low SOE for all outcomes.)

Transurethral resection of the prostate (TURP)

TURP vs. watchful waiting (WW)

TURP is more effective than watchful waiting in improving Qmax at 3 years follow up (moderate SOE). Significantly more men were re-catheterized perioperatively for the TURP group compared to watchful waiting; 3.2% of men following TURP were re-catheterized (low SOE). Significantly fewer men had reoperation or received surgery for the TURP group compared to the watchful waiting group during the follow up period (moderate SOE). There is no significant difference between TURP and watchful waiting in the number of all-cause mortality or number of men who experienced blood transfusions, urinary tract infections and urinary incontinence (low SOE).

Bipolar TURP vs. TURP

There is no statistically significant difference between Bipolar TURP and TURP in improving symptom score at any follow up interval (low to moderate SOE). There is no statistically significant difference between Bipolar TURP and TURP in improving IPSS QoL score at any follow up interval (low to moderate SOE). There is no statistically significant difference between Bipolar TURP and TURP in improving Qmax at 3 months or 1 year follow up (low SOE). There is no statistically significant difference between Bipolar TURP and TURP in number of men requiring transfusion (low SOE). There is no statistically significant difference between Bipolar TURP and TURP in number of men experiencing urinary retention, UTI, incontinence or strictures (low SOE). There is no statistically significant difference between Bipolar TURP and TURP in number of men experiencing TUR syndrome though the result is borderline in favor of Bipolar TURP (low SOE). There is no statistically significant difference between Bipolar TURP and TURP in reoperation rate or mortality rate (very low to low SOE).

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Prostatic Urethral Lifts vs. Sham

In a randomized controlled trial (RCT) of 206 patients comparing 140 patients treated by prostatic urethral lift against 66 patients treated by a sham procedure there was a significant difference in mean change in American Urological Association Symptom Index (AUASI) score (scores range from 0 to 35; higher score indicating greater severity) at 3-month follow-up. The mean score decreased by 11 points at follow-up from a baseline score of 22 in patients treated by prostatic urethral lift and by 6 points at follow-up from a baseline score of 24 in patients treated by the sham procedure (p=0.003 difference between the groups). Patients reported a significant difference in change in AUASI quality-of-life scores (scale 0 to 5; higher score indicating lower quality of life) at 3 months. The mean quality-of-life score decreased from 5 to 2 in patients treated by prostatic urethral lift and from 5 to 4 in patients treated by the sham procedure (p<0.001 difference between the groups). A significant improvement in mean flow rate at 3 months was also found. The mean improvement in flow rate was 4 ml/s in patients treated by prostatic urethral lift and 2 ml/s in patients treated by the sham procedure (from 8 ml/s at baseline for both groups; p=0.005 difference between the groups). Five percent (7/140) of patients treated by prostatic urethral lift were retreated by one year. Urinary tract infections (within 3 months of the procedure) were reported in 3% (4/140) of patients treated by prostatic urethral lift and 2% (1/66) of patients treated by a sham procedure (level of significance not reported).

Prostatic Artery Embolization (PAE)

No randomized trials of this procedure were identified. One case series of 47 patients reported a 19.4 point improvement in mean IPSS from 24.2 at baseline to 4.8 after prostate artery embolization. Mean prostate volume reduced by 42% from 117 ml to 68 ml. There was an increase in mean Qmax of 97% (from 9.6 ml/s to 18.9 ml/s) after prostate artery embolization reduction, and the mean post-void residual urine volume decreased from 184 ml to 3 ml (p value not reported for any outcome, follow-up ranged from 7 days to 2 years).

A case series of 15 patients reported a 6.5 point improvement in mean IPSS from 21.0 at baseline to 14.5 after the procedure (n=8, p=0.005). Mean reduction in prostate volume assessed by ultrasound decreased by 27% (from 97 ml to 71 ml, measured in 14 patients, p=0.0001) and by MRI decreased by 28% (from 105 ml to 76 ml, measured in 9 patients, p=0.008). There was an increase in mean Qmax of 54% (from 7.1 ml/s to 10.9 ml/s) after the procedure (n=8, p=0.015), and a mean reduction in post-void residual urine volume from 130.8 ml at baseline to 51.3 ml after the procedure (n=8, p=0.0004). Mean follow-up was eight months.

Recommendations of the NICE Guideline

If offering surgery for managing voiding LUTS presumed secondary to BPE, offer monopolar or bipolar transurethral resection of the prostate (TURP), monopolar transurethral vaporization of the prostate (TUVP) or holmium laser enucleation of the prostate (HoLEP). Perform HoLEP at a center specializing in the technique, or with mentorship arrangements in place.

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Offer transurethral incision of the prostate (TUIP) as an alternative to other types of surgery to men with a prostate estimated to be smaller than 30 g. (This recommendation is based on expert opinion of the Guideline Development Group; the majority of studies had an inclusion criteria of prostate size 20 to 40 grams.)

Only offer open prostatectomy as an alternative to TURP, TUVP or HoLEP to men with prostates estimated to be larger than 80 g.(This recommendation is based on expert opinion of the Guideline Development Group; the studies had an inclusion criteria of prostate size 70 to more than 100 grams.)

If offering surgery for managing voiding LUTS presumed secondary to BPE, do not offer minimally invasive treatments (including transurethral needle ablation [TUNA], transurethral microwave thermotherapy [TUMT], high-intensity focused ultrasound [HIFU], transurethral ethanol ablation of the prostate [TEAP] and laser coagulation) as an alternative to TURP, TUVP or HoLEP. (The Guideline Development Group rationale was that, while these minimally invasive techniques offer potentially lower morbidity and shorter lengths of stay than conventional TURP or HoLEP, the current evidence suggests they are less effective and there is little evidence regarding long term outcomes or side effects. They also found that TUNA and TUMT are not cost-effective in the UK setting.)If offering surgery for managing voiding LUTS presumed secondary to BPE, only consider offering botulinum toxin injection into the prostate as part of a randomized controlled trial.

If offering surgery for managing voiding LUTS presumed secondary to BPE, only consider offering laser vaporization techniques, bipolar TUVP or monopolar or bipolar transurethral vaporization resection of the prostate (TUVRP) as part of a randomized controlled trial that compares these techniques with TURP. (The Guideline Development Group rationale pertained to the rapid pace of change with these technologies, and they found that laser vaporization techniques are not cost-effective compared to TURP in the UK setting.)

Current evidence on the efficacy and safety of insertion of prostatic urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. During the consent process clinicians should, in particular, advise patients about the range of possible treatment options and the possible need for further procedures if symptoms recur.

Current evidence on the safety and efficacy of prostate artery embolization for benign prostatic hyperplasia is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.

For men with voiding symptoms, offer surgery only if voiding symptoms are severe or if drug treatment and conservative management options have been unsuccessful or are not appropriate. Discuss the alternatives to and outcomes from surgery.

[Evidence Source]

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Evidence summary

The table below summarizes the various comparisons for which evidence was identified.

Procedure	Comparator	Outcome Differences
TURP	HoLEP	HoLEP with significantly better flow rate, fewer transfusions. No significant differences in symptoms, QoL, other AE
	Thulium laser resection	No significant differences in any outcome (symptoms, flow rate, QoL, AE)
	Laser coagulation techniques	TURP with significantly more improvement in symptoms at 12 and 24 mos (but not 3 or 6), better QoL and flow rate. TURP with more transfusions, strictures, retrograde ejaculation, incontinence; laser coag techniques with more UTI, re-operations
	Laser vaporization techniques	TURP with significantly more improvement in symptoms at 1 and 3 yrs (but not other times), better QoL at 3 yrs and flow rate at 3 mos. TURP with more transfusions, strictures; laser vap techniques with more urinary retention
	TUMT	TURP with significantly more improvement in symptoms at 3, 6, 24 and 36 mos (but not 12, 48 or 60), better QoL at 24 mos and flow rate. TURP with more strictures, fewer re-operations, less urinary retention
	TUVP	No differences in symptoms or flow rate. TURP with better QoL at 6 mos, but TUVP with better QoL at 3 years. TURP with more transfusions, less urinary retention.
	Bipolar TUVP	TUVP with significantly more improvement in symptoms at 3, 6, 12 mos, but significantly less improvement at 2 and 3 years, worse flow rate. TUVP with significantly shorter catheterization time.
	TUNA	TURP with significantly more improvement in symptoms at 1,2,3 and 4 yrs (but not 3, 18 or 60 mos), better flow rate. TURP with more strictures, transfusions, incontinence, fewer re-operations
	TUIP	TURP with significantly less improvement in symptoms but better QoL at 24 mos. TURP with more

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		transfusions, retrograde ejaculation, fewer re-operations. In patients with AUR, there are no differences in any outcome except there are more transfusions with TURP
	TUVRP	TUVRP with significantly more improvement in symptoms at 12 mos only. No differences in any other outcome.
	Bipolar TUVRP	No difference in any outcome, but longest follow up is 3 mos.
	TEAP	No symptom, QoL or flow rate outcomes reported. No differences in any reported outcome except fewer transfusions with TEAP.
	Watchful waiting	No symptom or QoL outcomes reported. TURP with significantly better flow rate, more recatheterizations but fewer repeat or new operations.
	Bipolar TURP	No significant differences for any outcome.
HoLEP	TUIP/ HoBNI	No significant differences for any outcome (single study, very low SOE).
	OP	HoLEP with significantly less improvement in QoL at 3 mos, but not at later times. HoLEP with fewer transfusions.
Laser	OP	Laser with significantly less improvement in QoL at 6, 12 and 18 mos (but not 3 mos). Laser with fewer transfusions.
	TUMT	No significant differences in any outcome except laser with more UTIs.
	TUVP	Laser with significantly less improvement in symptoms at 6, 24 and 48 mos; less improvement in QoL at 2, 3 and 4 yrs. Laser with fewer retrograde ejaculations, more urinary retention and re-operations.
Laser vaporization techniques	Laser coagulation techniques	No differences in any outcome
HoLRP	VLAP	No differences in UTI or urinary retention

HoLAP	KTP laser vaporization	KTP laser with significantly more improvement in symptoms at 3 mos (but not 6 or 12 mos). No other significant differences.
TUMT	Sham	TUMT with significantly more improvement in symptoms at 3 and 6 mos, as well as flow rate. TUMT with fewer re-operations but more urinary retention
Botulinum toxin	Placebo	Botulinum toxin with significantly more improvement in symptoms at 1 and 2 mos as well as flow rate. No outcomes past 2 months.
HIFU	Any comparator	No evidence
Prostatic urethral lifts	Sham	Urethral lifts with significant improvement in symptoms, QoL and flow rate; longest follow up 3 months.
Prostatic artery embolization	None	PAE with improvement in symptoms, flow rate, prostate volume and post-void residual (statistical significance reported in only one small case series).

In general, TURP has significantly better symptomatic outcomes (symptoms, flow rate, QoL) than most of the alternative procedures, at the expense of a higher rate of transfusions, and in some cases, other adverse outcomes. The exceptions to this, where symptomatic outcomes are similar or better, are HoLEP, Thulium laser resection, TUVP, TUVRP and bipolar TURP. TURP comparators for which symptomatic outcomes were not reported or follow up time was 3 months or less are bipolar TUVRP, TEAP, urethral lifts and watchful waiting. Evidence is very low for all outcomes, limiting the ability to draw conclusions, for HoLEP compared to TUIP, HoLRP compared to VLAP, botulinum toxin, HIFU, PAE and bipolar TURVP compared to TURP.

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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[4]	Variability in values and preferences	Coverage recommendation	Rationale
HoLEP (vs. TURP)	Better flow rate, fewer transfusions	Very low to moderate	Moderate	Low	Recommend (strong)	Sufficient evidence; More effective than TURP and similar/less risk.
Thulium laser resection (vs. TURP)	No differences in outcomes	Low to moderate	Moderate	Low	Recommend (strong)	Sufficient evidence; similar effectiveness/risk to TURP; assumed similar/less cost. (Cost may be needed)
HoLEP (vs. HoBNI)	No differences in outcomes	Very low	Moderate			Insufficient evidence; similar or more risk than effective alternatives.

[4] If a procedure is generally undertaken as an outpatient and/or requires only local anaesthesia, resource allocation is listed as low; if it generally requires an inpatient stay and/or general or spinal anaesthesia, it is listed as medium.

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation[4]	Variability in values and preferences	Coverage recommendation	Rationale
HoLEP (vs. OP)	OP has better QoL at 3 mos but not later. HoLEP has few transfusions	Low to moderate	Moderate	Low		Sufficient evidence; more effective but also more risk than OP.
Laser coag techniques (vs. TURP) – general population	Less improvement in symptoms, QoL, flow; more UTI and re-op, fewer transfusions, stricture, RE, incontinence	Very low to moderate	Low	Low	Do not recommend (strong)	Sufficient evidence; less effective than alternatives, similar or more risk.
Laser coag techniques (vs. TURP) – AUR population	No differences in outcomes	Very low to moderate	Low	Low		
Laser vap techniques (vs. TURP)	Less improvement in symptoms, QoL, flow; more UR, fewer transfusions, strictures	Very low to moderate	Low	Low	Do not recommend (strong)	Sufficient evidence; less effective than alternatives, similar or more risk.
Laser vap (vs. OP)	Worse QoL, fewer transfusions	Moderate	Low	Low		
Laser coag (vs. TUMT)	More UTI	Low	Low	Low		
Laser vap (vs. TUVP)	Less improvement in symptoms, QoL; more UR, reoperations, fewer RE	Very low to moderate	Low	Low		

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation[4]	Variability in values and preferences	Coverage recommendation	Rationale
Laser vap (vs. laser coag)	No differences in outcomes	Very low to low	Low	Low		
HoLRP (vs. VLAP)	No differences in outcomes	Very low	Medium/ Low	Low	Do not recommend (weak)	Insufficient evidence; effective alternatives available but unknown which has more risk.
HoLAP (vs. KTP laser vap)	Less improvement in symptoms at 3 mos only	Low	Low	Low		
TUMT (vs. sham)	More improvement in symptoms, flow; more UR, fewer re-op	Low to high	Low	Low		
TUMT (vs. TURP)	Less improvement in symptoms, QoL, flow; more re-op, UR, fewer strictures	Very low to moderate	Low	Low	Do not recommend (strong)	Sufficient evidence; less effective with similar or more risk.
TUVP (vs. TURP)	Better QoL at 3 yrs, worse at 6 mos; more UR, fewer transfusions	Very low to moderate	Medium	Low	Recommend (strong)	Sufficient evidence; similar effectiveness and risk, similar or less cost. (? cost)
Bipolar TUVP (vs. TURP)	More improvement in symptoms early, less improvement later (>1 yr), worse flow; shorter cath times	Very low to low	Medium	Low	Do not recommend (weak)	Sufficient evidence; similar effectiveness and risk, similar or less cost. (? cost)

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation[4]	Variability in values and preferences	Coverage recommendation	Rationale
TUNA (vs. TURP)	Less improvement in symptoms, flow; more re-op, fewer strictures, RE, incontinence	Very low to moderate	Low	Low	Recommend (weak)	Sufficient evidence; less effective than alternatives with less risk. (? cost)
TUIP (vs. TURP) – general population	More improvement in symptoms at 24 mos only, worse QoL; more re-op, fewer transfusions, RE	Low to moderate	Medium	Low	Recommend (strong)	Sufficient evidence; similar effectiveness/risk vs alternatives. Cost assumed similar or less (?cost)
TUIP (vs. TURP) - AUR population	Fewer transfusions	Very low to moderate	Medium	Low		
Botulinum toxin (vs. placebo)	More improvement in symptoms, flow at 1 and 2 mos only	Very low	Low	Low	Do not recommend (weak)	Insufficient evidence; unknown whether available effective alternatives have more or less risk.
TUVRP (vs. TURP)	More improvement in symptoms at 1 yr only	Very low to moderate	Medium	Low	Recommend (strong)	Sufficient evidence; More effective than alternatives; similar or less risk.
Bipolar TURVP (vs. TURP)	No differences in outcomes	Very low	Medium	Low	Do not recommend (strong)	Insufficient evidence; similar or more risk than available effective alternatives

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation[4]	Variability in values and preferences	Coverage recommendation	Rationale
HIFU	No evidence	Very low	Low	Low	Do not recommend (weak)	Insufficient evidence; unknown risk vs. available effective alternatives.
TEAP (vs. TURP)	No symptom outcomes; fewer transfusions	Low	Low	Low	Do not recommend (weak)	Insufficient evidence; less risk than effective alternative; similar or more cost.
TURP (vs. watchful waiting)	Better flow; more cath, fewer re-op	Low to moderate	Medium	Low	Recommend TURP (strong)	Sufficient evidence; More effective than alternatives; similar or less risk.
Bipolar TURP (vs. TURP)	No differences in outcomes	Very low to moderate	Medium	Low	Recommend (strong)	Sufficient evidence; Similar effectiveness to alternatives with similar risk and similar or less cost.

Coag = coagulation; Vap = vaporization; AUR = acute urinary retention; RE = retrograde ejaculation; UR = urinary retention; re-op = reoperation; cath = catheterization

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee, with the exception of urethral lifts and PAE.

Note: GRADE framework elements are described in Appendix A

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POLICY LANDSCAPE

Quality measures

No pertinent quality measures were identified when searching the National Quality Measures Clearinghouse.

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.

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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[5]

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.

[5] Includes risk of bias, precision, directness, consistency and publication bias

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APPENDIX C. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
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 LUTS
600.91	Hyperplasia of prostate, unspecified, with urinary obstruction and other LUTS
ICD-10 Diagnosis Codes	
N40.1	Enlarged prostate with LUTS
N40.3	Nodular prostate with LUTS
ICD-9 Volume 3 (Procedure Codes)	
60.2	Transurethral Prostatectomy
60.3	Suprapubic Prostatectomy
60.4	Retropubic Prostatectomy
60.69	Other
60.92	Injection into prostate
60.96	Transurethral Destruction Of Prostate Tissue By Microwave Thermotherapy
60.97	Other Transurethral Destruction Of Prostate Tissue By Other Thermotherapy
60.99	Other
CPT Codes	
52450	Transurethral incision of prostate
52500	Transurethral resection of bladder neck (separate procedure)
52601	Transurethral electrosurgical resection of the prostate, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included)
52630	Transurethral resection; of regrowth of obstructive prostate tissue, including control postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included)
52647	Laser coagulation of prostate, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included if performed)
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)
52649	Laser enucleation of the prostate with morcellation, 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)
53850	Transurethral destruction of prostate tissue; by microwave thermotherapy
53852	Transurethral destruction of prostate tissue; by radiofrequency thermotherapy

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HCPCS Level II Codes	
None	

Note: Inclusion on this list does not guarantee coverage

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APPENDIX D. 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.

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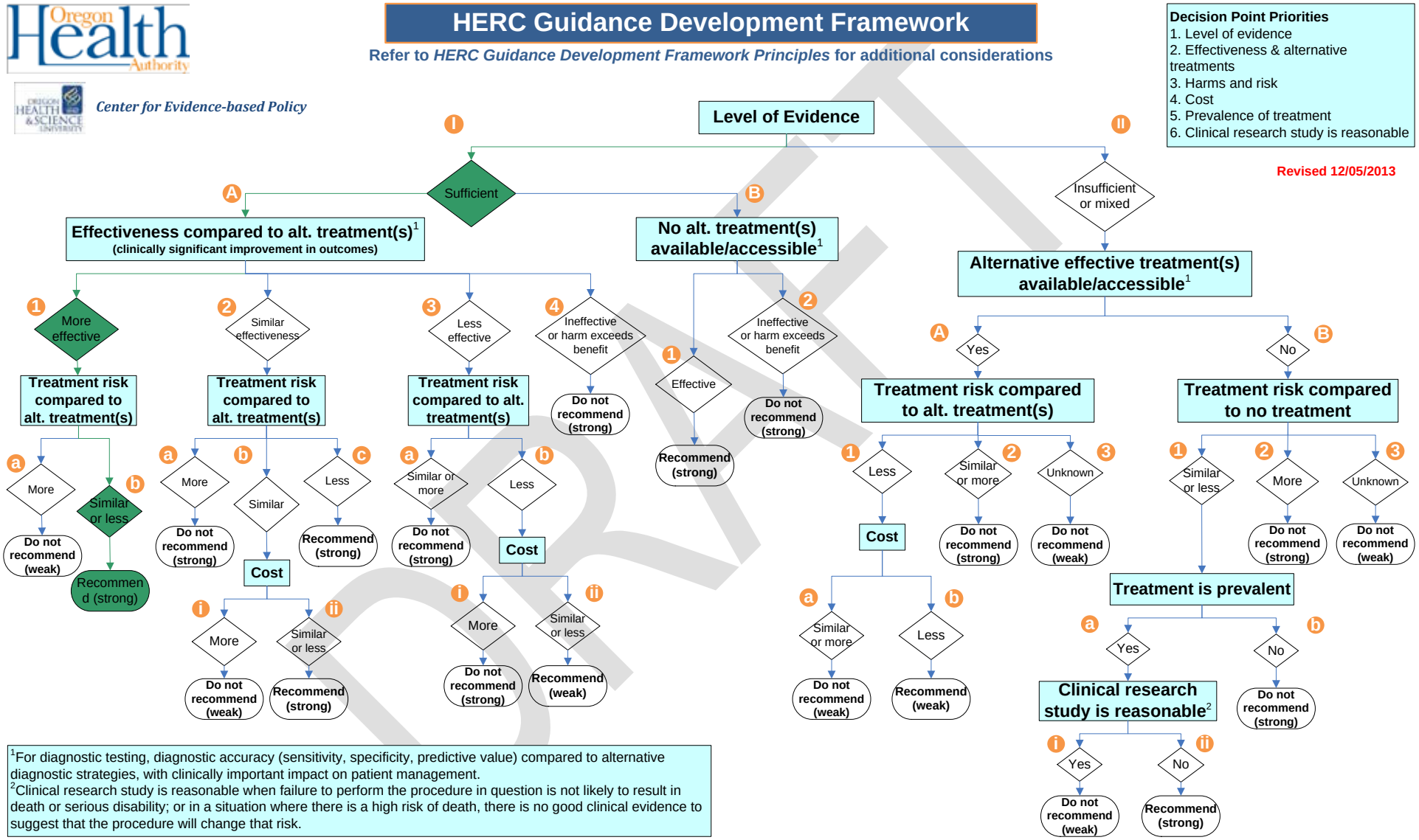
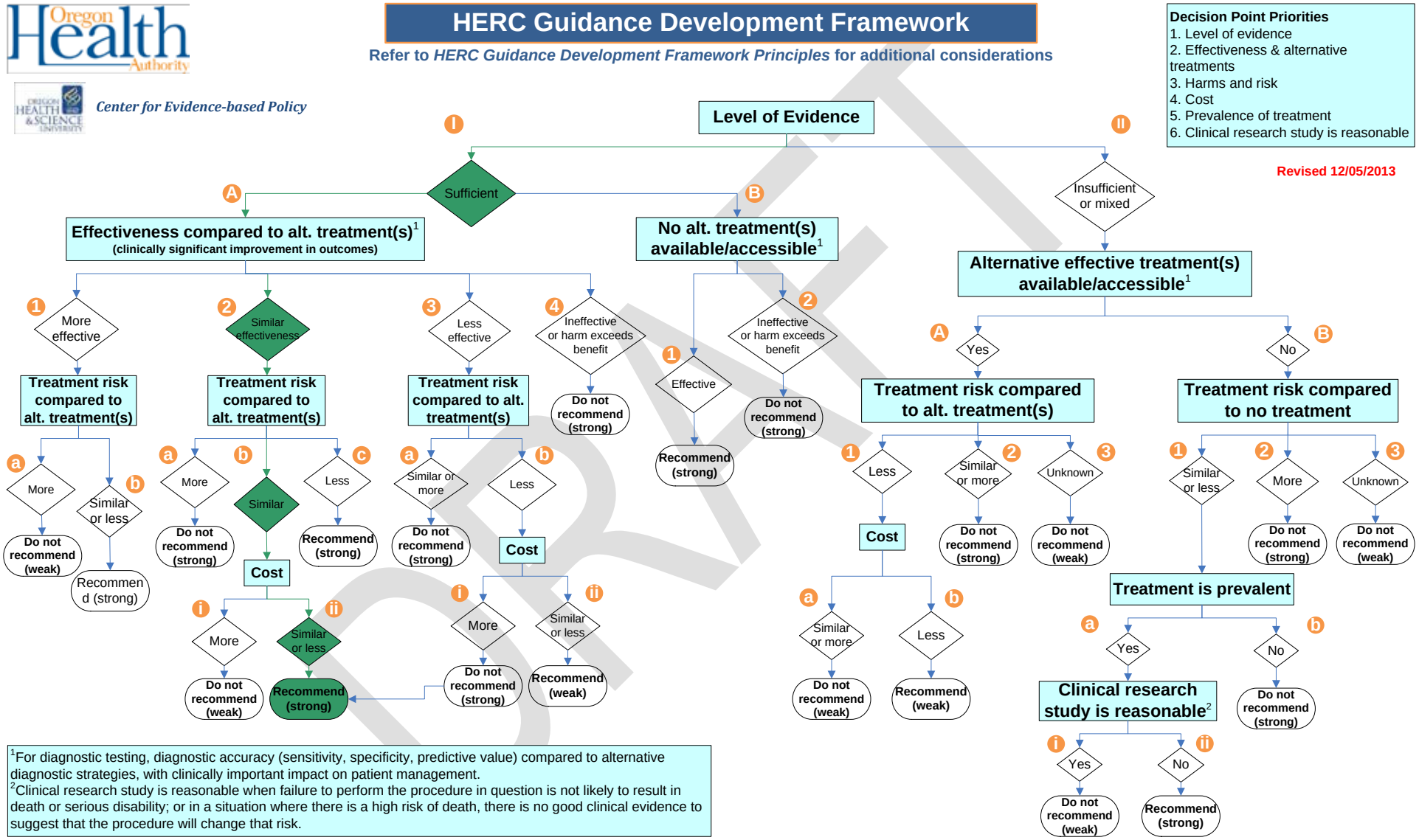
HoLEP, TUVRP (compared to TURP); TURP (compared to watchful waiting)



[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.

Thulium laser resection, TUVP, TUIP, and Bipolar TURP; compared to TURP



[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.

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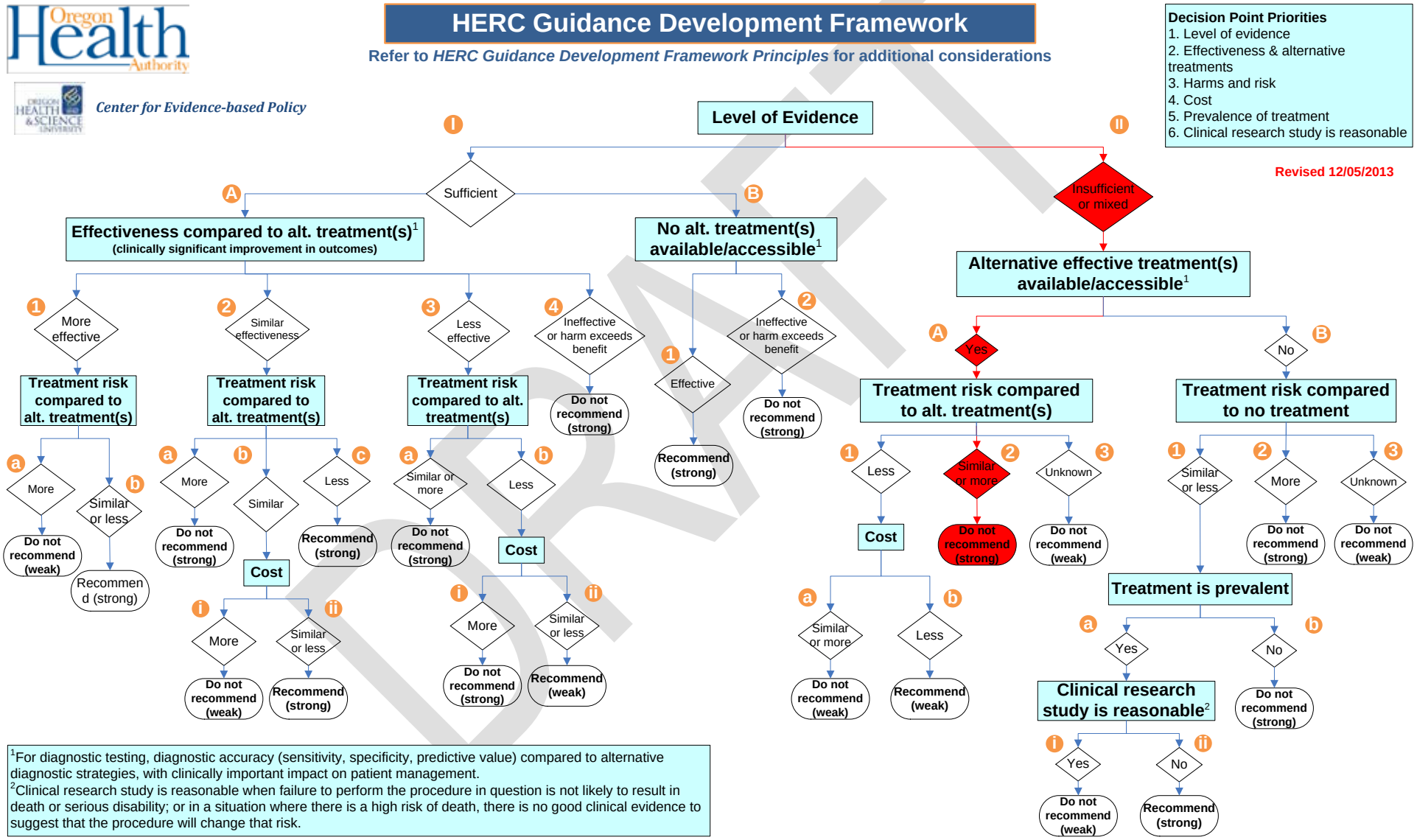
HoLEP (compared to HoBNI); Bipolar TURVP (compared to TURP)



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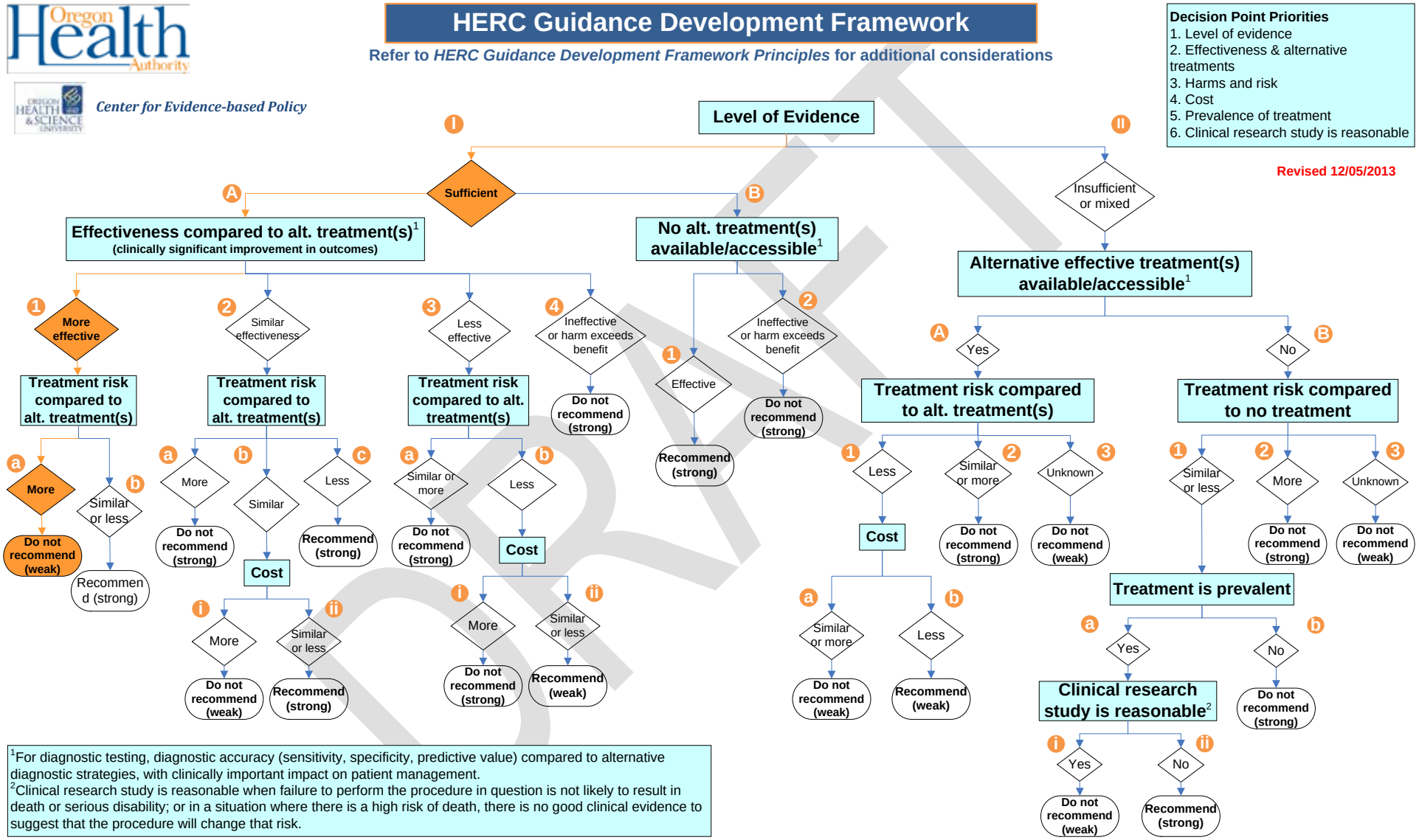
HoLEP; compared to OP



[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.

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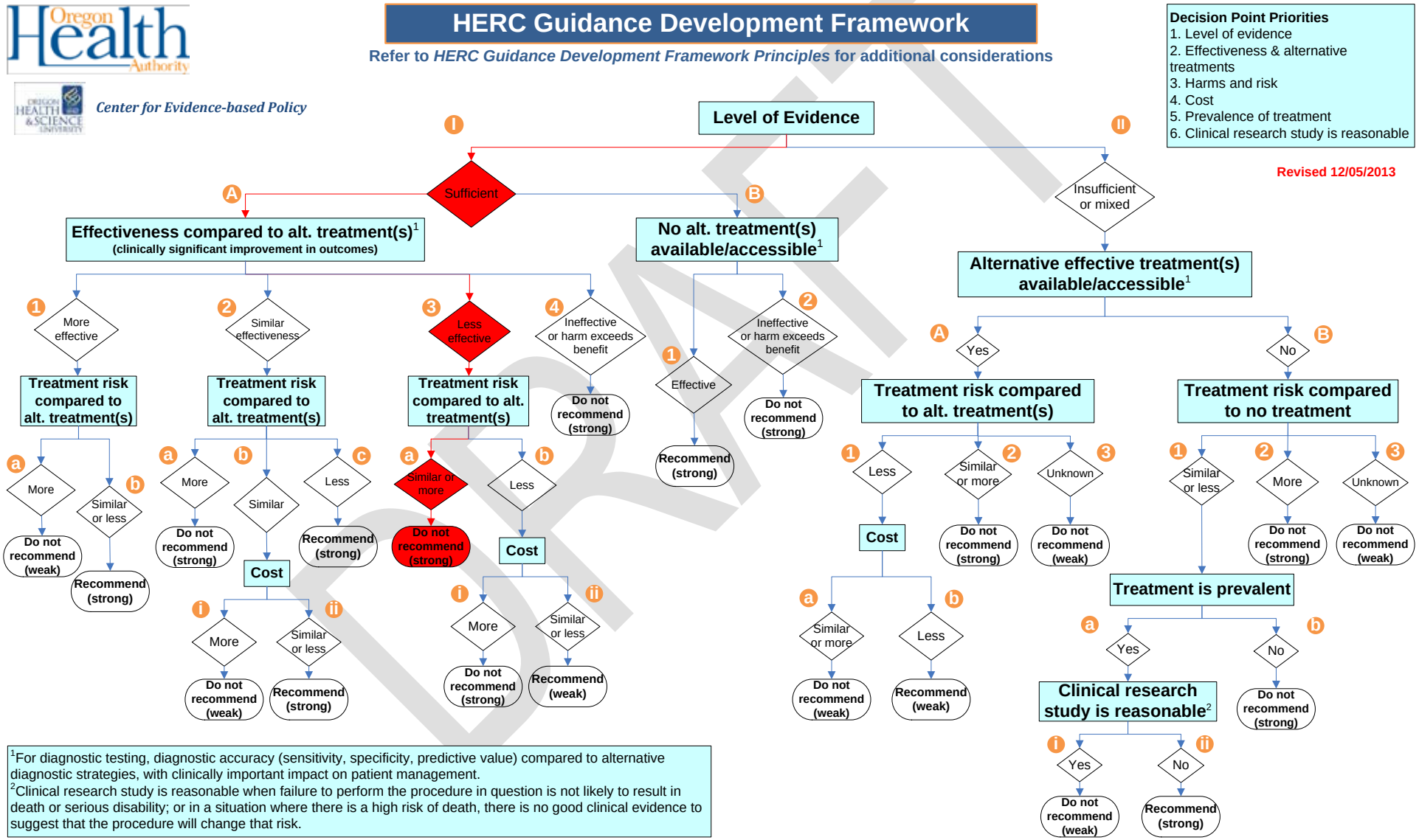
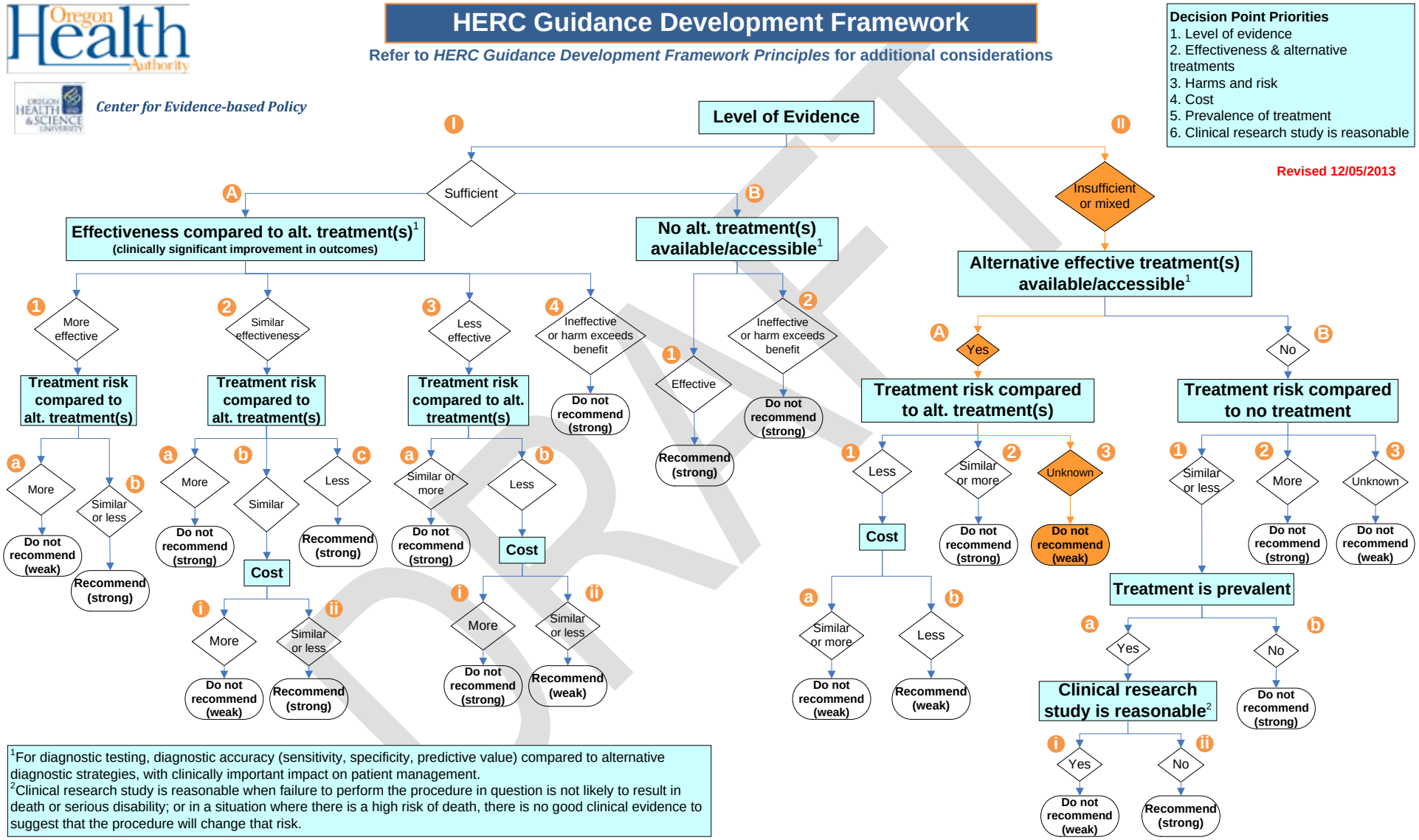
Laser coagulation techniques, Laser vaporization techniques, and TUMT; compared to TURP



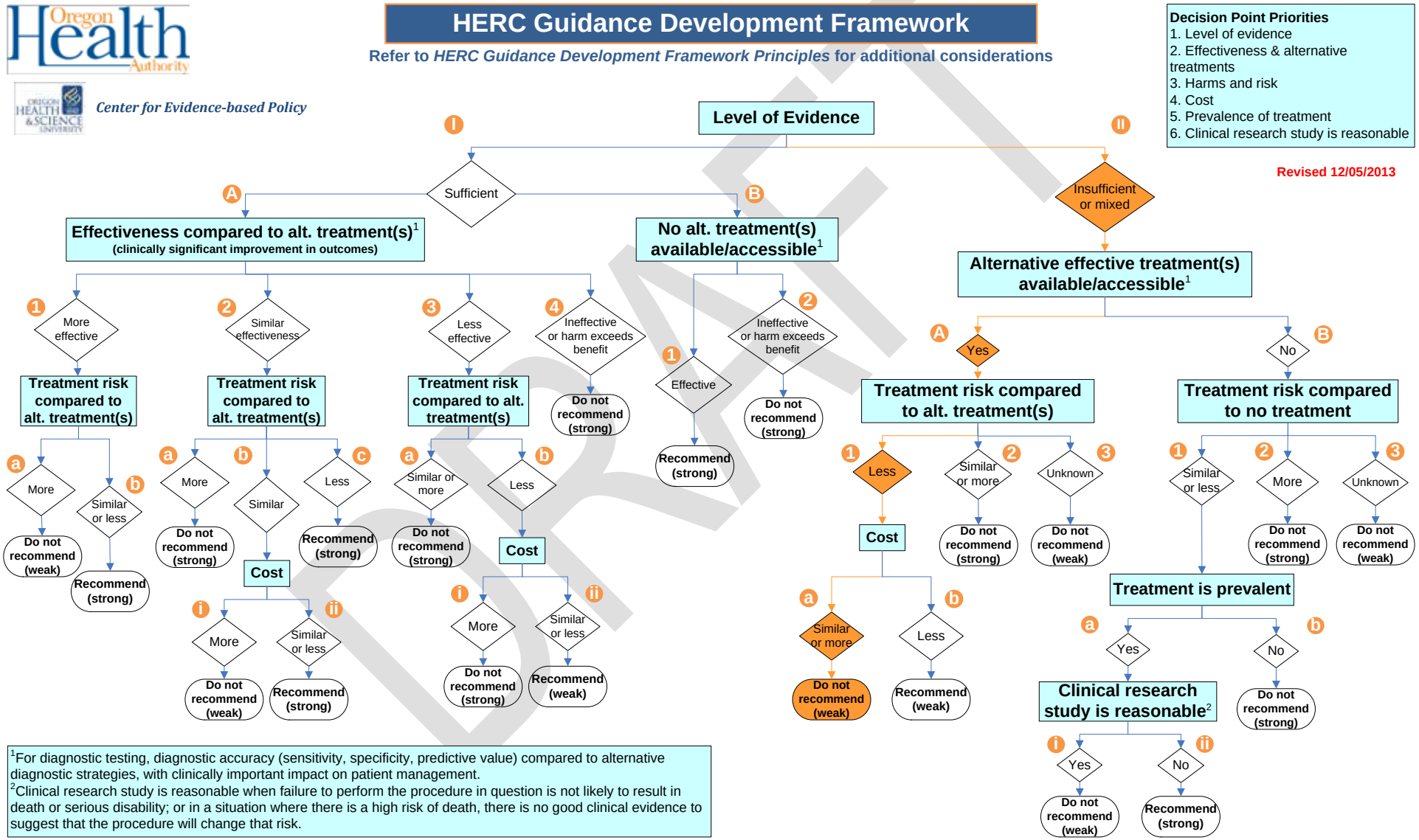
[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to 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.

HoLRP (compared to VLAP); Botulinum toxin (compared to placebo); HIFU



[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.

Bipolar TUVP and TEAP; compared to TURP



[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.

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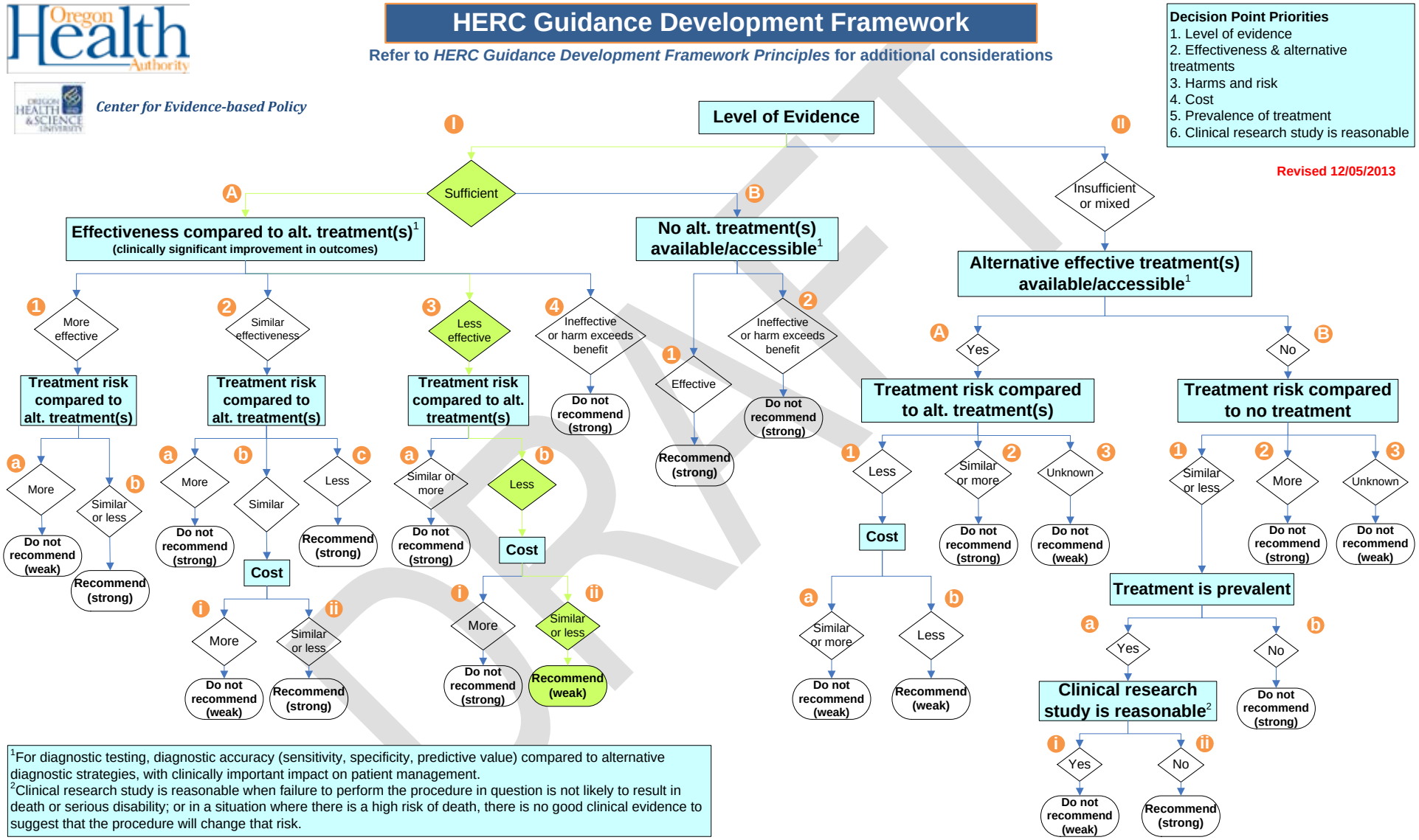
TUNA; compared to TURP



HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: ADVANCED IMAGING FOR STAGING OF PROSTATE CANCER

DRAFT FOR HTAS MEETING MATERIALS 9/22/2014

HERC Coverage Guidance

To determine risk status and treatment options, prostate cancer clinical staging that includes PSA level and prostate biopsy with Gleason score is recommended for coverage. *(weak/strong recommendation)*

MRI is recommended for coverage for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. *(strong recommendation)*

CT of the pelvis is not recommended for coverage in men with low- to intermediate-risk localized prostate cancer, unless MRI is contraindicated. *(strong recommendation)*

Radionuclide bone scanning is not recommended for [routine] coverage in men with localized prostate cancer. *(weak recommendation)*

Radionuclide bone scanning is recommended for coverage when hormone therapy is being deferred (through watchful waiting) in asymptomatic men who are at high risk of developing bone complications. *(strong recommendation)*

PET imaging is not recommended for [routine] coverage in prostate cancer. *(strong recommendation)*

Imaging is not recommended for [routine] coverage in men with prostate cancer who are not candidates for radical treatment. *(weak/strong recommendation)*

Note: Definitions for strength of recommendation are provided in Appendix B 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

National Institute for Health and Clinical Excellence. (2014). *Prostate Cancer: diagnosis and treatment*. London: National Institute for Health and Clinical Excellence. Retrieved from http://guidance.nice.org.uk/CG175/Guidance

The summary of evidence in this document is derived directly from this evidence source, and portions are extracted verbatim.

EVIDENCE OVERVIEW

Clinical background

Prostate cancer is the most common cancer in men and makes up 26% of all male cancer diagnoses in the United Kingdom. It is predominantly a disease of older men (aged 65–79 years) but around 25% of cases occur in men younger than 65. There is also higher incidence of and mortality from prostate cancer in men of black African-Caribbean family origin compared with white Caucasian men.

Prostate cancer is usually diagnosed after a blood test in primary care has shown elevated prostate-specific antigen (PSA) levels. The introduction of PSA testing has significantly reduced the number of men presenting with metastatic cancer since the 1980s. Most prostate cancers are now either localized or locally advanced at diagnosis, with no evidence of spread beyond the pelvis.

A number of treatments are available for localized disease, including: active surveillance, radical prostatectomy, external beam radiotherapy and brachytherapy. Hormone therapy (androgen deprivation or anti-androgens) is the usual primary treatment for metastatic prostate cancer, but is also increasingly being used for men with locally advanced, non-metastatic disease.

The TNM classification is used to stage prostate cancer (see Appendix A). It describes the extent of the primary tumor (T stage), the absence or presence of spread to nearby lymph nodes (N stage) and the absence or presence of distant spread, or metastasis (M stage). The clinical stage is determined from information that is available without surgery. The pathologic stage is based on the surgical removal and histological examination of the entire prostate gland, the seminal vesicles and surrounding structures and, if relevant, pelvic lymph nodes. The management of prostate cancer will depend on the TNM stage of the disease as well as both biochemical information (e.g. PSA) and pathological information (e.g. Gleason score), which have prognostic value. The optimum treatment for a man with prostate cancer requires an assessment of the risk of metastatic spread as well as the risk of local recurrence. For this, the results of imaging can be assessed in the light of information from clinical nomograms.

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EVIDENCE REVIEW

Men newly diagnosed with prostate cancer can initially be stratified into those for whom radical treatment is a possibility and those for whom it is not appropriate. The decision about treatment intent will be based on the man's life expectancy, his values, and the anticipated clinical course of the prostate cancer.

Recommendations:

- Determine the provisional treatment intent (radical or non-radical) before decisions on imaging are made.
- Do not routinely offer imaging to men who are not candidates for radical treatment.

Qualifying statement: There was guideline development group (GDG) consensus, in the absence of any research evidence, that this will reduce the amount of inappropriate investigation. The cost effectiveness of routine magnetic resonance imaging MRI could not be concluded.

Both the clinical presentation and the treatment intent influence the decision about when and how to image the individual. The risk of recurrence of prostate cancer after definitive local treatment is the basis for the stratification of men with localized prostate cancer into risk groups: low, intermediate and high (see Table 1). The recommendations for imaging of localized disease are similarly based on these prognostic groups.

Table 1

Level of risk	PSA		Gleason Score		Clinical stage
Low	< 10 ng/ml	And	≤ 6	And	T1-T2a
Intermediate	10-20 ng/ml	Or	7	Or	T2b
High	>20 ng/ml	Or	8-10	Or	≥ T2c

Imaging may inform the choice between different radical treatments (for example by determining whether the cancer has extended beyond the prostatic capsule). It also assists in the identification of metastatic disease thereby leading to more appropriate treatment options.

Imaging for T-staging and N-staging

The T-stage involves the assessment of the local extent of the primary tumor in the prostate and its relationship to surrounding structures. Using imaging to distinguish between T1 and T2 cancers does not usually affect treatment. But if radical treatment is being considered, it is important to decide whether a tumor is T2 (confined within the prostate) or T3/T4 (spread outside the prostate). MRI is now the commonly used imaging technique for T-staging men with prostate cancer. Many of the original publications used now-outdated MRI technology, and the accuracy reported for MRI is improving. After transrectal prostate biopsy, intra-prostatic hematoma can affect image interpretation for at least four weeks. It is important to know the

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nodal status of men with localized disease, as the spread of cancer to the pelvic lymph nodes will affect the choice of treatment. Partin's Tables (Partin et al. 2001) are the most commonly used clinical nomograms for determining the risk of nodal spread. Currently, imaging is of some value for N-staging because computed tomography (CT) and conventional MRI rely on size criteria to assess the likelihood of metastatic spread to the lymph nodes. CT cannot characterize the internal architecture of an enlarged node and MRI is only able to provide partial information. Newer MRI contrast agents such as superparamagnetic iron oxide (SPIO) may improve the overall specificity of MRI for evaluating lymph nodes but are not yet routinely available.

Recommendation:

- Do not offer CT of the pelvis to men with low- or intermediate-risk localized prostate cancer (see Table 1).

Qualifying statement: There is not enough evidence to support the routine use of CT in men with intermediate-risk disease and it is considered inferior to MRI in this clinical situation.

No studies measuring the impact of diagnostic imaging on patient outcomes were found; instead most studies were of diagnostic test accuracy.

Two studies showed better staging accuracy with MRI than with CT. Other systematic reviews have considered the staging accuracy of MRI and CT separately. There was contradictory evidence, from small observational studies, about the benefit of adding of magnetic resonance spectroscopy (MRS) to MRI. There was consistent evidence, from observational studies, that MRI tumor stage was a prognostic factor for PSA relapse. One of the studies, however, concluded that MRI tumor staging only added clinically meaningful information for men at intermediate pre-treatment risk of PSA relapse. MRI tumor stage did not stratify PSA failure risk well enough to guide clinical decision making for other patients.

Clinical question: Does staging with MRI improve outcomes in men with prostate cancer?

Biochemical recurrence-free survival

One study provided very low quality evidence of no significant difference in the proportion of patients experiencing biochemical recurrence between those which had undergone imaging and those which had not (p=0.50). However, the study was not limited only to those patients who underwent MRI (18%) and included patients who had received computerized tomography (81%) and bone scans (73%), with many patients receiving more than one type of imaging. [Very low strength of evidence (SOE).]

Overall survival, treatment-related morbidity, and health-related quality of life

No studies reported overall survival, treatment-related morbidity, or health-related quality of life.

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Clinical question: In which patients with prostate cancer will MRI staging alter treatment?

Four studies reported change in management following MRI, 23 reported change in staging following MRI, and eight reported the diagnostic accuracy of both clinical and MRI staging, using radical prostatectomy as reference standard. All studies were of low to very low quality evidence, with most (96%) considered unrepresentative of the patients who would receive MRI in practice. Many (68%) of the studies also used MRI as the reference standard which may not have classified the target condition correctly. A number of pre-specified sub-groups were available for analyses.

Change in management

Two studies found a change in the management of radiotherapy strategy following MRI in 31% and 9% of patients. Two further studies found a change in surgical procedure in 44% and 30% of patients following MRI respectively. (Low SOE.)

Change in stage

All studies found reported MRI to result in up-staging of a proportion of their patients, ranging from at least 5% to 100% of all patients. Where reported, MRI also resulted in down-staging of between 5% and 19% of patients. This was found for low, intermediate and high risk patients. (Very low SOE.)

Diagnostic accuracy

Four studies found that MRI was not consistently more sensitive, specific or accurate than staging by DRE or TRUS. Six studies found MRI to be more sensitive than clinical staging in identifying patients with extracapsular extension (stage T3a), but not consistently more specific or accurate. MRI was not consistently more sensitive, specific or accurate than clinical staging in identifying patients with seminal vesicle invasion (stage T3b). Three studies of patients with clinically localized disease found MRI to be more sensitive than clinical staging when identifying extracapsular extension or seminal vesicle invasion, but not consistently more specific or accurate. One study found MRI to have higher sensitivity but lower specificity than DRE or TRUS for overall staging of prostate cancer, while another found MRI to have higher accuracy.

Two studies only included patients with PSA < 10 ng/ml; one found the overall accuracy of staging to be the same between MRI and TRUS, while both found MRI to be more sensitive but less specific than TRUS when identifying extracapsular extension and less sensitive when identifying seminal vesicle invasion but not consistently more specific. Another study conducted a subgroup analysis by PSA level and found MRI to be more sensitive than TRUS in identifying both extracapsular extension and seminal vesicle invasion in patients with either PSA > 17 ng/ml or PSA < 10 ng/ml.

Two studies only included patients with Gleason ≤ 6; one found MRI to be more sensitive but less specific than TRUS when identifying extracapsular extension and less sensitive when identifying seminal vesicle invasion but of similar specificity. The other found MRI to have the

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same rate of false positives as clinical staging when identifying stage T3-T4 disease. Another study only included intermediate- and high-risk patients and found MRI to be more sensitive but less specific than clinical staging when identifying extracapsular extension, and to be more sensitive but have the same specificity when identifying seminal vesicle invasion.

Recommendations:

Consider multiparametric MRI, or CT if MRI is contraindicated, for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management.

Imaging for M-staging

Isotope bone scans can be used to look for bone metastases at the time of presentation. The positivity rate for bone scans increases with PSA or Gleason score.

Recommendation:

Do not routinely offer isotope bone scans to men with low-risk localized prostate cancer.

Qualifying statement: This recommendation is supported by case series evidence and will reduce unnecessary investigation.

Two systematic reviews looked at the role of radioisotope bone scans in the staging of men with newly diagnosed prostate cancer. One summarized bone scan results by serum PSA level in men with newly diagnosed prostate cancer. Serum PSA level and risk of a positive bone scan were strongly correlated. The other review concluded that PSA level was the best means of identifying those at risk of a positive bone scan and that men with PSA less than 10 ng/ml were unlikely to have a positive bone scan.

Recommendation:

Offer isotope bone scans when hormonal therapy is being deferred through watchful waiting to asymptomatic men who are at high risk of developing bone complications.

Qualifying statement: In the absence of any evidence there was GDG consensus that making this recommendation would reduce the risk of patients developing spinal cord compression.

Searches found no direct evidence about the influence of imaging on the timing of systemic treatment or frequency of clinical follow-up in men for whom radical treatment is not intended. Small case series reported outcomes in men with positive bone scans at presentation. Two of these series found extensive disease on bone scan was an adverse prognostic factor for survival. There is observational evidence that extensive disease on bone scan is an independent risk factor for spinal cord compression in men without functional neurological impairment.

Role of Positron-emission tomography (PET) in staging prostate cancer

Positron-emission tomography imaging using the radiopharmaceutical agent 18-FDG does not reliably show primary prostate cancer. This is because of the relatively low metabolic activity in

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tumors which are slow-growing and because the radiopharmaceutical agent accumulates in the bladder, obscuring the prostate. Newer positron-emitting tracers are under evaluation.

Recommendation:

Do not offer PET imaging for prostate cancer in routine clinical practice.

Qualifying statement: There was a lack of evidence to support the use of PET imaging.

Evidence Summary

When determining when and how to image an individual, men with localized prostate cancer should be stratified into risk groups based on PSA level, Gleason score and clinical stage. There is insufficient evidence to support the routine use of CT of the pelvis in men with low- or intermediate-risk localized prostate cancer, and it is considered inferior to MRI in this clinical situation. The evidence is insufficient to determine whether staging with MRI improve outcomes in men with prostate cancer. There is low SOE that staging with MRI can result in change in management, and a very low SOE that MRI results in up-staging or down-staging a highly variable proportion of patients. Most studies found staging with MRI more sensitive than staging with DRE or TRUS, but not consistently more specific or accurate.

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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
CT of pelvis	Inferior to MRI	Low	Low	Moderate variability (many would prefer to avoid radiation exposure)	Do not recommend (strong)	Insufficient/mixed evidence, similar or more risk than available alternatives.
MRI staging of prostate cancer	MRI may result in change in management, and possibly change in stage; may be more sensitive than DRE and/or TRUS	Low to Very Low	Low, if other diagnostic testing can be limited	Low variability	Recommend (strong)	Sufficient evidence shows more effective, less risk and similar or less cost than alternatives.
Bone scan in evaluation of newly diagnosed, low risk prostate	Positive bone scan highly correlated with PSA level; those with PSA level < 10 unlikely	Low	Low	Moderate variability (avoidance of multiple tests vs. perceived	Do not recommend (weak)	Sufficient evidence; similar risk and effectiveness to alternatives, but higher cost.

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Indication/ Intervention	Balance between desirable and undesirable effects	Quality of evidence*	Resource allocation	Variability in values and preferences	Coverage recommendation	Rationale
cancer	to have positive bone scan.			value from those tests)		
Bone scan in asymptomatic high-risk men	May result in earlier treatment of metastatic disease, resulting in prevention of spinal cord compression	Very Low	Low	Low variability (avoidance of spinal cord compression)	Recommend (strong)	Insufficient/mixed evidence, no alternatives available, similar or less risk than no treatment. Treatment is prevalent and research study is not reasonable.
PET for staging of prostate cancer	Unknown	Very Low	Moderate	Low variability	Do not recommend (strong)	Insufficient/mixed evidence; risk is similar or more than available alternative effective treatments

*The Quality of Evidence rating was assigned by the primary evidence source, not the HERC Subcommittee

Note: GRADE framework elements are described in Appendix B

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POLICY LANDSCAPE

Quality measures

One quality measure was identified when searching the National Quality Measures Clearinghouse that was pertinent to this coverage guidance. It was formulated by the American Urological Association, and is endorsed by the National Quality Forum. It states the following:

Prostate cancer: percentage of patients, regardless of age, with a diagnosis of prostate cancer, at low risk of recurrence, receiving interstitial prostate brachytherapy, OR external beam radiotherapy to the prostate, OR radical prostatectomy, OR cryotherapy who did not have a bone scan performed at any time since diagnosis of prostate cancer.

Choosing Wisely® is part of a multi-year effort of the ABIM Foundation to help physicians be better stewards of finite health care resources. Originally conceived and piloted by the National Physicians Alliance through a Putting the Charter into Practice grant, more than 50 medical specialty organizations, along with Consumer Reports, have identified a number of tests or procedures commonly used in their field, whose necessity should be questioned and discussed. Each participating organization was free to determine how to create its own list, provided that it used a clear methodology and adhered to the following set of shared guidelines:

- Each item should be within the specialty's purview and control.
- The tests and/or interventions should be used frequently and/or carry a significant cost.
- Each recommendation should be supported by generally accepted evidence.
- The selection process should be thoroughly documented and publicly available on request.

One of the organizations that chose to participate in the Choosing Wisely® campaign is the American Society of Clinical Oncology. The first list created by this organization states the following:

Don't perform PET, CT, and radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.

- Imaging with PET, CT, or radionuclide bone scans can be useful in the staging of specific cancer types. However, these tests are often used in the staging evaluation of low-risk cancers, despite a lack of evidence suggesting they improve detection of metastatic disease or survival.
- Evidence does not support the use of these scans for staging of newly diagnosed low grade carcinoma of the prostate (Stage T1c/T2a, prostate-specific antigen (PSA) <10 ng/ml, Gleason score less than or equal to 6) with low risk of distant metastasis.
- Unnecessary imaging can lead to harm through unnecessary invasive procedures, over-treatment, unnecessary radiation exposure, and misdiagnosis.

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Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

The Center is not engaged in rendering any clinical, legal, business or other professional advice. The statements in this document do not represent official policy positions of the Center. Researchers involved in preparing this document have no affiliations or financial involvement that conflict with material presented in this document.

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APPENDIX A. TNM STAGING FOR PROSTATE CANCER

Stage	Sub-Stage	Definition
Tumor (T)		**Primary Tumor**
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		**Clinically inapparent tumor, neither palpable nor visible by imaging**
	T1a	Tumor incidental histological finding in 5% or less of tissue resected
	T1b	Tumor incidental histological finding in more than 5% of tissue resected
	T1c	Tumor identified by needle biopsy, e.g., because of elevated prostate-specific antigen (PSA)
T2		**Tumor confined within prostate**
	T2a	Tumor involves one-half of one lobe or less
	T2b	Tumor involves more than one-half of one lobe, but not both lobes
	T2c	Tumor involves both lobes
T3		**Tumor extends through the prostatic capsule**
	T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck improvement
	T3b	Tumor invades seminal vesicle(s)
T4		**Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall**
Node (N)		**Regional lymph nodes**
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph nodes metastasis
	N1	Regional lymph node metastasis
Metastasis (M)		**Distant metastasis**
	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Non-regional lymph node(s)
	M1b	Bone (s)
	M1c	Metastasis at other site(s)

APPENDIX B. 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

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APPENDIX C. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
185	Malignant neoplasm of prostate
233.4	Carcinoma in situ of prostate
ICD-10 Diagnosis Codes	
C61	Malignant neoplasm of prostate
D07.5	Carcinoma in situ of prostate
ICD-9 Volume 3 (Procedure Codes)	
88.38	Other computerized axial tomography
88.95	Magnetic resonance imaging of pelvis, prostate, and bladder
92.14	Bone scan
92.19	Scan of other sites
CPT Codes	
72192	Computed tomographic, pelvis; without contrast material
72193	Computed tomographic, pelvis; with contrast material(s)
72194	Computed tomographic, pelvis; without contrast material, followed by contrast material(s) and further sections
72195	Magnetic resonance, pelvis; without contrast material
72196	Magnetic resonance, pelvis; with contrast material(s)
72197	Magnetic resonance , pelvis; without contrast material, followed by contrast material(s) and further sequences
78300	Bone and/or joint imaging; limited area
78305	Bone and/or joint imaging; multiple areas
78306	Bone and/or joint imaging; whole body
78315	Bone and/or joint imaging; 3 phase study
78320	Bone and/or joint imaging; tomographic (SPECT)
78811	Positron emission tomography (PET) imaging; limited area
78812	Positron emission tomography (PET) imaging; skull base to mid-thigh
78813	Positron emission tomography (PET) imaging; whole body
78814	Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; limited area
78815	Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; skull base to mid-thigh
78816	Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; whole body
HCPCS Level II Codes	
	None

Note: Inclusion on this list does not guarantee coverage

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APPENDIX C. HERC GUIDANCE DEVELOPMENT FRAMEWORK

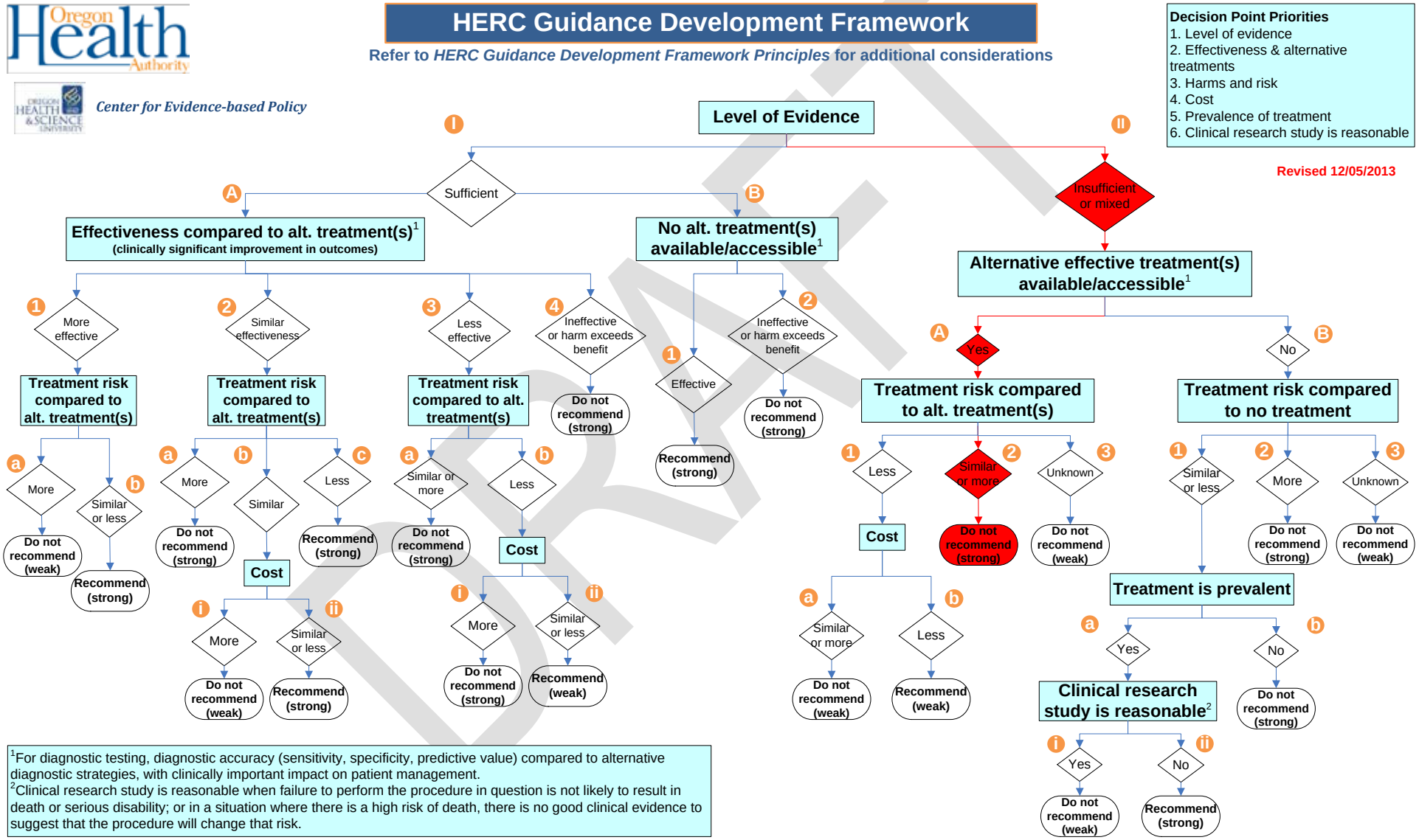
HERC Guidance Development Framework Principles

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.

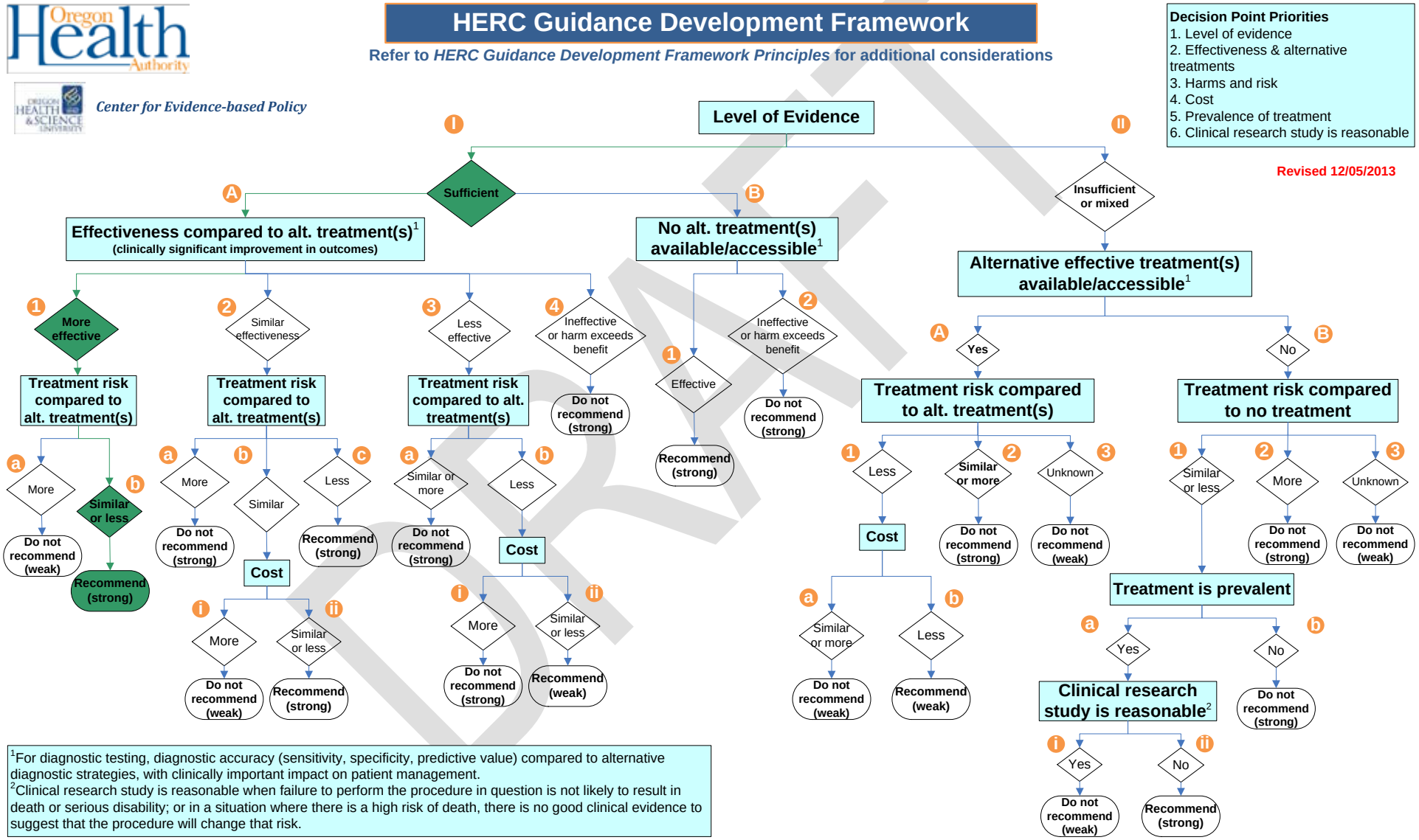
DRAFT

CT of pelvis; PET for staging of prostate cancer



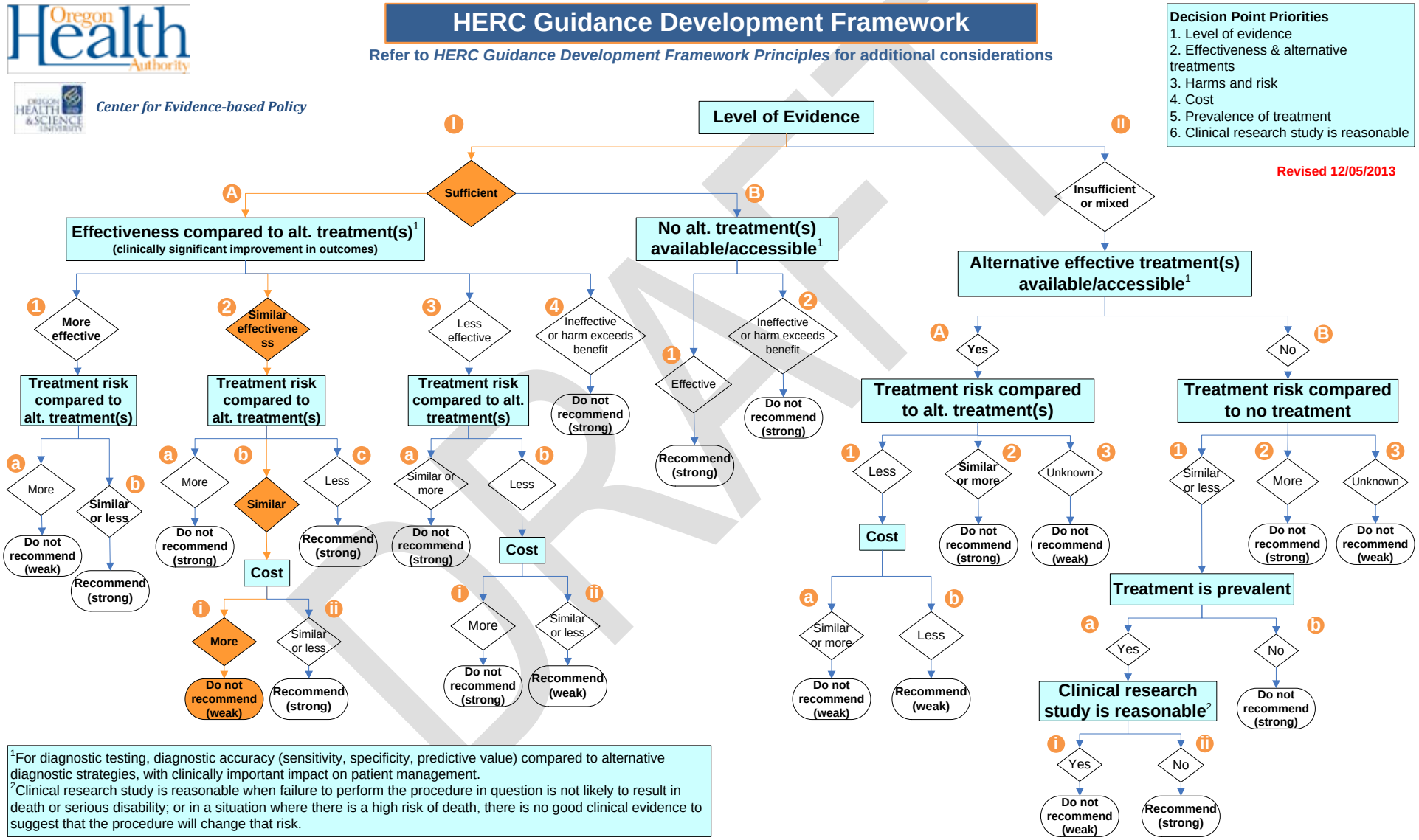
[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to 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.

MRI staging of prostate cancer



[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.

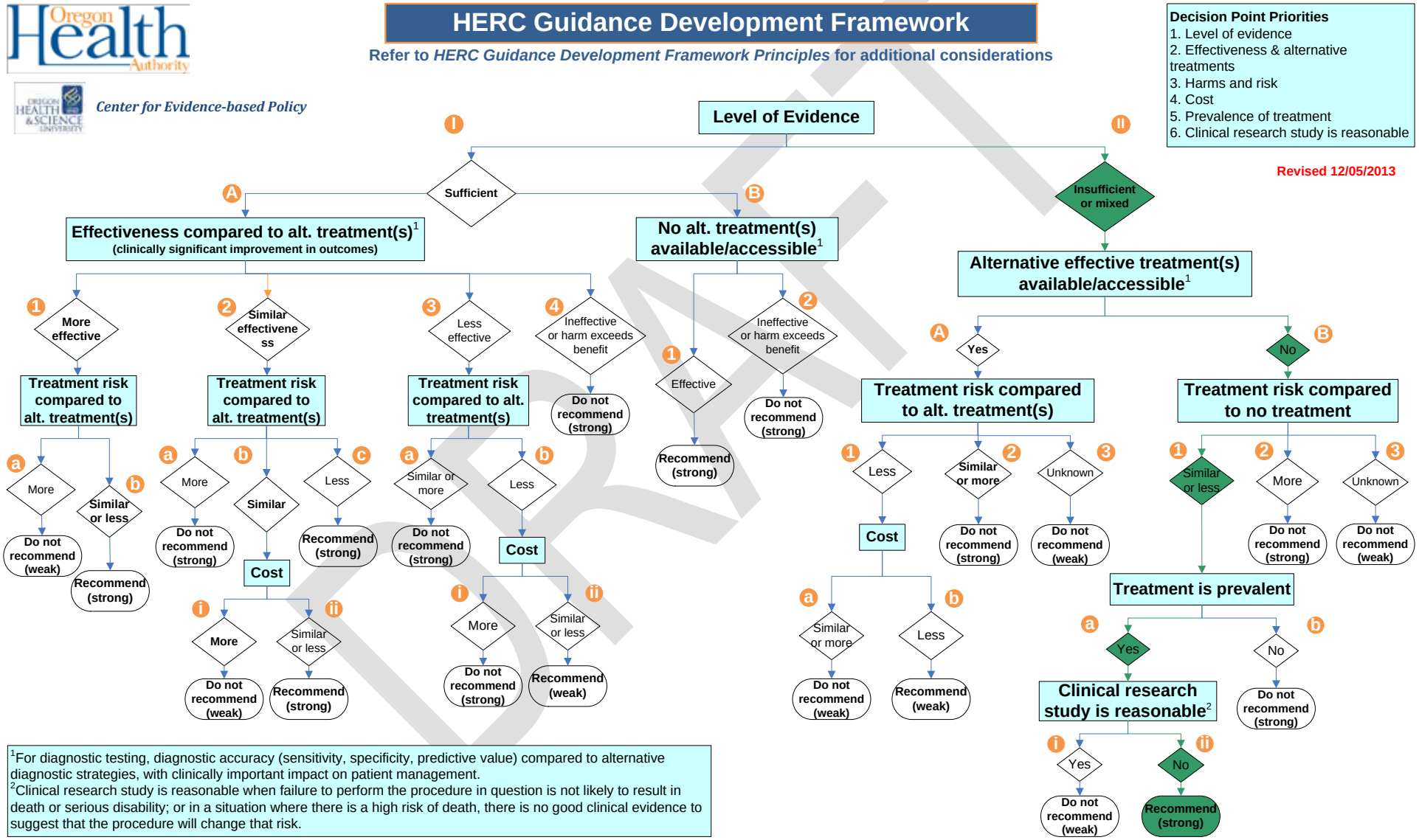
Bone scan in evaluation of newly diagnosed, low-risk prostate cancer



[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.

DRAFT

Bone scan in asymptomatic high-risk men



[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.

Section 3.0

Coverage guidance

monitoring HTAS 2012 topics

Topic: ARTIFICIAL DISC REPLACEMENT

Coverage Recommendation (Box Language):

Artificial disc replacement should be a covered service only when all of the following criteria are met:

Lumbar artificial disc replacement

1) Patients must first complete a structured, intensive, multi-disciplinary program for management of pain, if covered by the agency;

2) Patients must be 60 years or under;

3) Patients must meet FDA approved indications for use and not have any contra-indications. FDA approval is device specific but includes:

- Failure of at least six months of conservative treatment
- Skeletally mature patient
- Replacement of a single disc for degenerative disc disease at one level confirmed by patient history and imaging

Cervical artificial disc replacement

1) Patients must meet FDA approved indications for use and not have any contra-indications. FDA approval is device specific but includes:

- Skeletally mature patient
- Reconstruction of a single disc following single level discectomy for intractable symptomatic cervical disc disease (radiculopathy or myelopathy) confirmed by patient findings and imaging.

Source report:

Washington State Health Care Authority Health Technology Assessment Program. (2008). HTA report: Artificial discs replacement (ADR). Olympia, WA: Health Technology Assessment Program. Retrieved from http://www.hta.hca.wa.gov/documents/adr_final091908.pdf

Scanning results:

Five reviews were identified in the core sources that were published after the date of the WA HTA, as well as two guidelines.

Blue Cross Blue Shield Association (2014). Artificial Intervertebral Disc Arthroplasty for Treatment of Degenerative Disc Disease of the Cervical Spine. Technology Evaluation Center Assessment Program. http://www.bcbs.com/blueresources/tec/vols/28/28_13.pdf

"Artificial intervertebral disc arthroplasty (AIDA) for the treatment of patients with cervical degenerative disc disease does not meet the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria."

- Has regulatory approval
- Evidence is insufficient to support conclusions about the comparative effect of AIDA on health outcomes
- While studies show non-inferiority to fusion (6 RCTs), however, the design of the trials allows some margin of inferiority.
- Similar clinical outcomes at 2 years, continued to 4-5 years but with high drop out in the longer studies, resulting in a lack of certainty about long term outcomes
- Have not been evaluated outside the investigational setting

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Blue Cross Blue Shield Association (2014). Artificial Lumbar Disc Arthroplasty. Technology Evaluation Center Assessment Program. http://www.bcbs.com/blueresources/tec/vols/28/28_07.pdf

"the use of an artificial disc in lumbar spine arthroplasty for chronic symptomatic degenerative disc disease unresponsive to conservative management does not meet the TEC criteria."

- Has regulatory approval
- This evidence is insufficient to demonstrate a relative clinical benefit of ProDisc versus fusion (1 RCT), particularly because the effectiveness of the comparator— fusion—versus nonsurgical treatments is not well defined. Thus, the randomized trial of ProDisc is suspect as a valid noninferiority trial and does not prove superiority.
- The evidence is insufficient to determine whether use of ProDisc in lumbar spine arthroplasty improves the net health outcome of patients with symptomatic DDD.
- The evidence is insufficient to determine whether use of ProDisc in lumbar spine arthroplasty is as beneficial as lumbar spinal fusion. The artificial disc was not compared with nonsurgical approaches.
- Have not been evaluated outside the investigational setting

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Hayes. (2012). Artificial Disc Replacement for Cervical Degenerative Disc Disease. Reviewed Dec 17, 2013. https://www.hayesinc.com/subscribers/subscriberArticlePDF.pdf?articleId=11387

Conclusions: Several moderate-size randomized controlled trials (RCTs) comparing different types of artificial cervical discs with anterior cervical discectomy and fusion (ACDF) have been published. Evidence to date demonstrates that total disc replacement (TDR) is at least as effective as ACDF in improving signs and symptoms associated with degenerative disease and improving quality of life (QOL)

for up to 2 years. The evidence also shows that total disc replacement (TDR) reduces the need for reoperation and reduces the incidence of dysphagia. Low-quality evidence suggests that TDR reduces the risk of new adjacent segment disease (ASD) but may have higher rates of intraoperative and perioperative complications. Reliable follow-up data for more than 3 years are lacking, which is an especially serious limitation regarding the evidence for the intended advantage of TDR (reduction in long-term ASD). Positive but sparse evidence suggests that bilevel TDR is less safe than single-level TDR, but a few studies with several limitations suggest that it is comparable to bilevel ACDF in safety and efficacy.

Hayes Rating (based on 12 RCTs): B - For single-level TDR for the treatment of cervical disc disease in patients who are candidates for ACDF and who do not have forms of degenerative disc disease, allergies, comorbidities, or concomitant treatments that are expected to interfere with successful arthroplasty.

D2 – For TDR in patients with multilevel cervical disc disease who are candidates for ACDF. This Rating is based on positive but very sparse evidence regarding the efficacy and safety of TDR for the treatment of multilevel disease.

Hayes. (2013). Lumbar Total Disc Replacement for Degenerative Disc Disease.
https://www.hayesinc.com/subscribers/subscriberArticlePDF.pdf?articleId=6963

Conclusions: The available evidence suggests that, compared with spinal fusion, lumbar total disc replacement (LTDR) for degenerative disc disease (DDD) using the ProDisc or Charité may lead to improved outcomes lasting ≥ 5 years after surgery. However, the longer-term clinical outcome of LTDR is still unclear. The evidence from uncontrolled long-term studies suggests that potential degeneration of adjacent discs and facets and wear of the polyethylene part of the disc may occur and that, in some cases, revision surgery may be needed. Long-term follow-up results from randomized controlled studies are available from only 2 randomized trials, and it is, therefore, not known if the benefits of LTDR are maintained. Furthermore, patient selection criteria still need to be refined.

Hayes Rating (based on 9 RCTs): C For LTDR using the ProDisc or Inmotion (formerly Charité) in patients with DDD who would otherwise undergo lumbar spinal fusion. This Rating is based on the evidence suggesting that these discs may lead to improved outcomes compared with spinal fusion, the concern about potential degeneration of adjacent discs and wear of the disc itself, and the potential need for revision surgery.

D 2 – For LTDR using the Maverick, FlexiCore, or Kineflex discs in patients with DDD who would otherwise undergo lumbar spinal fusion. This Rating is based on the paucity of evidence for these types of artificial discs.

Jacobs W, Van der Gaag NA, Tuschel A, de Kleuver M, Peul W, Verbout AJ, Oner FC. (2012). Total disc replacement for chronic back pain in the presence of disc degeneration. Cochrane Database of Systematic Reviews. Issue 9. Art. No.: CD008326. DOI:10.1002/14651858.CD008326.pub2. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008326.pub2/pdf

Based on 7 RCTs.

"Although statistically significant, the differences between disc replacement and conventional fusion surgery for degenerative disc disease were not beyond the generally accepted clinical important differences with respect to short-term pain relief, disability and Quality of Life. Moreover, these analyses only represent a highly selected population. The primary goal of prevention of adjacent level disease and facet joint degeneration by using total disc replacement, as noted by the manufacturers and distributors, was not properly assessed and not a research question at all. Unfortunately, evidence from observational studies could not be used because of the high risk of bias, while these could have improved external validity assessment of complications in less selected patient groups. Non-randomised studies should however be very clear about patient selection and should incorporate independent, blinded outcome assessment, which was not the case in the excluded studies. Therefore, because we believe that harm and complications may occur after years, we believe that the spine surgery community should be prudent about adopting this technology on a large scale, despite the fact that total disc replacement seems to be effective in treating low-back pain in selected patients, and in the short term is at least equivalent to fusion surgery."

NICE. (2009). Prosthetic intervertebral disc replacement in the lumbar spine. http://www.nice.org.uk/guidance/ipg306/resources/guidance-prosthetic-intervertebral-disc-replacement-in-the-lumbar-spine-pdf

"Current evidence on the safety and efficacy of prosthetic intervertebral disc replacement in the lumbar spine is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit.

NICE. (2010). Prosthetic intervertebral disc replacement in the cervical spine. http://www.nice.org.uk/guidance/ipg341/resources/guidance-prosthetic-intervertebral-disc-replacement-in-the-cervical-spine-pdf

"Current evidence on the efficacy of prosthetic intervertebral disc replacement in the cervical spine shows that this procedure is as least as efficacious as fusion in the short term and may result in a reduced need for revision surgery in the long term. The evidence raises no particular safety issues that are not already known in relation to fusion procedures. Therefore this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit."

Summary:

The recently published evidence is conflicting, with two sources supporting the current coverage guidance recommendations for cervical artificial disc and one contradicting them. Similarly, one source supports the current coverage guidance recommendations for lumbar artificial disc and two sources contradict them. However, since the recommendations for this coverage guidance relied primarily on FDA indications rather than the evidence source, updating this guidance document may not be required.

Topic: MRI FOR BREAST CANCER SCREENING

Coverage Recommendation (Box Language):

Breast MRI should not be covered for screening for breast cancer.

Source report:

Washington State Health Care Authority Health Technology Assessment Program. (2010). *HTA Report: Breast MRI in diagnosis and treatment of cancer in women at high risk*. Olympia, WA: Health Technology Assessment Program. Retrieved from http://www.hta.hca.wa.gov/documents/breast_mri_072310_final.pdf

Scanning results:

One AHRQ review was identified on the use of breast MRI for evaluation of abnormalities identified during routine screening (mammography). Two reviews and one guideline were identified in the core sources that specifically addressed the use of MRI for breast cancer screening and were published after the date of the WA HTA report (an update is in progress and due for publication in December 2014). In addition, the USPSTF report on Screening for Breast Cancer is currently being updated; the final research plan was posted in July 2014. Summary results and/or conclusions of the two completed reviews and the one guideline are presented below:

Hayes. (2014). Magnetic Resonance Imaging (MRI) for Surveillance for Breast Cancer Recurrence Following Mastectomy and Breast Reconstruction
https://www.hayesinc.com/subscribers/subscriberArticlePDF.pdf?articleId=16955

- While the risk of locoregional recurrence is low after mastectomy, recurrences in residual breast tissue or the chest wall may be difficult to detect in a timely manner. Breast MRI is more sensitive than mammography for diagnosis of breast cancer; however, the rates of false-positive findings on postoperative MRI images of the breast limit the clinical utility of this test in women who have undergone reconstruction.
- Because there are numerous surgical techniques for reconstruction after breast cancer, and various histological types of breast cancer, designing a clinical trial with adequate power to examine the usefulness of breast MRI for surveillance for recurrence in patient subgroups could be challenging.
- The use of breast MRI increases facility utilization and costs due to the need for contrast media and the possibility that the test findings will prompt additional testing including

biopsy. Centers that provide breast MRI for surveillance should be equipped to perform MRI-guided breast biopsy.

Hayes Rating: D2

BCBS. (2014). Screening Asymptomatic women with dense breasts and normal mammograms for breast cancer. Accessed on September 9, 2014 from http://www.bcbs.com/blueresources/tec/vols/28/28_15.pdf

Author's Conclusions and Comment

As with mammography in general, the decision on which imaging modality(s) to use hinges in part on the tradeoff between detecting cancers and performing a much higher number of unnecessary biopsies to detect those cancers. This topic is clearly subject to continued controversy, as the response to recommendations to potentially reduce the number of screening mammograms for asymptomatic women in their 40s has shown. A related, but probably less difficult, issue is how many screening tests women undergo.

There are several areas where technologies are changing and where future studies may clarify the choices to be made. For example, ABUS performs faster and is less operator-dependent than handheld ultrasound. How the differences between ABUS and handheld US will translate into differences in health outcomes for women with dense breasts remain to be seen. Additional research on tomosynthesis may also be helpful. Given the variety of potential choices, careful studies of multiple modalities on the same women are useful. Because different types of imaging may be more or less accurate in detecting different types of breast cancer (e.g., invasive tumors versus ductal carcinoma in situ or larger [e.g., greater than 1 cm] or smaller tumors) or detecting it in women with different characteristics besides breast density (e.g., large versus small breasts), comparing the results of various types of breast imaging in different populations cannot be addressed simply by adjusting for women's age, tumor stage, etc. There is also a trade-off between enhancing the number of expected cancers by, for example, selecting women with additional risk factors, versus testing these technologies in a true screening population likely to be encountered in clinical practice. Finally, the assumption that finding more cancers using additional techniques besides mammography produces better health outcomes on a population level will need to be verified.

Women with dense breasts on mammography are at higher risk of breast cancer and of having any cancer missed by mammography. One possibility is to use additional imaging for women with dense breasts and normal mammograms. Both MRI and US have been

suggested by different groups. Existing evidence on US suggests that adding it to mammography will increase the cancer yield while also increasing the number of recalls and unnecessary biopsies. One study showed that adding MRI to mammography and US increases the sensitivity while decreasing the specificity. Digital mammography is more sensitive than film mammography for women with dense breasts. Insufficient evidence is available on other modalities, such as tomosynthesis and automated breast ultrasound.

NICE. (2013). Familial breast cancer: Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. Accessed on September 9, 2014, from http://www.nice.org.uk/guidance/cg164/resources/guidance-familial-breast-cancer-pdf

Surveillance for women with no personal history of breast cancer

MRI surveillance

1.6.7 Offer annual MRI surveillance to women:

- aged 30–49 years who have not had genetic testing but have a greater than 30%
- probability of being a BRCA carrier[1]
- aged 30–49 years with a known BRCA1 or BRCA2 mutation
- aged 20–49 years who have not had genetic testing but have a greater than 30% probability of being a TP53 carrier
- aged 20–49 years with a known TP53 mutation. [new 2013]

1.6.8 Consider annual MRI surveillance for women aged 50–69 years with a known TP53 mutation. [new 2013]

1.6.9 Do not offer MRI to women:

- of any age at moderate[2] risk of breast cancer
- of any age at high[3] risk of breast cancer but with a 30% or lower probability of being a BRCA or TP53 carrier

[1] Guidance recommends use of carrier probability calculation method such as BOADICEA (http://ccge.medschl.cam.ac.uk/boadicea)
[2] Lifetime risk of developing breast cancer is at least 17% but less than 30%.
[3] Lifetime risk of developing breast cancer is at least 30%. High risk group includes rare conditions that carry an increased risk of breast cancer, such as Peutz-Jegher syndrome, (STK11), Cowden (PTEN), familial diffuse gastric cancer (E-Cadherin).

- aged 20–29 years who have not had genetic testing but have a greater than 30% probability of being a BRCA carrier
- aged 20–29 years with a known BRCA1 or BRCA2 mutation
- aged 50–69 years who have not had genetic testing but have a greater than 30% probability of being a BRCA or a TP53 carrier, unless mammography has shown a dense breast pattern[4]
- aged 50–69 years with a known BRCA1 or BRCA2 mutation, unless mammography has shown a dense breast pattern.[5] [new 2013]

Surveillance for women with a personal and family history of breast cancer

MRI surveillance

1.6.13 Offer annual MRI surveillance to all women aged 30–49 years with a personal history of breast cancer who remain at high risk of breast cancer, including those who have a BRCA1 or BRCA2 mutation. [new 2013]

1.6.14 Do not offer MRI surveillance to any women aged 50 years and over without a TP53 mutation unless mammography has shown a dense breast pattern. [new 2013]

1.6.15 Consider annual MRI surveillance for women aged 20–69 years with a known TP53 mutation or who have not had a genetic test but have a greater than 30% probability of being a TP53 carrier. [new 2013]

Surveillance for women who remain at moderate risk of breast cancer

1.6.16 Ensure that surveillance for people with a personal history of breast cancer who remain at moderate risk of breast cancer is in line with Early and locally advanced breast cancer (NICE clinical guideline 80). [new 2013]

[4] Surveillance recommendations for this group reflect the fact that women who at first assessment had a 30% or greater BRCA carrier probability and reach 60 years of age without developing breast or ovarian cancer will now have a lower than 30% carrier probability and should no longer be offered MRI surveillance.
[5] Surveillance recommendations for this group reflect the fact that women who at first assessment had a 30% or greater TP53 carrier probability and reach 50 years of age without developing breast cancer or any other TP53-related malignancy will now have a lower than 30% carrier probability and should no longer be offered MRI surveillance.

Summary:

The recently published evidence addresses three different clinical scenarios, which are distinct from the current coverage guidance. One addresses women with a personal history of breast cancer, another women with dense breasts and the third, women with a history of familial breast cancer. Because there are two sources that are currently being updated and likely apply to a broader population, it may be desirable to delay update of this guidance until those reports are available.

Topic: LUMBAR DISCOGRAPHY

Coverage Recommendation (Box Language):

Lumbar discography should not be a covered service for patients with low back pain and uncomplicated lumbar degenerative disc disease.

Source report:

Washington State Health Care Authority Health Technology Assessment Program. (2007). *Spinal fusion and discography for chronic low back pain and uncomplicated lumbar degenerative disc disease.* Olympia, WA: Health Technology Assessment Program. Retrieved from http://www.hta.hca.wa.gov/discography.html

Scanning results:

One review and one protocol were identified in the core sources that was published after the date of the WA HTA report. Summary results and/or conclusions are presented below:

Hayes. (2010). Discography for Diagnosis of Low Back Pain. Accessed on September 9, 2014, from https://www.hayesinc.com/subscribers/subscriberArticlePDF.pdf?articleId=1893

Conclusions: The available evidence indicates that lumbar discography can result in high false-positive rates in identifying pain-producing discs, although pressure-controlled injection and strict classification of results can reduce the false-positive rate to ≤ 10%. When surgical outcome was used as the reference standard, some studies found a high degree of correlation between discography findings and degree of pain relief following surgery, while others failed to find any contribution of discography to surgical outcome. Inconsistencies among studies may relate to the variable results of these surgical approaches and/or to differences in discography protocol. In the only study comparing discography with an alternate diagnostic approach, outcome after spinal fusion was worse in patients undergoing discography than in patients undergoing discoblock (intradiscal anesthesia) but the source of pain differed in the discography and discoblock groups. Therefore, available data do not clearly establish the efficacy of lumbar discography or the comparable value of lumbar discography relative to other methods in identifying the source of low back pain or determining surgical candidacy and do not clarify whether a positive discogram is sufficient to warrant surgery, particularly when using updated standards for defining positive discograms. Data do suggest that lumbar discography, as currently performed, is not commonly associated with serious adverse effects.

Based on available data, the following Hayes Ratings are assigned:

C – For lumbar discography using pressure-controlled injection and updated criteria for positive discograms in patients with chronic severe low back pain who are potential candidates for spinal surgery, when conservative care has failed, and other diagnostic tests have not clearly confirmed a suspected disc as the source of pain.
D – For lumbar discography in patients who have a contraindication to the procedure. This Rating reflects concerns regarding the safety of this procedure in these patients.

Chou, R., Qaseem, A., Snow, V., Casey, D., Cross, J.T., Jr., Shekelle, P., Owens, D.K.; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Annals of Internal Med. 2007; 147(7); 478-491. Retrieved from http://www.annals.org/content/147/7/478.long

This guideline is in the process of being updated, with an anticipated publication date in 2015.

Summary:

The recently published evidence does not contradict the current coverage guidance recommendations.

Topic: HIP RESURFACING

Coverage Recommendation (Box Language):

Hip resurfacing should be a covered service for patients who are likely to outlive a traditional prosthesis and who would otherwise require a total hip replacement, and should only be done by surgeons with specific training in this technique.

The following criteria should be required:

- Diagnosis of osteoarthritis or inflammatory arthritis;
- Individual has failed nonsurgical management; and
- The device is FDA approved.

Patients who are candidates for hip resurfacing must not have FDA contraindications including:

- Patients with active or suspected infection in or around the hip joint, or sepsis
- Patients who are skeletally immature
- Patients with any vascular insufficiency, muscular atrophy, or neuromuscular disease severe enough to compromise implant stability or postoperative recovery
- Patients with bone stock inadequate to support the device, including severe osteopenia or a family history of severe osteoporosis or osteopenia
- Patients with osteonecrosis or avascular necrosis with >50% involvement of the femoral head
- Patients with multiple cysts of the femoral head
- Females of childbearing age
- Patients with known moderate-to-severe renal insufficiency
- Patients who are immunosuppressed with diseases such as AIDS or persons receiving high doses of corticosteroids
- Patients who are severely overweight
- Patients with known or suspected metal sensitivity

Source report:

Washington State Health Care Authority Health Technology Assessment Program. (2009). *HTA final report: Hip resurfacing.* Olympia, WA: Health Technology Assessment Program. Retrieved from http://www.hta.hca.wa.gov/documents/hip_final_report_102309.pdf

Scanning results:

Two reviews were identified in the core sources that were published after the date of the WA HTA, one of which is an update to the WA HTA report, as well as a Cochrane protocol and one guideline.

CADTH. (2012). Metal on Metal Total Hip Replacements or Hip Resurfacing for Adults: A Review of Clinical Effectiveness and Cost Effectiveness. http://www.cadth.ca/media/pdf/htis/nov-2012/RC0405%20MOM%20Final.pdf

- Metal on metal (MOM) hip resurfacing arthroplasty (HRA) patients experienced higher rates of revision, femoral neck fractures and component loosening than total hip replacement (THR) patients.
- There was a reduced incidence of dislocation following HRA compared to THR.
- Stemmed MOM THR had survival rates of 71% and 100% at mean follow-ups ranging from 36 months to 336 months.
- MOM HRA had survival rates of 84% to 100% at mean follow-ups ranging from 39 to 89 months.
- No significant differences in the rates of mortality, dislocation or deep hip joint infection were found between groups.

Washington State Health Care Authority Health Technology Assessment Program. (2013). HTA final report: Hip resurfacing (Re-review). Olympia, WA: Health Technology Assessment Program. Retrieved from http://www.hca.wa.gov/hta/Documents/hip_final_report_100913.pdf

Efficacy (≤2 year): There is MODERATE evidence from three small randomized controlled trials that total hip replacement (HR) is similar to total hip arthroplasty (THA) with respect to short-term (<2 year) functional, quality of life, and activity outcome.

Efficacy (>2 year): There are NO DATA available to assess efficacy beyond two-year follow-up.

Effectiveness (Short-term, <5 years): There is LOW evidence from studies directly comparing total HR with THA to suggest that short term (≤5 years) patient-reported outcomes, clinician-based outcomes, and pain are similar comparing total HR and THA. Activity scores tend to be slightly higher (better) in total HR patients.

Effectiveness (Mid-term, 5-10 years): There is INSUFFICIENT evidence from one cohort study to suggest that at an average of 5.9 years follow-up, patients treated with total HR may have better quality of life and activity outcome scores, but similar functional scores, compared with those treated with THA.

Revision (Short-term, ≤5 years): There is HIGH evidence from three large registry studies that short-term revision risks are higher in patients treated with total HR compared with those treated with THA. At three years, there is between 20-50% higher risk of revision among those receiving HR vs. THA. The absolute risk is 3% in the HR group and between

2- 3% in the THA group. At five years, the higher risk is between 30-80%. The absolute risk ranges from 5 to 6% in the HR group and 1 to 4% in the THA group.

Revision (Mid-term, 6-10 years): There is HIGH evidence from three large registry studies that 7 and 10-year revision risks are higher ranging from 40-100% in patients receiving total HR versus THA. The absolute risk at 7 years is between 6-9% in the HR group and between 3- 4% in the THA group.

Revision (Long-term, 10+ years): There is LOW evidence from one registry study that 11-year revision risks are higher in patients receiving total HR (10%) versus THA (7%).

Complications: There is HIGH evidence from up to 3 RCTs and up to 6 observational studies that

- femoral component loosening occurs 8 times more frequently in HR patients than in THA patients, 2.7% vs. 0.3%
- heterotopic ossification occurs nearly twice as often in HR patients compared with THA patients, 19.8% vs. 11.4%.
- dislocation occurs less frequently in HR vs. THA patients, 0.5% vs. 2.8%.

There is MODERATE evidence that deep infection occurs less frequently in patients undergoing HR compared with THA, 0.4% vs. 1.8%. The risk of femoral neck fracture and avascular necrosis in HR patients is 2% and 1%, respectively.

Metal Ion Safety: There are consistently higher median concentrations of the primary metal ions cobalt and chromium in the blood or hair of HR patients compared with non-MoM THA (MoP and ceramic) patients in 5 studies with up to 3-year follow-up. High blood levels of cobalt and chromium are associated with poor outcomes (revision or poorly functioning hip) compared with low blood levels in patients receiving HR in 3 studies. Higher serum ion levels of cobalt and chromium are associated with pseudotumor formation following MoM HR and MoM THA in 3 studies. MoM hip prostheses (both HR and THA) are not associated with an increased risk of cancer compared with THA with other bearing surfaces in 3 registry studies. There is no negative impact on renal function across 6 studies evaluating patients following MoM HR or MoM THA.

Revisions: There is INSUFFICIENT evidence from one small study reporting similar functional and quality of life outcomes comparing HR revision with THA revision at final follow-up (range, 2-7 years).

Subpopulations: There is HIGH evidence from a large registry study that the diagnosis of developmental dysplasia (DD) modifies the rate of revision in HR and THA; those with DD receiving HR have significantly higher revision rates than those receiving THA or those with other diagnoses receiving HR or THA. There is HIGH evidence from a large registry study that gender modifies the rate of revision in HR and THA; females receiving HR have significantly higher revision rates than females receiving THA or males receiving HR or THA. Smaller femoral component head size results in significantly higher revision rates for those receiving HR while larger femoral component heads result in higher revision rates in those receiving THA.

NICE. (2014). Total hip replacement and resurfacing arthroplasty for end-stage arthritis of the hip (review of technology appraisal guidance 2 and 44).
http://www.nice.org.uk/guidance/ta304/resources/guidance-total-hip-replacement-and-resurfacing-arthroplasty-for-endstage-arthritis-of-the-hip-review-of-technology-appraisal-guidance-2-and-44-pdf

Prostheses for total hip replacement and resurfacing arthroplasty are recommended as treatment options for people with end-stage arthritis of the hip only if the prostheses have rates (or projected rates) of revision of 5% or less at 10 years.

Summary:
The recently published evidence does not contradict the current coverage guidance recommendations.

Topic: VISCOSUPPLEMENATION FOR OSTEOARTHRITIS OF THE KNEE

Coverage Recommendation (Box Language):

Viscosupplementation should not be covered for the treatment of pain associated with Osteoarthritis (OA) of the knee.

Source report:

Hayes, Inc. (2010). *Hyaluronic Acid/Viscosupplementation.* Produced for the Medicaid Evidence-based Decisions Project and the Washington Health Technology Assessment Program. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University. Retrieved September 10, 2012, from http://www.hta.hca.wa.gov/documents/ha_final_report_042610.pdf Coverage Guidance: Viscosupplementation for Osteoarthritis of the Knee 10/11/2012 2

Hayes, Inc. (2010). *Viscosupplementation for osteoarthritis of the knee.* Produced for the Medicaid Evidence-based Decisions Project. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University. Retrieved September 10, 2012, from http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/med/index.cfm

Samson, D. J., Grant, M. D., Ratko, T. A., Bonnell, C. J., Ziegler, K. M., & Aronson, N. (2007). *Treatment of primary and secondary osteoarthritis of the knee.* AHRQ Evidence Report/Technology Assessment No. 157. AHRQ Publication No. 107-E012. Evidence Report/Technology Assessment, (157), 1-157. Retrieved September 10, 2012, from http://www.ncbi.nlm.nih.gov/books/NBK38385/

Scanning results:

Two reviews and one guideline pertaining to OA of the knee were identified in the core sources that were published after the date of the MED report. In addition, an AHRQ report is in progress, and a Hayes report addressed post-operative viscosupplementation for a variety of knee conditions. Summary results and/or conclusions of the two completed reviews and the guideline are presented below:

CADTH.(2014). Viscosupplementation for the Treatment of Osteoarthritis of the Knee: Clinical Effectiveness and Guidelines
http://www.cadth.ca/media/pdf/htis/mar-2014/RB0647%20Viscosupplementation%20for%20Knee%20OA%20Final.pdf

Of the nine systematic reviews (SR) identified, five SRs indicated some benefit regarding the use of intra-articular hyaluronic acid (IAHA) for the treatment of knee osteoarthritis (OA), whereas the other four SRs did not identify any benefit. In the SRs identifying benefits, IAHA was noted to be most efficacious around eight weeks. Prolonged effects of IAHA were observed in studies that compared it to other active treatments, particularly intra-articular corticosteroid injections. In the SRs that observed no benefits of IAHA for knee OA, one highlighted a particularly large placebo effect which appeared to skew the IAHA effectiveness, while another noted that probable industry bias swayed results in favour of IAHA. The other two SRs observed no clinical benefit; however, it was proposed that IAHA could be an alternative to non-steroidal anti-inflammatory drugs in older populations at risk for adverse events, due to its comparable favourable safety profile.

Three of the identified guidelines do not recommend IAHA for the treatment of knee OA10- and another does not include any conclusive recommendations. Of the four guidelines that recommend IAHA use for knee OA, one conditionally recommends IAHA for patients with inadequate response to initial therapy, another recommends IAHA use for moderate to severe knee OA (noting this was based on consensus only), and the other two guidelines provide algorithms for IAHA use.

Rutjes, A. W., Jüni, P., da Costa, B. R., Trelle, S., Nüesch, E., & Reichenbach, S. (2012). Viscosupplementation for Osteoarthritis of the KneeA Systematic Review and Meta-analysis. Annals of internal medicine, 157(3), 180-191.
http://eds.b.ebscohost.com/ehost/pdfviewer/pdfviewer?vid=4&sid=daad4ec3-c5c4-41d9-b425-6257dfbd50ff%40sessionmgr114&hid=106

Data Synthesis: Eighty-nine trials involving 12 667 adults met inclusion criteria. Sixty-eight had a sham control, 40 had a follow-up duration greater than 3 months, and 22 used cross-linked forms of hyaluronic add. Overall, 71 trials (9617 patients) showed that viscosupplementation moderately reduced pain (effect size, -0.37 [95% CI, -0.46 to -0.28]). There was important between-trial heterogeneity and an asymmetrical funnel plot: Trial size, blinded outcome assessment, and publication status were associated with effect size. Five unpublished trials (1149 patients) showed an effect size of -0.03 (CI, -0.14 to 0.09). Eighteen large trials with blinded outcome assessment (5094 patients) showed a clinically irrelevant effect size of -0.11 (CI, -0.18 to -0.04). Six trials (811 patients) showed that viscosupplementation increased, although not statistically

significantly, the risk for flare-ups (relative risk, 1.51 [CI, 0.84 to 2.72]). Fourteen trials (3667 patients) showed that viscosupplementation increased the risk for serious adverse events (relative risk, 1.41 [CI, 1.02 to 1.97]).

Limitations: Trial quality was generally low. Safety data were often not reported.

Conclusion: In patients with knee osteoarthritis, viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events.

VADOD.(2014). Clinical practice guideline for the non-surgical management of hip & knee osteoarthritis.
http://www.healthquality.va.gov/guidelines/CD/OA/VADoDOACPGFINAL090214.pdf

Recommendations

22.For patients with symptomatic osteoarthritis of the knee, clinicians may consider intra-articular corticosteroid injection. [C]

23.There is insufficient evidence to recommend for or against the use of intra-articularhyaluronate/hylan injection in patients with OA of the knee; however it may be considered forpatients who have not responded adequately to nonpharmacologic measures and who havean inadequate response, intolerable adverse events, or contraindications to otherpharmacologic therapies. [I]

Summary:

Although the evidence is somewhat mixed, it does not appear to be substantially different from when the current coverage guidance recommendations were made. In addition, another review is currently in progress, it may be reasonable to consider updating this guidance once it has been completed.